Non-invasive Wearable Solutions to Identify Individuals with Mild Cognitive Impairments from Healthy Controls

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Submitted in partial fulfillment
of the requirements of the Degree of Doctor of Philosophy

School of Electronic Engineering and Computer Science
Queen Mary University of London

2022

Statement of Originality

I, Eaman Alharbi, declare that, to the best of my knowledge that this thesis has been composed solely by myself. I confirm that this thesis has not been submitted, in whole or in part, in any previous application for a degree except where states otherwise by reference or acknowledgment. The copyright of this thesis rests with the author. No quotation from it is permitted without full acknowledgement

Abstract

Wearable technologies are becoming an increasingly popular platform for healthcare services due to their wide range of clinical applications in the era of remote, decentralised, and personalized patient care. The flexibility of wearables and sensing technologies have led to a wide range of applications, including gait monitoring, motion tracking, and circadian rhythm assessment. Several evidence supports the use of wearable devices in multiple disease monitoring, diagnosis and treatment, prevention and rehabilitation. In this thesis, we consider the suitability of using these novel wearable and sensing devices in order to detect early cognitive impairment.

Within this thesis, we have conducted 3 studies on healthy participants, and participants with dementia and Mild Cognitive Impairment (MCI). Having the 3 sample groups are significant and bring credence to an argument that wearables can play a role in detecting early sign of cognitive impairment. At first, we needed to investigate the reliability of using wearables in detecting changes in HRV through different conditions. Then, the dementia group were significant for investigating the link between HRV and cognitive function, and lastly the MCI group to investigate if wearables can detect the early signs of cognitive impairment.

Firstly, we have conducted a pilot study of young healthy participants. We investigated the reliability of the state-of-the- art wearable sensing devices in detecting autonomic nervous system reactions to stress. We employed photoplethysmogram (PPG) sensors to collect HRV before, during and after the cognitive test. Finding showed a significant difference in HRV before and during the cognitive test.

Secondly, using data available from the UK Biobank data, a large, population-based study containing more than 500,000 participants recruited from across the UK. we investigated the relationship between heart rate variability (HRV) and cognitive performance in several cognitive domains. We first explored the HRV parameters of dementia patients in comparison with controls of the same age group, and then assessed the strength of the association between HRV and cognitive impairment in these two groups.

Lastly, we used off-the-shelf HRV monitor device to assess whether real-time measures of HRV can be used as an early indicator of cognitive decline in individuals with MCI who still have intact cognitive abilities relative to healthy controls. Our findings showed reduced HRV indices is associated with MCI

participants. This suggests that the autonomic dysfunction represented by HRV is detectable in baseline conditions using PPG sensors.

In conclusion, this thesis has investigated wearable sensing techniques towards assessing cognitive function in patients with MCI and dementia. Within this thesis, different studies demonstrated the feasibility of using wearables to collect real-time HRV could be used as an early indicator of cognitive decline in individuals with MCI.

Acknowledgements

First and foremost, I owe a great debt of gratitude to my supervisor Dr Akram Alomainy for his never-ending support, and continuous guidance during my PhD journey. I would also like to thank my co-supervisor, Dr Janelle M. Jones who read my numerous revisions and taught me how to continue a constant writing development. A special thanks to Dr Tony Stockman for his positive spirit and valuable feedback during this unforgettable journey.

I am incredibly grateful to Dr Charles Marshall, clinical Lead for Neurology at Barts Health NHS Trust, for giving the honour to be part of the UK BioBank data study which allowed me to conduct meetings and conversations that were vital and inspiring to complete my thesis. I would like to extend my gratitude to Join Dementia research organisation for their contributions that facilitated data collection and all the participants who were so generous with their time to be part of this research.

I am especially grateful to my parents, Abdulaal and Maryam, who sometimes watched me from a distance while I worked towards my degree, and at other times traveled over 1000 miles to support me and my family. You are my true strength in life and my motivation. I am very proud to be a daughter of theirs. I hope that I have made you proud. I would also like to thank my sisters and brothers (Amal, Turky, Ayman, Bshayer and Ghaida) for all of the love, support, encouragement and prayers they have sent my way along this journey.

I am incredibly grateful to Ahmed, my husband, my love, my best friend and partner in the trenches who made it possible for me to pursue my dream and supported me every step of the way with patience, love, and humor and to my son, Faisal, who has been the light of my life for the last three years, and my inspiration to achieve success without whom I would not have been able to complete this research.

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List of abbreviations

AD	Alzheimer's Disease
ANS	Autonomic Nervous System
ANN	Artificial neural networ
BMI	Body mass index
BP	Blood pressure
CNS	Central Nervous System
DLB	Dementia With Lewy Bodies
DT	Decision Tree
ECG	Electrocardiogram
HR	Heart rate
HRV	Heart Rate Variability
HF	High frequency
IBI	Interbeat interval
KNN	K-nearest Neighbour
LDA	Linear Discriminant Analysis
LF	Low Frequency
LF/HF	Low frequency to high frequency ratio
PPG	photoplethysmogram
PNS	parasympathetic nervous system
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
ms	Milliseconds
RF	Random Forest
RMSSD	Root mean square of successive RR interval differences
SDNN	Standard deviation of NN intervals
SNS	SympatheticNervous System
SVM	Support Vector Machine

Part I

Motivation and Introduction

CHAPTER 1

Introduction

This introductory chapter presents the motivation, which will direct us to research questions, and the contributions of this thesis. Finally, we will present an outline of the thesis.

Wearable health monitoring technologies have attracted an increasing interest in the past few years [2; 3]. Much of that interest was driven not only by the rapidly expanding demand for the ubiquitous, continuous, and pervasive monitoring of vital signs, but also by the state-of-the-art technological advancement in sensor technology and wireless communications. Wearable and biosensors devices are no longer limited to fitness trackers that track ones steps, calories burned, and sleep status; they also monitor vital physiological signs including Heart Rate Variability (HRV), glucose levels, blood pressure, and oxygen levels. Wearables have been widely adopted in several fields such as healthcare, education, military, and fire protection. The market value for wearable medical devices was USD 29.76 billion in 2019 and is expected to grow to USD 195.57 billion by 2027, with an annual growth rate of 26.4% during the forecast period [1].

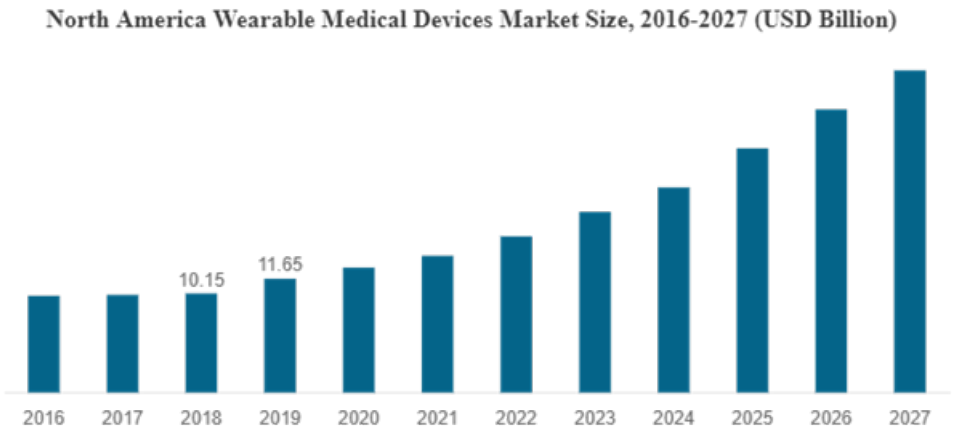

Figure 1.1: Wearable medical devices Market size from 2016 to 2027 (Data Source: [1])

Wearable health monitoring applications are among the fastest expanding segments on the wearable technology market because of the growing demand to monitor chronic diseases and ageing populations[4]. Moreover, the pandemic has led to a significant increase in the demand for remote health monitoring systems. The COVID-19 pandemic has brought forward the need for advancement in patient monitoring systems, with manufacturers focusing on increasing production to meet the growing demand for health monitoring devices including pulse oximeters, blood glucose, cardiac, and temperature monitoring devices. Consequently, this led to increased adoption of digital pervasive health monitoring. For instance, Philips Biosensor BX100 received a clearance from the U.S. Food and Drug Administration (FDA) for its wearable biosensor to help managing confirmed and suspected COVID-19 patients in hospitals. The biosensor helps clinicians in detecting risk to help with the early intervention and improve care for patients in lower acuity care areas [5].

There is growing body of evidence of the potential benefits of healthcare wearables. To begin with, they offer a reliable real-time, non-invasive continuous monitoring along with their ability to store and share health records. Next, wearables provide users with feedback that allows them to make necessary modifications to their daily routines or behaviour [6]. Finally, since wearables facilitate remote monitoring, this can result in significant cost savings to healthcare [7]. Wearable health monitoring devices can be especially beneficial to patients with chronic conditions [8], individuals with cardiovascular risks [9], and ageing populations [10]. Moreover, continuous and real-time monitoring through wearable devices promises to improve the current care of people with dementia in several aspects.

Most of the state-of-the-art sensing-based dementia care focuses on early dementia detection as well as quantitative evaluation of therapeutic interventions for cognitive care[11; 12]. Early detection and intervention to delay the onset of dementia are beneficial for patients and their caretakers and for reducing the prevalence of dementia [13]. Mild cognitive Impairment (MCI) can be an early stage and a feature of predementia in Alzheimer's disease (AD). However, the diagnosis of MCI is not yet fully developed [14]. Employing wearable and biosensors devices to collect user's physiological parameters can significantly help with the early detection of AD. For instance, gait has been shown to be a non-invasive biological biomarker of cognitive function [13; 15]. However, continuous and real-time sensing-based inference and prediction to prevent cognitive impairment are still an open research.

1.1 Motivation

This dissertation is primarily motivated from a research perspective and attempted to focus on wearables and sensing technologies and their potential future applications in dementia care. Due to the gradual increase in life expectancy, the prevalence of dementia and Alzheimer's disease has dramatically increased [16]. This fact raises some critical questions about the economic feasibility of traditional dementia care programmes approach. Until now, there is no proven pharmacological or non-pharmacological intervention that can cure dementia or stop its progression. Accordingly, there is an urgent need to develop more coordinated solutions to provide high-quality and patient-centred health services for patients with dementia.

It is generally believed that the possibility of reversing anatomic and physiologic changes such as neuronal death reduces drastically as the disease progresses, emphasising the importance of early cohort detection and patient stratification in any future clinical investigations [17]. Early detection of the cognitive impairment has been shown to enable interventions which slow down the progression of the disease such as physical activity interventions [18] and pharmaceutical interventions [19]. A significant body of research suggests that cognitive, sensory, and motor changes may occur several years before clinical signs of dementia [20]. While clinically valid, current cognitive assessment for diagnosing neurodegenerative diseases is frequently less effective in detecting the decline in its early stages [17]. Moreover, theses assessments are subjective and require a continuous attention of the administrator which limit the type and amount of data points captured [21].

The diagnosis of MCI and dementia based on clinical features alone is often challenging and relatively unreliable [22]. As a result, current research

is focusing on the identification of biomarkers that aid in the early detection of neurodegenerative diseases such as MCI. The use of wearables and digital biomarkers has had a particular influence on neurology, where there is a significant unmet need for objective and non-invasive biomarkers [23]. Wearables and biosensors devices provide an opportunity to maintain consistent data collection in real-world environments across longer periods of time. Furthermore, they can be used to monitor progression of the condition through non-invasive assessments. Advancements in wearables and sensing technologies have created numerous opportunities for researchers to investigate the possibility of detecting early cognition changes in older adults. Currently, a number of wearable-based biomarkers are being tested for feasibility and reliability in dementia and clinical outcome assessments [17]. Moreover, numerous studies employed wearable and sensing technologies to monitor daily activities of older adults and detect behavioural changes [24].

It is important to examine whether biomarkers other than traditional cognitive assessment could be utilised to successfully predict dementia in its early stages. If effective, it would give a low-cost and simple technique to screening for dementia at the pre-clinical stage, allowing for the development of relevant interventions to delay its clinical manifestations. As a result, current research tries to identify prodromal biomarkers for the early identification of dementia. This would help addressing the significant need to accelerate patient diagnoses and empower clinician and individuals to take timely action.

1.2 Research Questions

The intent of the proposed research study is to answer the main question:

> ***How suitable are wearables and sensing technologies for detecting cognitive impairment in people with MCI using Heart rate variability?***

It is not easy to answer this question due to the multitude of wearable devices, various sensors technology, as well as their rapid development. Different approaches have been taken to address this question. Starting from exploring the reliability of wearables devices in capturing the differences in HRV before, during, and after the cognitive assessment towards a more generalised conceptualisation of the problem is taken. Finally, multiple techniques in identifying individuals with MCI are presented.

Firstly, we should assess the current State-of the-Art in Wearable Technologies for persons with MCI and dementia.

> ***RQ 1*** *What is the current State-of the-Art in Wearable Technologies for persons with MCI and dementia ?*

Secondly, we should assess the reliability of wearables devices in capturing the differences in HRV before, during, and after the cognitive assessment.

> ***RQ 2*** *what is the reliability of wearables devices in capturing the differences in HRV before, during, and after the cognitive assessment?*

and after aspects of the reliability of wearables devices in capturing the differences have been considered, it should be explored how is the association between HRV and cognitive performance. to answer the question:

> ***RQ 3*** *Is there a significant correlation between HRV derived from wearables and cognitive performance using wearables technology?*

Then and after exploring the relationship between HRV and cognitive performance, we will explore to assess the relationships between HRV and cognitive performance in Dementia patients.

> ***RQ 4*** *Will measures of HRV amongst dementia patients be lower relative to controls?*
>
> ***RQ 5*** *How strong is the association between HRV and cognitive function among older group?*

Finally, to investigate whether wearable sensors can offer reliable, non-invasive techniques to identify MCI patients from healthy controls by measuring HRV as a novel physiological biomarker

> ***RQ 6*** *Will wearable biosensor devices be a useful tool for assessing physiological changes associated with MCI?*

Different approaches have been taken to address these research questions. At first we have conducted a comprehensive review to answer the first research question (RQ 1) which is what is the current State-of the-Art in Wearable Technologies for persons with MCI and dementia? we investigated to date into the use of wearable technologies to support people living with MCI and with dementia. In order to answer the second and the third research questions (RQ 2&3) regarding the reliability of wearables devices in capturing the differences in HRV before, during, and after the cognitive assessment and the correlation between HRV derived from wearables and cognitive performance using wearables technology, we conducted a pilot study to assess the reliability of wearable

sensing technologies.

Moreover, to answer the fourth and fifth research questions (RQ 4& 5) regarding the association between HRV and cognitive function among dementia group, we have used data from UK biobank to analyse the link between HRV and cognitive function in older group with dementia.

At last, we have conducted a study on people with MCI. We have collaborated with Join dementia research organisation to recruit the participants in order to answer the last research questions (RQ 6) regarding the usability of wearable biosensor devices for assessing physiological changes associated with MCI.

1.3 Contributions and Thesis structure

The objective of this dissertation is to explore and investigate the potential of wearables and sensing technology toward early detection of cognitive decline among people with MCI and dementia. This work will test the feasibility of using HRV wearable based as a biomarker in order to detect disorders in the Autonomic Nervous System (ANS), identifying potential opportunities for clinical intervention. At first, we explored and built the foundation of this dissertation by providing A Review on the use of wearable devices for dementia assessment, monitoring and cognitive intervention, next we tested the feasibility of using sensing technology to assess the changes in HRV. Further, we tested the association between dementia and HRV in people with dementia. Lastly, we investigated the feasibility in detecting cognitive declining in group of MCI patients using Physiological Sensing technology.

Chapter 2: A Review on the use of wearable devices for dementia assessment, monitoring and cognitive intervention. To answer RQ 1, this review, we present a comprehensive overview of the investigations to date into the use of wearable technologies to support people living with MCI and with dementia and the resulting benefit to their well-being. We assess the role of wearables in three broad categories: in the assessment of the presence of dementia symptoms, their role as an assistive technology, and their role as a cognitive intervention. We also review the use of wearables in combination with non-wearable technologies or alone and the potential to monitor multiple parameters at once using a single wearable. We detail the limitations of wearable technologies, identify the unmet needs and challenges in the implementation of wearables-based interventions, and propose the required next steps to improve the outcomes of people living with dementia using wearable technologies.

Chapter 3: Detecting Autonomic nervous system reactions using HRV. To answer RQ 2 and RQ 3, chapter 3 investigates the reliability of the state-of-the-art wearable sensing devices in detecting autonomic nervous system reactions to stress, and the associations between cognitive performance and HRV in young healthy participants in order to detect the autonomic nervous system reactions using wearable sensors. The pilot study presented result from utilising the CorSense devices to collect sensing data.Then, It has been discussed how data obtained from sensors can be used to assess ANS reactions. As main contribution, this chapter evaluates the reliability of wearables devices in capturing the differences in HRV before, and during the cognitive test. Further, it asses the relationship between short-term HRV and cognitive performance on multiple cognitive tests using wearable based device.

Chapter 4: Association between cognitive performance and HRV in individuals with dementia. To answer RQ 4 and RQ 5, Chapter 4 ties together findings from the previous exploratory chapter. Here, we discuss the experiment design and the findings of ultra-short term (10 sec) HRV measures from UK Biobank, and it's association with cognitive function in Dementia patients. Further, we discusses the findings of using machine learning classifiers to predict cognitive performance in individuals with dementia.Then, We evaluated the data, and presented the results. Finally, a discussion of the results is presented. As main contribution, this chapter proved the significant difference in HRV time-domain parameters between dementia and Healthy individuals. Further, Results showed that ML was able to to estimate cognitive performance using only HRV data. The results indicated that high HRV was associated with better performance on tasks involving executive function, processing speed, and working memory.

Chapter 5: Association between cognitive performance and HRV in individuals with MCI. To answer RQ 6, This chapter presents a study on using wearable sensing to help identifying individuals at higher risk of Dementia. We investigated whether wearable sensors can offer reliable, non-invasive techniques to identify MCI patients from healthy controls by measuring HRV as a novel physiological biomarker.Further analysis was performed to test the association between HRV parameters and cognitive status controlling for both age and gender. Finally, a discussion of the results is presented.As main contribution, this chapter shows that RMSSD, SDNN, and HF measures can be used to reliably distinguish MCI patients from healthy controls with Average accuracy of 76.5%.

1.4 Associated publications

Portions of the work detailed in this thesis have been presented in national and international scholarly publications, as follows (journal publications highlighted in bold):

- Chapter 3: Detecting Cognitive Decline in Early Alzheimer's Patients Using Wearable Technologies was published in **2020 IEEE International Conference on Healthcare Informatics (ICHI).** [25].
- Chapter 4:Machine Learning approach to Predict Cognitive Performance using HRV. some of the work was presented at the **2022 2nd International Conference on Computing and Information Technology (ICCIT)** [26].
- Chapter 6: Accepted for publication in the **IEEE journal of translational engineering in health and medicine**

1.5 Submitted for Publications

- Chapter 2.1: A Review on the use of wearable devices for dementia assessment, monitoring and cognitive intervention was submitted to **ACM Transactions on Computing for Healthcare**
- Chapter 5: some of the work was submitted for publication in **2022 IEEE-EMBS International Conference on Biomedical and Health Informatics (BHI)**.

Part II

Foundation

CHAPTER 2

Background and Literature Review

This chapter presents background reading and extensive literature on wearables for dementia and its relation to HRV. This chapter covers in-depth information about HRV, and its analysis using machine learning techniques. It covers the possibility of wearable sensor technologies to be used for detection of cognitive decline and for dementia patients. It outlines what wearable technologies are now available, as well as what sensing options are available within wearables and how these can be used to capture physiological changes. It discuss the The neurovisceral integration Model and how it links HRV to Cognitive Function.

2.1 A Review on the use of wearable devices for dementia assessment, monitoring and cognitive intervention

In this section, we assess the role of wearables in three broad categories: in the assessment of the presence of dementia symptoms, their role as an assistive technology, and their role as a cognitive intervention. We also review the use of wearables in combination with non-wearable technologies or alone and the

potential to monitor multiple parameters at once using a single wearable. We detail the limitations of wearable technologies, identify the unmet needs and challenges in the implementation of wearables-based interventions, and propose the required next steps to improve the outcomes of people living with dementia using wearable technologies.

2.1.1 Introduction

Dementia, a set of syndromes associated with a decline in cognitive functioning, affects approximately 50 million people globally, with nearly 10 million new cases diagnosed every year [27]. In the United Kingdom, 850,000 individuals are currently living with dementia, and approximately 225,000 individuals develop dementia each year [28]. Dementia also has a huge economic impact, with the global annual cost to the health and social care sector estimated to exceed $817 billion [29].

The extent of the decline in cognitive function associated with dementia varies from mild to severe. In severe cases, individual abilities become progressively worse in one or more measured dimensions, including memory, recall, decision-making and emotional disturbances [30]. Mild cognitive impairment (MCI) is a defined period which may occur between normal aging and dementia when decrements in cognitive function are not severe enough to interfere with everyday life but do impact instrumental activities of daily living (e.g., taking medication, using transportation) [31]. Early recognition and monitoring of MCI is important as it can give individuals and their families the opportunity to put appropriate interventions in place to delay the onset of dementia and have important discussions with the individual about their preferences on their care moving forward. For this reason, assessment of the use of wearables from detection of MCI onward have been included in this review. As MCI progresses to dementia, the cognitive decline becomes severe enough to interfere with daily life activities, such as eating and grooming. Some individuals may also develop behavioural and psychological symptoms of dementia (BPSD), which include apathy, depression, irritability, anxiety, agitation, and wandering [32]. BPSD can affect daily functioning and is associated with decreases in quality of life and for these reasons, the potential use of wearables to manage these symptoms has been included here [33].

As stated, dementia is an overarching term used to describe an individual experiencing progressive cognitive decline. Within this bracket are four common subtypes of dementia; Alzheimer's disease (AD), Vascular dementia, Lewy body dementia and Frontotemporal dementia, which each have their own distinguishing features and clinical presentations. The differences between the clinical

presentations of these subtypes may warrant stratification of wearable devices as some may appear more useful for some subsets of dementia than others.

Although people living with dementia may present with varying clinical manifestations, common symptoms include loss of memory, language and communication difficulties, apraxia, agnosia, and disruption of executive functioning [34]. These cognitive, behavioural, and language impairments predispose people living with dementia to gait disorders which are associated with falls, fall-related injuries, and even mortality [35]. Monitoring individuals on an on-going basis will measure overall deterioration and detect development of gait disorders and therefore predict likelihood of such injuries, enabling people living with dementia and carers to put measures in place to reduce risk. Early detection of symptoms of cognitive decline allows the opportunity for early intervention before symptoms progress to severe cognitive deterioration. Because dementia has a tremendous impact on affected individuals, their families, and the healthcare system, it is clear that solutions are needed to support earlier diagnosis, monitor identified dementia, and better support both diagnosed individuals and their caregivers.

Across different medical specialties, there have been ongoing investigations and proposals into the use of novel technologies to improve and support patient diagnosis and monitoring. Within dementia care, these assistive technologies can be broadly divided into non-wearable and wearable solutions.

Non-wearable technologies include passive infrared sensors, cameras, motion sensors, or pressure sensors which can be integrated into individuals' homes and used to monitor aspects such as walking speed, night-time wandering, sleep patterns and gait [27]. However, non-wearable technologies are limited due to their fixed placement and associated costs and additionally could be seen to be invasive solutions given their placement in the individual's home.

In contrast to the limitations listed above, wearable technologies are typically small, portable, digital solutions which can be kept on the individual and easily removed as needed. Common examples include wrist or ankle bracelets, and further examples are discussed in detail below. They may be used to monitor a variety of parameters not limited to heart rate, sleep and waking cycles, gait, level of exercise, emotional disturbances, location and more and as they are kept on the individual themselves, they offer the opportunity to monitor throughout the day, not just when the individual is in their home. They often also allow for the opportunity to monitor multiple parameters at once, such as heart rate, gait, location and sleep. Given these features and benefits, they may address any concerns associated with non-wearable technologies and may encourage better patient uptake than the alternative.

The potential of non-wearable technologies has not been discounted in this

review and many studies into novel technologies have investigated the combined use of wearable and non-wearable solutions to build a comprehensive picture of the patient and their well-being as well as compensating for the limitations of using only one particular technology. For example, people living with dementia might use a wearable bracelet or ankle piece to monitor heart rate, temperature and movement alongside non-wearable motion and pressure sensors within the home to monitor changes in sleeping patterns or to gait. These combined approaches are discussed later in this review.

There may also be some benefits to wearable technologies over other monitoring devices such as smartphones. Smartphones usually come with built -in pedometers, GPS tracking and accelerometers and there are a vast number of apps developed for such types of monitoring. However, smartphones require users to have some baseline understanding of their use and require the user to continue to be able to use the technology. They may also be considerably larger than a wearable device such as a wristband and then require the user to carry these around with them. A wearable device removes the need to remember to carry the monitor throughout the day and doesn't require understanding of the technology itself.

Method

Literature Search Strategy

The initial literature search was conducted in August 2019, and the search was updated in November 2021. We searched several databases (IEEE Xplore, ACM Digital Library, Web of Science, Google Scholar, PubMed). Titles, abstracts, and texts were searched for the following keywords/terms: ((dementia) AND wearable), ((IoT) AND dementia), ((health) AND dementia), ((mobile health) AND dementia), wristband AND dementia, ((Alzheimer's disease) AND wearable), ((AD) AND wearable), ((mild cognitive impairment) AND wearable) and ((MCI) AND wearable). Identified papers were then grouped into the following categories:

- Wearables for assessment and monitoring symptoms of dementia
- Wearables for assisting individuals with dementia in daily life
- Wearables that support cognitive interventions

Eligibility Criteria

The following inclusion criteria were used: enrolment of individuals diagnosed with MCI or with dementia in any stage of the disease; publication between

2009 and 2021; and use of at least one wearable technology. All included papers were published in English.

This review examined three fundamental questions: (1) what the wearable technologies can do; (2) which wearables were used and whether they were used alone or with other ambient sensors (i.e., non-wearables); and (3) what type of support the wearables provided in relation to dementia (assessment and monitoring, or intervention).

2.1.2 Review of wearables for assessment and monitoring symptoms of dementia

Many different techniques exist to diagnose cognitive change or MCI. These techniques include neuropsychological tests, neuroimaging techniques and laboratory testing. Several computerized cognitive tests are also available to assess mental status. Some of these computerized tests, such as the Cantab Mobile, Cognigram, Cognivue and Automated Neuropsychological Assessment Metrics, have been approved by the U.S. Food and Drug Administration and hold real value in their clinical use, particularly in light of recent shifts in healthcare practices, as they can be administered remotely and still provide the same clinically relevant results [36]. A computerised approach has several benefits over traditional in-person testing including cost- and time- savings, accuracy and standardisation of recorded responses, and allows for quick and simple comparison of an individual's successive test results. Tests can be administered by health professionals following limited training or self-administered. However, unfamiliar technology can be intimidating to older adults, and this can deter them from completing these tests [28].

Wearables present as a potential solution to limitations to traditional and computerised testing or simply be a potential alternative when the former are not possible to perform. Further, the wearable could be used as an adjuvant to the aforementioned testing methods, providing further insight to the person's wellbeing.

Incorporating a wearable into a person's life is a small daily adjustment and the continuous recording and monitoring of information provides a valuable insight for their healthcare professional. By giving the individual the choice to use the wearable, it provides the opportunity to include the individual in the development of their care plan and thereby empowers them. Another instance in which a wearable could be used is in the monitoring of BPSD, a condition affecting some people with dementia which causes disturbed perceptions, thoughts, moods, or behaviours [37]. Solutions that promote more accurate diagnoses and a deeper understanding of BPSD patterns and triggers are urgently needed and

could be furthered with the use of a wearable device. A summary of the studies that have used wearable sensors to determine and assess cognitive change or impairment is presented in Table 2.1, however this is not an exhaustive list.

The studies present an attempt to harness wearables as a potential method of monitoring the elderly population and identifying early the initial signs of the development of MCI and/or dementia itself. Some approaches use only a wearable [30] [33] [34] while several others combine the use of a wearable with passive non wearable technologies that can be integrated into the home [31], [32]. While all studies aimed at the determination and assessment of cognitive decline, the parameters measured varied. Tan et al. measured features such as forgetfulness, physical activity and sleep quality [32] while Cinaz et al. opted to measure reaction times. [34] The assessment of different parameters such as reaction times [34], task completion [33], forgetfulness [32] and gait and walking speed [30] were also used to attempt to differentiate between normal, healthy individuals and those who may have early signs of dementia, thereby showing the use of wearables as stratification tools in this field. The range of parameters investigated across studies is useful to review to understand the range of monitoring which can be achieved by a wearable. Further, we can deduce that monitoring more than one parameter would be a useful approach to take to expand understanding of patient well-being.

There were some limitations identifiable in these studies such as Chen et al. [31] who conducted their study on early detection of MCI using a wristband and home-based non-wearable technologies; however, the study was conducted over the limited time period of two months. Their conclusion of sleep state variability being a reliable measure of detecting MCI in older adults is therefore contestable and further investigations should be taken.

A sound conclusion to draw from the list of studies presented is that wearable technologies do appear to consistently present as a reliable option of detecting and assessing presence of cognitive decline, whether used alone or in combination with non-wearables. However, further research may be warranted into determining the most appropriate features and/or parameters to be measured which will allow the optimal parameters for monitoring to be selected, to the benefit of both the individual and the managing physician.

Limitations in dementia assessments

As above, several papers assess the use of wearable technologies in assessing the presence of dementia by monitoring behavioural and psychological changes and show promise in differentiating between healthy subjects and those with MCI or early-stage dementia. Traditional tests—such as the Montreal Cogni-

tive Assessment [29]—can be impracticable because they must be administered in clinical settings and with the recent challenges associated with the COVID-19 pandemic, face-to-face appointments in a clinical setting are limited and long delays are common. Wearable technologies can provide a practical alternative to assess cognitive changes because they offer a high level of accuracy in measuring speed and time of response to a given task with a level of sensitivity not possible in standard neurocognitive assessments. They provide an alternative which could potentially be set-up at home by an allied healthcare professional rather than a managing physician and therefore additionally remove the need for a formal set-up with a consultant. Wearables can assess cognitive changes amongst older adults, including those with amnestic MCI and AD and it has been shown to be possible through use of wearable sensors which detect physical responses to movement-based requests [38].

An important distinction to draw is that traditional testing is a method of directly monitoring cognitive decline and contrastingly, wearables present as a method to indirectly monitor. For example, wearables may monitor a physical behaviour which is shown to change as a patient experiences cognitive decline. For this reason, wearables can be said to provide a sound indication of the presence of cognitive decline or change, rather than a definitive diagnosis and perhaps present as a potential method of screening the elderly population before more formal, direct testing is carried out.

Early detection of cognitive impairment can be captured by continuous behavioural monitoring through traditional or novel testing methods which evaluate cognitive capacity. For instance, forgetfulness is recognised as an important indicator in cognitive decline. Studies conducted may measure forgetfulness by integrating multimodal devices into individual homes to detect the number of times individuals miss a medication dose or forget their wallet upon leaving the house [39].

Continuous monitoring of physical activity can also provide important insights into cognitive decline. For instance, Suzuki et al [40] estimated cognitive functioning in older adults by observing their gait. Using acceleration and angular velocity sensors attached to the waist to calculate the walking speed, stride and walking variability, the authors were able to build an accurate formula to estimate the Mini Mental State Examination score. While change in gait has been proven to be an indicator of early-stage dementia and cognitive decline, it is worth noting that gait impairments are also a sign of normal aging and, as such, gait changes should be considered on a case-by-case basis. Moreover, while gait-impairments have been linked to dementia-related cognitive decline, a more comprehensive assessment would be to assess dual-tasking, such as an individual walking and also performing another task, in individuals who have

been shown to have MCI. One study took this approach to assess gait impairment in Parkinson's disease (PD) by combining use of a wearable device with a commonly used stepping in place test. It concluded combining the two gave a more comprehensive picture of the individual's ability and stage of disease and proposed this to be a new method for evaluating dual-task deficits in PD [41].

Table 2.1: Wearables for the determination and assessment of cognitive decline or impairment

Authors	Year	Objective(s)	Wearable Device(s)	Domain
Arai et al [42]	2021	To detect signs of dementia by focusing on events that occur in daily life	Wearable Sensors attached to individual and other ultra-small sensors attached to different objects in the house	Behavioural changes
Suzuki et al [40]	2020	To use walking information obtained from wearables to estimate cognitive function.	Wearable Acceleration and angular velocity sensor to capture the walking speed, stride and walking variability.	Behavioural changes
Chen et al [43]	2019	To determine presence of MCI in seniors who live alone and to categorize individuals into positive and negative MCI groups by monitoring mobility, self-care, leisure activity, sleep quality, and risk of depression	Wearable and in-home sensor system to capture sleep and monitor activities.	Sleep monitoring
Tan et al [39]	2018	To assess the feasibility of continuous monitoring using multi-modal wearable sensors and to distinguish between MCI, people living with dementia and healthy subjects	Heart rate and daily pedometer wearables along with other passive sensors, such as motion, door, bed, medication box and key sensors, placed in the elderly's home.	Physical activity monitoring , adherence to medication, and behavioural changes
Zhou et al [38]	2017	To use wearable sensors to examine the feasibility, accuracy and reliability of an instrumented trail-making task to identify motor cognitive decline amongst older adults.	Ankle band wearable sensor attached to an individual's leg to track ankle motion.	Ability changes
Cinaz et al [44]	2011	To develop reaction time tests that can be conducted throughout everyday life using wearables to detect and monitor MCI and dementia	Wrist band acceleration sensor placed at the wrist to measure wrist movement.	Ability changes

2.1.3 Review of wearables for the detection and monitoring of people with BPSD

BPSD affects up to 90% of all people living with dementia [45]. BPSD may cause gait changes, agitation, depression, apathy, aggression, sleep problems, and wandering [46]. Although no pharmacological treatment is approved for BPSD, several psychotropic medications, such as antipsychotics, mood stabilizers and antidepressants, are regularly used to treat these symptoms [47]. However, treatment with antipsychotic medications has been linked to increased morbidity and mortality in people with dementia [48]. With this in mind and the associated issues described here, BPSD should be determined and monitored with measures put in place to reduce risks to the diagnosed individual.

The studies summaries in 2.2 assess the use of wearables in monitoring dementia and associated risk by monitoring behavioural changes, agitation, gait and falls, indicators of BPSD. The studies again use wearables alone or in combination with non-wearable technologies to monitor at-risk individuals.

Gait changes are one symptom that can be detected by wearable sensors [49], [50], [51]. Walking patterns in people living with dementia tend to notably vary from healthy individuals, with a distinct difference in step length and timing [43]. Wearables can facilitate the measurement of spatial and temporal gait parameters such as velocity, stride length and speed velocity, stride length and speed, and these measures can become biomarkers of gait impairment [52],[53],[54] .

Detection of other BPSD symptoms, such as agitation, is also feasible using wearables. Agitation can be exhibited via physical behaviours, such as irregular limb movements, or verbal behaviours, such as raising one's voice. Monitoring physical and behavioural changes via postural orientation, movement and voice in real environments can be achieved with accelerometers, gyroscopes, sole sensors, pressure sensors and microphones. Moreover, those sensors may be integrated with other ambient sensors, such as video cameras, motion sensors and door sensors to build a more complete view of the patient in their home environment and allow detection of cognitive decline [28],[35],[38],[45],[49],[55],[56]. In doing so, the needs of the patient can be evaluated in real-time and should the patient be seen to be progressing into the later stages of disease, appropriate interventions can be put in place by their practitioner in a timely way to ensure the people living with dementia continued wellbeing and safety.

Falls and fall-related injuries are more common in people living with dementia than in healthy peers [57]. Wearables are useful for fall detection because of their accuracy, privacy and lightweight portability relative to cameras [58; 59; 60]. Schwenk et al [60] revealed that using wearable sensors led to

higher accuracy than using conventional fall risk measures in predicting falls among people with dementia.

Combined monitoring evidently affords useful and comprehensive information about the individual and can be collected through use of multiple monitors. Goerss et al. (2020) combined the use of a wrist and ankle wearable device with a home video recording system and augmented real-time observation by a primary carer [51]. This approach aimed to investigate how early detection of the development of challenging behaviours would be possible and how this could be used as a prognostic indicator. The study was implemented in a nursing home, where such interventions and monitoring may be put in place with more ease than in the patient home. While this study focussed on changes in gait and increased levels of agitation, a second study (Rawtaer et al [61]), also combined the use of wearable and non-wearable technologies to monitor forgetfulness. A wearable wristband combined with home-based motion sensors and medication box sensors were used to monitor the individual's ability to remember key points of their day. An important finding from this study was that 80% of individuals were happy to have motion sensors installed in their home and they did not find these to be as invasive as to object to their use [61].

Table 2.2: Wearables for the assessment of behavioural and psychological symptoms of dementia (BPSD)

Authors	Year	Objective(s)	Wearable Device(s)	Domain
Khan et al [56]	2021	To examine the predictive ability of this multimodal sensor data to replicate a common behaviour clinical documentation tool, the Pittsburgh Agitation Scale	Empatica E4 wristwatch	Behavioural changes
Favela et al [62]	2020	To evaluate the progression of BPSD using activity trackers	Fitbit wristwatch	Behavioural changes
Goerss et al [51]	2020	To investigate the automatic detection of challenging behaviours in people living with dementia living in nursing homes via long-term accelerometric recordings.	Hand and ankle bracelet to measure accelerometric motion scores, Video recording in the home	Behavioural changes - presence of agitation, and Changes to gait
Rawtaer et al [61]	2020	To establish the feasibility and acceptability of using sensors in the homes of senior citizens to unobtrusively detect changes in behaviours.	Wearable wristband to measure pedometer and heart rate PIR motion sensors Medication box sensors	Behavioural changes, forgetfulness, Sleep monitoring, and Physical activity monitoring
S. Khan [63]	2019	To use multi-modal sensor data to subsequently build predictive models for agitation detection in people living with dementia	Empatica E4 wristband, Pressure mats to collect sleep data, Motion sensors and door sensors to monitor movement. and video cameras.	Behavioural changes
Wu-Lin Chen et al [64]	2018	To develop a warning system for elderly behavioural differences.	Wearable glasses for acceleration, angular velocity to identify daily movements, actions and locations.	Behavioural changes, Movement monitoring, and Location monitoring
Kikhia et al [65]	2018	To assess sleep and stress patterns for people with BPSD using sensors in nursing home settings.	Philips's sensor bracelet (GSR accelerometers, skin and environment temperature)	Sleep and stress detection

2.1.4 Review of wearables used in assisting individuals with dementia in daily life

Wearables that assist people living with dementia can address several pressing health needs such as supporting daily functioning and activities, promoting physical functioning and social interaction, enabling self-monitoring of health status, and improving treatment adherence. As demonstrated in Tables 2.1 and 2.2, there are a variety of wearable devices on offer which can be selected specifically to meet the individual's requirements and support those living with dementia and MCI. In this section, we categorize the wearable technologies that assist people living with dementia according to their uses for physical and physiological activity monitoring and for localization and navigation.

Wearables for Physical and Physiological Activity Monitoring

To date, several studies have focused on continuous monitoring for people living with dementia, and notably focus on monitoring of daily routines and recognition (Table 2.3). By providing reliable long-term assessments about individual health and well-being (e.g., daily activities and physical ability), continuous monitoring can ensure patient safety, provide people living with emergency assistance and support when necessary, and offer unobtrusive assessment of disease progression. Deviations from what is interpreted as being the norm for each individual provide valuable and tailored insights into their overall well-being, in a much more comprehensive way than what could be achieved through face-to-face assessment with a practitioner.

Monitoring of activities on a continuous basis may help identify changes to an individual's behaviour or changes to their physiological wellbeing and thereby create the opportunity for early intervention. Continuous monitoring can also benefit the individual by alerting them to take their medication or alerting others if the individual has potentially had a fall. In addition, wearables investigated for this purpose can measure multiple parameters at once to evaluate physical health [66; 67; 68] and physiological status, including heart rate, temperature, sleep patterns and stress levels [69][70][71] meaning they can provide a comprehensive picture of patient well-being without the need to use multiple devices. In the literature, sensors have been mounted on different areas of the body (e.g., wrist, legs, ankles, arms) to monitor activity and recognize patterns. A variety of wearable devices is important to give individuals the choice to pick one which works well for them. For some, the need to wear the sensor on the body could be considered intrusive and, in some cases, may impact the uptake of wearables among the target older population but the research seems to show good adherence and acceptance which could be due to the wearable being a familiar item

such as a watch or wristband. With the same point in mind, wearables need to be developed with their end user in mind and have considerations made for weight, size, cost and be expertly developed for ease of use.

Table 2.3 outlines studies conducted with the use of a single wearable device without combination with a non-wearable solution and each assesses the scope of the wearable to allow for activity and wellbeing monitoring in individuals with dementia and MCI and largely the wearable device of preference was a wristband or wristwatch, with the exception of a wearable chest pin [72] and wearable pouch / bag [73].

The wearables were used to monitor a variety of physiological parameters including sleep patterns, stress levels, heart rate and temperature. In several instances, they were also used as location devices alongside monitoring other parameters [66],[74]. While these types of monitoring can support the individual on a day-to-day basis, they also provide a comprehensive picture for the managing physician to review at and between appointments and also have been shown to support the individual's carers. Aljehani et al. [75] developed an iOS app in which the carer could remotely monitor the individual by tracking their GPS location and reviewing their heart rate through use of an Apple watch. Another group [59] used the wearable to detect stress levels throughout the day to provide carers with pin-pointed times which the individual with dementia perceived to be the most stressful, allowing the carers to make mindful changes to these times to support the person. Finally, Chun Fang et al. used a similar wearable to recognise daily activities such as eating, drinking and walking to alert caregivers when abnormal activities occurred. [76]

As previously discussed, there are four common subtypes within the overarching term of 'dementia', each with their own distinguishing clinical features. Individuals between these subsets may require different levels and types of support so a defined diagnosis is paramount. Ardle et al [13] have investigated the potential of a single wearable device to differentiate between dementia disease subtypes through analysis of gait through use of seven gait characteristics. They drew the conclusion that this method could be used with moderate accuracy to differentiate between subtypes. These findings could indicate a potential use of a wearable device to be used as an informing component in the initial diagnosis of dementia, alongside traditional testing methods to ensure the most accurate diagnosis is reached.

Importantly, the ease of use and comfort of the wearable device needs to be considered. A recent study shown in 2.3used a wearable device located on the lower back to monitor gait and mobility [76]. The placement of the device in this study is not optimal as it would not be comfortable for the individual. Not only would it be perceived as invasive to the individual and impact on their

overall contentedness, it would also impact on adherence to wearing the advice. However, a similar type of device was used by Xie et al [**?**] to both assess gait and memory in diagnosed individuals. In this case the wearable used the same technology but used as a wristband instead, meaning a less invasive type of wearable for the individual.

Table 2.3: wearable technology for activity and well-being monitoring

Authors	Year	Objective(s)	Wearable Device(s)	Domain
Mulas et al [76]	2021	To verify the feasibility of wearable inertial sensors in a clinical setting to screen gait and functional mobility	Inertial wearable located in the lower back.	Gait and Mobility assessment
Ardle et al [13]	2020	To assess whether a single accelerometer-based wearable could differentiate dementia disease subtypes through gait analysis.	Accelerometer-based wearable fixed to the skin above the fifth lumbar	Gait assessment
Xie et al [77]	2019	To characterize gait disorders in patients with amnestic mild cognitive decline and determine the association between the performance of the gait function and cognition.	Inertial-sensor-based wristband	Gait and memory assessment
Chun Fang et al [74]	2018	To monitor elderly people constantly and send alerts to the caregiver every time abnormal activities occurred.	Smartwatch (accelerometer, gyroscope, Bluetooth) to monitor location.	Wellbeing monitoring
Aljehani et [75]	2018	To track and find people with AD and track their heart rate.	Apple Watch	Location monitoring

Table 2.3: wearable technology for activity and well-being monitoring

Authors	Year	Objective(s)	Wearable Device(s)	Domain
Tabakis et al [66]	2017	To monitor people living with dementia' locations, heart rate, and sleep.	Wristband (9-axis motion tracking plus sensors)	Heart rate, Sleep and location monitoring
Alhassan et al[70]	2017	To develop an application to track and inform people living with mild AD about their daily activities and provide some assessments.	Empatica E4 wristband.	HR monitor, activity reminders, and activities recall assessments.
Stavropoulos et al [78]	2017	To monitor dementia symptoms using a framework that integrates a variety of sensors with interdisciplinary methods such as image and audio analysis.	Wristband to measure accelerometer movement, physical activities, electrodermal activity, wearable camera, and ambient sensors	Physical activity, and Sleep monitoring
Merilahti et al [67]	2016	To analyse whether physical status is correlated with the rhythm of diurnal activities and sleep patterns measured with wearable sensors in nursing home residents.	Wristband	Sleep monitoring

Table 2.3: wearable technology for activity and well-being monitoring

Authors	Year	Objective(s)	Wearable Device(s)	Domain
Lutze et al [71]	2015	To help the elderly in four dimensions; communication, orientation, localization, detection of health hazards and detection of fluid intake.	Smartwatch - accelerometer, gyrometer and magnetometer	Location monitoring, Assessment of fluid intake, Safety monitoring to detect falls, and physical activity monitoring
Sun et al [72]	2014	To design a wearable that works as a data collection hub. It includes a number of applications to evaluate diet and physical activities and sedentary behaviour and to assist the elderly and blind.	Chest pin (two wide-angle cameras, UV sensor to detect indoor/outdoor environments, 3-axis accelerometer, gyroscope, magnetometer for motion/orientation measurements, a proximity sensor to track hand movements in GPS)	Evaluation of diet, physical activities and sedentary behaviours.
Barreto et al [73]	2014	To create a remote monitoring system for people living with dementia suffering from Alzheimer's disease by providing environmental conditions and location of the people living with dementia. Wearable pouch	(3-axis accelerometer for physical activity and fall detection, temperature and humidity sensors, GPS).	Monitoring for environmental, temperature; and humidity changes; location, Patient movements, including falls

Wearable Technology for Localization and Navigation

The disorientation associated with dementia can make navigating on a daily basis very challenging [79]. Many studies have focused on developing solutions to locate people living with dementia and alert their caregivers to abnormal activities. Using wearable technologies may reduce the time needed to locate these people living with dementia. Moreover, using wearables may increase the independence, autonomy and freedom of some people living with dementia in early to moderate stages of dementia and, consequently, lower caregiver burden [80]. Table 2.4 summarizes studies that used wearables for location monitoring, assisting navigation and monitoring safety, in addition to the several studies shown in Table 2.3 which demonstrate use of location monitoring technologies in combination with physiological and wellbeing monitoring. Some research carried out included the use of novel technologies developed for localisation and navigation (Table 2.4) in mind, for instance a wearable belt to facilitate route navigation [81] or adapted shoes to track location [82]. However, a significant portion of the studies looked into the use of a wearable wristband, for instance one study investigated [83] acquiring real-time information on patient location with results showing 94.7% accuracy overall in monitoring steps. This suggests that instead of developing new technology and devices, there is certainly the potential to utilise existing technologies for alternative purposes to yield positive results. Further to this point, a patient would be more likely to adhere to the use of a wearable if the piece was familiar to them in the first place, for instance a watch. as this requires little change to daily routine. While the studies investigating the use of a wearable camera [84],[85] showed positive results and the people living with dementia were receptive to the use of the device, wearing a camera is quite an adjustment to make and it remains to be determined if these results can be replicated outside of the clinical study.

Table 2.4: wearable technology for localization, navigation, and safety

Authors	Year	Objective(s)	Wearable Device(s)	Domain
Kolakowski et al [86]	2020	To introduce a localization system supporting people with cognitive impairment and their caregivers	Wearable tags worn by monitored users or attached to the localized objects	Location monitoring
Su et al [87]	2018	To track the path of the elderly with dementia in an indoor environment.	Bracelet (accelerometer sensor, gyroscope sensor, Bluetooth).	Location monitoring

Table 2.4: wearable technology for localization, navigation, and safety

Authors	Year	Objective(s)	Wearable Device(s)	Domain
Li et al [88]	2017	To improve the spatial memory ability of people living with mci.	Radio frequency identification bracelet.	Spatial navigation training
Bhargava et al [89]	2017	To help outdoor localization of people living with ad by proposing a low-cost wireless sensor networks (wsn) system, comprising a single wearable device and a cloud gateway.	Wearable activity tracker to measure individual acceleration and orientation.	Location monitoring , Safety monitoring, and alerting carers upon detection of abnormal activities such as fall or wandering.
Mendoza et al [90]	2017	To develop a tracking system that helps caregivers in a nursing home locate people living with and if they wander off.	Wearable device connected to a belt for localization.	Location monitoring
Hadwen et al [91]	2017	To build an energy-efficient wristband tracker for people living with dementia	Wristband (accelerometer and magnetometer) to estimate location and assist with the dynamic GPS.	Location monitoring
Kashimoto et al [92]	2016	To provide the elderly with the visual cues to assist with simple daily navigational tasks.	Wearable eyeglasses (camera, GPS tracker, accelerometer, gyroscope, step detector sensors and Bluetooth headset) to provide visual cues.	Location monitoring
Huang et al [80]	2015	To locate people living with dementia using a low-cost and easy-to-maintain device.	Wristband embedded with near field communication tag.	Safety monitoring

Table 2.4: wearable technology for localization, navigation, and safety

Authors	Year	Objective(s)	Wearable Device(s)	Domain
Oh et al [82]	2015	To assist with self-alert and location tracking for AD people living with dementia.	Wearable shoes	Location, and Safety monitoring
Yonesaka et al [84]	2014	To help caregivers and people living with dementia find lost objects together.	Wearable camera attached to the chest	Finding lost objects
Shin et al [83]	2014	To improve their health and safety.	Smartwatch - GPS, accelerometer, illumination sensor	Location, Safety, and Physical activity monitoring

2.1.5 Review of wearables that supports cognitive intervention

Cognitive interventions intended to help with memory impairment can be categorized into stimulation, training, and rehabilitation [89]. Several studies have indicated the potential value in improving memory functioning as many aspects of memory remain fairly intact in the early stage of dementia [93].

Interventions which focus on cognitive stimulation can involve activities such as reality orientation therapy and reminiscence therapy. Reality orientation therapy presents individuals with orientation information such as time and place and information about themselves in order to give them a greater understanding of their current surroundings. Reminiscence therapy encourages individuals to recall and connect with their memories. Both therapies are considered to be valuable in making people living with dementia feel content and less isolated leading to improved overall quality of life.

Training-based interventions can focus on different aspects of cognition, including memory and executive functioning, and involve a series of tasks to improve or maintain an individual's normal functionality. Tasks can include learning something new or playing a game with someone else. Rehabilitation-based interventions adopt an individualized approach to encourage people living with dementia and their caregivers to work together with healthcare providers to define specific goals and establish plans to overcome cognitive impairments such as

completing typical daily tasks effectively or continuing to make decisions about their lives and care.

A few studies have used wearable devices (Table 2.5) to improve cognitive skills in people living with dementia by reviewing past events to retain memories. Wearable cameras, for instance, can enhance memory by capturing images from daily life and using these images to help people living with dementia recall their old memories [94; 95; 96]. Research into the use of wearable technologies for cognitive interventions (Table 2.5) used an array of types of devices, with one study looking at the use of a sonic device. The study utilised a wearable sonic device in the form of a necklace that plays songs that help trigger memories and provide context in people living with AD [97]. These subtle cues provided by the auditory signals provide a non-invasive and simple way of stimulating the individual, and should the individual not experience any memory recall, the simple nature of playing music is inoffensive and unlikely to upset the individual.

Another study, Boyd et al. [98], sought to assess the potential of a tracking app paired with a wearable eye-tracking device which worked by displaying images to the individual through the app, using the eye tracking device to assess cognition. The app allowed this reminiscence therapy to be tailored to the individual in a cost-effect way. Of an important note, the app and wearable device in this instance were co-created with people living with dementia and their carers. The subsequent conclusion drawn by the researchers that there were no barriers to use identified and that there was a general ease of use associated with the app and the device is therefore reliable, as individuals being included in the development process will have ensure that the device met the needs of the end-user.

The studies presented in 2.5 concluded strong user acceptance of new technologies into patient lives, particularly when these are integrated early when individuals are diagnosed with MCI rather than dementia. Furthermore, some groups conclude that wearables have increased patient quality of life through enabling memory recall [97] and stimulating meaningful discussion with others [94].

Silva et al [99] compared participants with mild AD who had been randomly assigned to one of three memory training strategies: using a wearable camera to capture images of their daily activities, using paper and pencil for a cognitive training program based on pencil-and-paper tasks to practice motivation, attention and memory, or using a personal written diary that required people living with dementia to write down their daily activities. Findings indicated that the wearable camera group had better autobiographical memory performance on a standardized autobiographical memory assessment measure compared with the other two groups.

Several studies acknowledged potential limitations to the use of wearable devices among older adults, and one study subsequently evaluated uptake and acceptance of wearable devices such as cameras. This study found that older adults could adequately use the cameras and were able to integrate their use into their lives [97].

Table 2.5: wearable technology for cognitive intervention

Authors	Year	Objective(s)	Wearable Device(s)	Domain
Boyd et al [98]	2021	Investigate the use of a tracking app and paired wearable device to support personalised reminiscence	Eye-tracking wearable device	Reminiscence therapy
Gelonch et al [96]	2019	To evaluate the acceptability of lifelogging wearable camera in older adults diagnosed with mild cognitive decline	Wearable camera	Memory prosthesis
Druga et al [97]	2017	To create a wearable device that can function as an auditory cueing system for people living with memory concerns	Wearable sonic device	Memory prosthesis

Critical Analysis of the State-of-the-art

We have presented an up-to-date and comprehensive review of current research in the field of wearable technologies and dementia. In addition to reporting the range of possible uses for wearables to detect and monitor cognitive change and behavioural and psychological symptoms, this review provided a discussion of current wearables that support cognitive interventions in dementia. This work is an important contribution in understanding how wearables can support the needs of people living with dementia and their caregivers. There are two significant considerations which should be taken into account when considering the use of a wearable device. The first is deciding which parameters should be measured and what benefit the information will provide. By choosing to monitor

multiple parameters, for instance location, heart rate and sleeping patterns, the managing physician can gain a more comprehensive picture of the individual's overall well-being. It also gives caregivers the opportunity to monitor an at-risk individual's location remotely and therefore will provide them with a degree of respite. The approach has been taken by many of the studies discussed here and results are more definitive as compared to monitoring just one parameter. The second consideration follows the same thread whereby the decision needs to be made on if to use the wearable device in combination with non-wearable technologies, again with the aim of benefitting the individual as well as their physician and the carer. Again, several studies as discussed here have used this approach to cover off the limitations of a selected individual wearable and provide further oversight on the individual's condition and well-being.

A core theme across studies was that wearable devices which were familiar items, in particular a wristwatch, were particularly well-received by the study population and were not perceived to be invasive. The incorporation into the individuals' lives was quite straight-forward and adherence, over-all, was high. Another important conclusion from Boyd et al. was that by including patients in the discussions and the development of a wearable device, the device was much better received, and adherence is high. Co-creating solutions for individuals with dementia and their carers is of paramount importance to creating a solution fit for purpose. By gathering real patient insights and being informed on what matters most to those people, researchers can ensure the end product is optimised for use. Despite the useful findings in this review, there are several limitations. First, the accuracy of the methods used, and their applications are often not comparable across studies. Studies tend to identify or detect different sets of activities using different algorithms or approaches. Consequently, there is an urgent need for a standard approach to activity monitoring and its evaluation. Second, the lack of standardization in the placement of wearable sensors on the body can result in different measurements. For instance, in Table 4 summarising publications into the use of wearables in localisation, navigation and safety, the placement of wearables varies greatly including use in belts, shoes, wristbands, on the chest and glasses. As above, from a practicality and ease of adoption viewpoint, the wristband would seem to be the most appropriate option to move forward with as it does not require significant change to an individual's typical attire and is potentially something that can be adopted by all patient candidates. In comparison, not all people wear glasses or belts or would feel comfortable wearing something on their chest. Third, user acceptance of wearables also represents a challenge. Often, this relates to the ease of use of the device. Factors that can contribute to ease of use include the design of interfaces, the physical design, the device's weight and its battery

consumption. These parameters shape the acceptance among people living with dementia a given that the group are older and so less likely to be receptive to new technology unless it is easy to use and does not require much maintenance or additional thought, so an optimal balance among these parameters should be met to avoid rejection related to negative perceptions [97]. Finally, security and privacy remain concerns in the use of wearable devices. For example, patient privacy is a challenge associated with wearable cameras. Piasek et al [100] identified a number of factors that must be considered when using life-logging technology to assess dementia including the risk of exposing everyday private details of people living with dementia and the damage to people living with dementia' self-confidence from knowing about the vast amount of detail they can no longer recall. Piasek et al [100] partially solved this issue by providing a privacy button that allowed people living with dementia to stop recordings during private or intimate moments. This awareness of and sensitivity to patient privacy is an important consideration to be applied to the real-world application of wearables.

Given the usefulness of employing wearables to detect dementia in its early stage, along with their ability to support people living with dementia, we believe that longitudinal, and larger-population studies are needed to understand the full benefits of wearables for the well-being of older adults. Large longitudinal studies can account for inter-patient variability and document changes over time, which can help to identify points of intervention. For future research to be effective, we also contend that collaboration between health professionals and computer scientists should be encouraged to enable the design of innovative clinical trials that continuously assess people living with dementia. As several digital biomarkers, such as walking speed, sleeping routine and physiological parameters, have been tested to evaluate cognitive decline, these collaborations might make it possible to investigate which digital biomarker(s) are most strongly correlated with cognitive decline, and help to support the development of targeted technology that support older adults are various stages in their lives.

Moreover, we have discussed and drawn comparisons to traditional testing and computerised testing, both of which have their own merits and drawbacks. It should be noted that while wearables are becoming an increasingly useful tool in a clinician's arsenal to detect and diagnose dementia, other methods of testing still have their place and can be used concurrently to build a complete patient picture. In this way, the patient remains at the centre of the treatment and management regime. This ensures the best possible care and most accurate diagnosis is delivered.

With progressive cognitive decline, people living with dementia will naturally engage less and less with their care plan and this responsibility often shifts to

their carers. A potential with the use of wearables is that it gives individuals with MCI and early-stage dementia the ability to opt in to this particular care plan and as the wearable will be in place for a number of years, it gives the people living with dementia some responsibility and input back which is important for patient confidence and overall well-being.

Wearables Research Challenges and Questions

Future research could focus on the comparative analysis of existing applications of wearables. Since current studies use different sets of activities, algorithms, or approaches in assessing the function of wearables in the management of dementia, a standard protocol in evaluating wearables should be proposed. Studies on user acceptance, ease of use, user interface, physical design and structure of wearables can also be conducted to evaluate how people living with dementia perceive the use of wearables and additionally, surveys on what people living with dementia perceive their needs and the gap in wearable technology can be carried out to ensure the patient voice is heard. Larger population studies and clinical trials on the use of wearables are also encouraged to gain broader understanding on the advantages of using wearables in the management of symptoms and in preserving cognitive function among people living with dementia.

One area investigated by just one research group (Ardle et al. [13]) was the potential to use wearable devices to stratify patients diagnosed with dementia into one of the four subtypes of dementia. With the understanding that each of these subgroups has a different and distinct clinical manifestation, correct subtyping could ensure the most appropriate care is provided for the individual. It would be useful to investigate further the use of wearable devices for this purpose in tandem with general monitoring of various selected parameters as discussed.

2.2 Heart rate variability as a potential biomarker for dementia detection

It is vital to understand the involvement of the Autonomic Nervous System (ANS) when describing physiological variables such as HRV, since the ANS influences every organ in the human body. The nervous system is divided into the Central Nervous System (the brain and spinal cord) and the Peripheral Nervous System. The peripheral nervous system is divided into sensory and motor components. The sensory component transmits nerve impulses from peripheral organs to the central nervous system. To perform an action, the motor com-

ponent transfers impulses from the CNS to the peripheral organs. The motor component is also known as the ANS.

The ANS is composed of two subsystems: the sympathetic and parasympathetic nervous systems. Both systems control vital bodily functions such as breathing, heart contractions, and digestion. The SNS mobilises energy while the PNS functions conserve energy and restore somatic equilibrium. The SNS and the PNS innervate the heart and are accountable for heart rate acceleration and deceleration, respectively. The parasympathetic signals are relayed through the vagus nerve, which normally promotes the resting cardiac autonomic balance, nullifying the sympathetic system [101]. Individual differences in cognitive performance have been associated with the two branches of the ANS. Both increased sympathetic nervous system (SNS) activity and decreased parasympathetic nervous system (PNS) activity have been linked to increased risk of cognitive impairment [102]. Several researchers have linked parasympathetic withdrawal to impaired cognitive performance among people with Alzheimer's disease (AD) and mild cognitive impairment (MCI). [103].

The ANS has been linked both directly and indirectly to various physiological processes related to cognitive performance[104]. This concept is supported by several theoretical frameworks that examine the link between HRV and cognitive function. Among these is the neurovisceral integration model, which proposes that both the parasympathetic nervous system (PNS) and cognitive function are regulated by an overlapping collection of neuronal structures [105]. Another theory that supports the brain-heart connection is the polyvagal theory [106], which describes similar theoretical frameworks and highlights the importance of autonomic activity, particularly in the vagus nerve. This theory describes the functions of the vagus nerve in detail, since it mediates all communications between the heart and the brain. These findings suggest a significant link between cognitive performance and HRV that has crucial consequences for physical and mental health.

2.2.1 Heart Rate Variability

HRV measures the time variation between successive heartbeats. This variation is controlled by the ANS. Conventionally, heartbeats signals are obtained with either of two widely used methods to measure the cardiac cycle: electrocardiography (ECG) and photoplethysmography (PPG). For years, ECG has been used as the dominant cardiac monitoring system to detect any abnormalities. By placing electrodes on the skin, ECG can record the heart's electrical activity over a period of time. PPG is a non-invasive tool using light-based technology

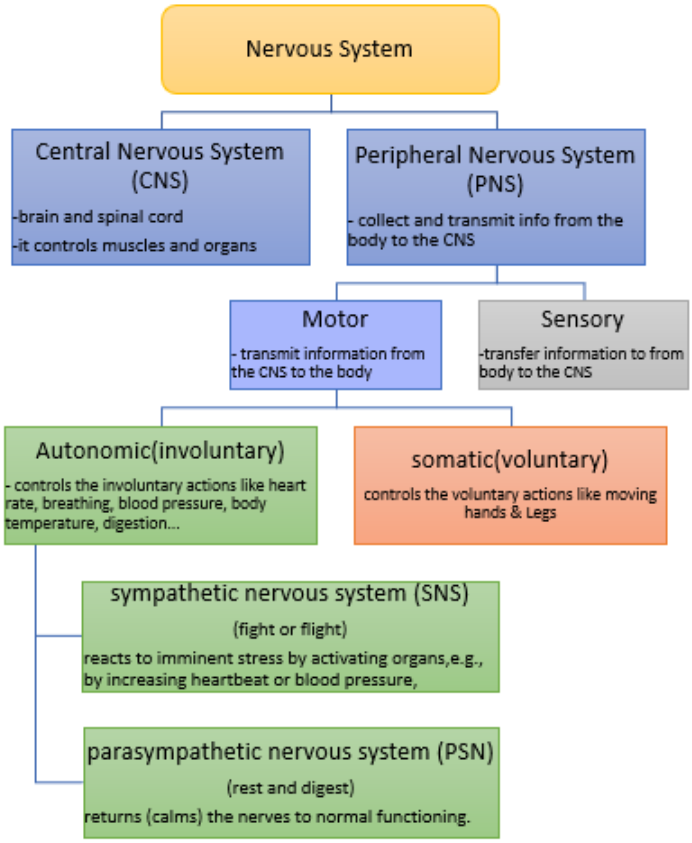

Figure 2.1: Hierarchy of the human nervous system

to measure volumetric variations in blood circulation. Heart rate variability (HRV) is a physiological measure of autonomic function. Low vagally mediated HRV has been linked to a range of anxiety symptoms and neurodegenerative diseases.

HRV is considered one of the most rapidly obtainable and noninvasive real-time tools for assessing the autonomic system [38]. Recently, it has become a strong focus of psychophysiological research because HRV is an index of the parasympathetic nervous system [107]. This is especially interesting given the parasympathetic nervous system's involvement in many aspects of psychophysiology, including self-regulation mechanisms associated with cognitive, affective, social, and health issues [106][104]. In addition, the sensitivity of HRV to both physiological and psychological changes has popularised its use [108]. HRV measurements have been used in the treatment of multiple diseases and to monitor many health metrics.

HRV has been widely used in clinical research as a non-invasive and effective

method to assess autonomic function. Furthermore, many studies have reported an existing association between cognitive function and parasympathetic HRV indices in AD patients [109]. Several studies show a significant correlation between participants' performance on cognitive tasks and HRV among different groups [110] [111][112][113][114][115][116].

Analysis of Heart Rate Variability

Typical ECG data includes a set of QRS complexes. The resulting period between adjacent QRS complexes resulting from sinus node depolarisations is known as the (N-N) (normal-normal) interval. HRV is the measurement of the variability in the NN intervals. Three primary classes of signal processing techniques are used to analyse HRV: the time domain, the frequency domain, and non-linear methods. Many factors affect the analysis of HRV, including the length of HRV measurement, the time of measurement, and other standards based on the suggestions of the Task Force[107].The gold standard for short-term HRV assessment is 5 minutes [117]

Time Domain Methods

Time domain refers to beat-to-beat variations in the time between successive heartbeats. Time domain methods are the simplest to implement. Time domain analyses cover multiple statistical parameters. The simplest time domain parameters that can be calculated include the mean NN interval and the mean heart rate. Other parameters can be calculated, such as the standard deviation of the NN intervals (SDNN), which is known to reflect total cardiac variability and thus the joint sympathetic and parasympathetic modulation of HRV. The predominant source of variation in short-term 5-minute recordings is parasympathetically mediated. Nonetheless, in longer-term recordings, SDNN readings are substantially linked to lower frequency rhythms. Another commonly used statistical variable obtained from interval differences is RMSSD, the root mean square of successive differences between normal heartbeats, which more narrowly represents parasympathetic activity only. Reduced HRV in time domain parameters has been linked by various studies to lower cognitive function in general and specific cognitive domains [102]. A brief of the most used HRV time-domain measures can be found in 2.6.

Table 2.6: Time Domain Parameters

PARAMETER	Unit	DESCRIPTION
SDNN	ms	standard deviation of normal NN intervals
SDRR	ms	standard deviation of normal RR intervals
SDANN	ms	Standard deviation of the average NN intervals
RMSSD	ms	Root mean square of squared differences between each heartbeat
PNN50	%	Percentage of adjacent RR intervals that vary by more than 50 ms

Frequency Domain Methods

The power spectrum of HRV analysis in the frequency domain represents an estimate of the power spectrum of the RR interval time series. Power spectral density (PSD) analysis can be performed using a parametric or non-parametric approach. In parametric approaches, the signal is modelled using an autoregressive (AR) model, while non-parametric estimation typically includes a fast Fourier transform (FFT) or periodogram computation. The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [117] divided heart rate (HR) oscillations into ultra-low-frequency (ULF), very-low-frequency (VLF), low-frequency (LF), and high-frequency (HF) bands .For short-term recordings of 2 to 5 minutes, two critical frequency domain parameters obtained from spectral analysis are widely used: the High-Frequency band (HF), and the Low-Frequency band (LF). The HF (0.15-0.40 Hz) reflects parasympathetic or vagal activity in the heart; it is highly associated with RMSSD. The HF-HRV analysis is the most frequently reported parameter in dementia studies [102]. Another common component is the Low-Frequency band (LF) (0.04 - 0.15 Hz), which reflects a combination of sympathetic and vagal effects. A summary of the most-used HRV frequency-domain indices can be found in 2.7.

Table 2.7: Frequency Domain Parameters

PARAMETER	Unit	DESCRIPTION
ULF power	ms2	Absolute power of the ultra-low-frequency band (0.003Hz)
VLF power	ms2	Absolute power of the very-low-frequency band (0.0033–0.04Hz)
LF peak	Hz	Peak frequency of the low-frequency band (0.04–0.15Hz)
LF power	ms2	Absolute power of the low-frequency band (0.04–0.15Hz)
LF power	nu	Relative power of the low-frequency band (0.04–0.15Hz) in normal units
LF power	%	Relative power of the low-frequency band (0.04–0.15Hz)
HF peak	Hz	Peak frequency of the high-frequency band (0.15–0.4Hz)
HF power	ms2	Absolute power of the high-frequency band (0.15–0.4Hz)
HF power	nu	Relative power of the high-frequency band (0.15–0.4Hz) in normal units
HF power	%	Relative power of the high-frequency band (0.15–0.4Hz)
LF/HF	%	Ratio of LF-to-HF power

2.2.2 The Neurovisceral Integration Model: Linking HRV to Cognitive Function

Thayer and Lane [105; 104] have proposed the neurovisceral integrated model (NIM) of the heart-brain connection, which asserts that HRV is controlled by the prefrontal and limbic regions. They offer a model in which a set of neural structures that regulate physiological, behavioural, emotional, and cognitive responses can be indexed via peripheral indices such as HRV. They conclude that the central autonomic network (CAN) is an integral component of a complex internal regulation system by which the brain controls visceromotor, neuroendocrine, and behavioural responses. The CAN consists of several regions, such as the medial prefrontal cortex (mPFC), nucleus ambiguus (NA), anterior cingulate cortex, insula, and orbitofrontal cortex. All of these areas are mutually related, allowing information to flow bidirectionally between lower and higher brain levels. They clearly play roles in controlling human behaviour by connecting the prefrontal cortex, physiological reactions, and the autonomic response via the NA and vagus nerve activities that govern the sinoatrial node.

Thayer et al. [104] have identified an association between stress, HRV, and cognitive impairment, hypothesising that HRV measures key aspects of prefrontal brain activity. Their argument is based on neuroimaging data indicating that the CAN's primary output is mediated by preganglionic sympathetic and

parasympathetic neurons, which primarily affect the heart via the stellate ganglia and the vagus nerve. Thus, a growing body of evidence suggests that high HRV is associated with improved neuropsychological performance, whereas low HRV is linked to worse neuropsychological performance. As a result, HRV has emerged as a key biomarker for autonomic function. High HRV indicates better autonomic function. in contrast, Lower HRV is associated with a higher risk of mortality and cardiovascular events. Studies show that low HRV is related to risk factors that precipitate declining cognitive function, such as depression, hypertension, and diabetes.

2.2.3 Findings Supporting HRV and Cognitive Function Interaction

Neuroimaging research provides further evidence for the association between HRV and cognitive function. Cognitive functions such as general arousal[118], orientation/alerting [119], and emotion regulation [120] have been tied to autonomic changes. A study conducted by Raskin et al. [121] on 48 male Michigan State University students highlights the relationship between HRV and attention by accounting for the components of attention (respiration and heart rate). These researchers randomly assigned their study population into one of four categories: the heart rate estimation group, light count group, light tone group, and light group. This study aimed to elicit the respiratory and heart rate changes associated with participants' concentration on external and internal stimuli. Their results show that participants who were directed to focus on the stimuli recorded a lower HRV. Consequently, they concluded that HRV is linked to cognitive (executive) function, secondary to a decline in HRV with concentration on external or internal stimuli.

Hansen et al. [122] conducted a study to shed light on the relationship between HRV and working memory and sustained attention. Their group evaluated 53 Royal Norwegian Navy sailors by administering tests for working memory and continuous performance tasks. The participants completed these tasks as the authors monitored their heart rate and HRV. Their results indicate that the group with high HRV outperformed the group with low HRV on all assessments. A correlational analysis of the data shows that resting HRV was positively correlated with cognitive performance. These findings align with the neurovisceral integration model, which links prefrontal cortex activity to HRV.

Luque-Casado et al. [123] performed a study to investigate the connection between HRV and cognitive performance. Their study population was selected

based on physical fitness level and categorised as either low-fitness or high-fitness, depending on physical characteristics and anthropometry. These twenty-eight male students from the University of Granada in Spain were subjected to three tasks: duration discrimination, psychomotor vigilance, and temporal orientation tasks. These researchers discovered that the high-fitness group reacted more quickly on the psychomotor vigilance task and had a higher HRV, whilst the low-fitness group had a lower HRV. Therefore, they concluded that HRV can be used to measure cognitive function. Additionally, Gianaros et al. [124] assessed HRV by exploring neural activity among 93 adults preoccupied with a working memory task, using a Position Emission Tomography (PET) scan. These researchers unveiled a correlation between high-frequency HRV and the anterior cingulate cortex in their participants. The anterior cingulate cortex is related to cognitive functions such as attention, emotion, and decision-making.

The neurovisceral integration model hypothesises that HRV predicts an individual's ability to adapt to changing circumstances [125]. Therefore, the executive function of individuals with low HRV is affected more than the executive function of individuals with high HRV. Hansen, Johnsen, and Thayer [104] divided participants into low-HRV and high-HRV groups based on their median scores on baseline HRV recordings. These study subjects were randomly further grouped into either threat or non-threat groups. Participants in the threat group were warned that they would be shocked using electrodes placed on their fingers and that the intensity of the shock would be increased subsequently. However, these participants were not actually subjected to the shock. Participants from the high-frequency HRV group outperformed their counterparts when there was no threat of stress. The performance of the high-frequency HRV group changed little with the introduction of a stressor. However, the low-frequency HRV group experienced a significant impact on their cognitive performance with the introduction of a stressor.

On the contrary, Dupuy et al. [126] concluded that evidence is lacking for a linkage between the cardiac PNS and executive function, after studying 11 male trainees in athletics. These participants were subjected to Stroop tasks and treadmill tests that had been graded while their HRV was being measured.

2.2.4 Evaluating the Association Between HRV and Cognitive Function in Patients with Dementia

Age-related neurocognitive diseases such as MCI and dementia share risk factors with cardiovascular diseases [127]. HRV is a common diagnostic tool for assessing the cardiac autonomic system; it has been linked to several diseases, such as cardiovascular disease and dementia. A reduction in HRV is attributed to

decreased activity in vagus innervation to the heart and is considered an indication of autonomic dysfunction. Autonomic dysfunction in dementia is thought to be caused by the combined effects of ageing and neurodegeneration in the telencephalic tissues, as well as in the hypothalamus and brainstem [128]. In fact, autonomic dysfunction may constitute an early indicator of dementia, as deterioration in the insular cortex and brainstem occurs early in the development of this disease. Several studies have shown that dementia patients have autonomic dysfunction, using clinical autonomic tests [129] or HRV analyses [130].

Duschek et al. [131] link cardiac vagal tone to emotional and cognitive control by eliciting a connection between high-frequency HRV and the parasympathetic effect on the heart. These parasympathetic influences are crucial for individual adaptation to changing environmental stimuli. Thayer et al. [132] postulate that cardiovascular and autonomic dysfunction worsen cognitive function. Thus, a reduction in vagal tone may indicate an inability to appropriately respond to changing environmental stimuli, which limits an individual's ability to generate responses that are situation-appropriate and to avoid inappropriate responses. Furthermore, Heathers [133] links the poor cognitive function seen in dementia to lower low-frequency HRV (under PNS and SNS control). Heathers considers cognitive domains such as memory and language. Lower high-frequency HRV (a reflection of vagal modulation) was linked to poor global cognitive functionality.

Acharya et al. (2006)[134] and Collins et al. [135] have linked low high-frequency HRV to an increased risk of developing cognitive impairment. These authors hypothesise that low high-frequency HRV affects cognition through associated damage to white matter in patients with dementia and Alzheimer's disease. A cross-sectional study by Silva et al. found autonomic dysfunction in dementia patients who had been evaluated using HRV. These authors compared and contrasted 97 relevant materials on dementia and HRV. Their results indicate an effect size that was negative. According to their study, this negative effect size suggests a correlation between dementia and MCI.

Table 2.8 gives a brief review of the literature on HRV and cognitive performance.

Table 2.8: A brief review of research examining HRV and cognitive performance.

Title	**Objectives**	**Participants**	**HRV Parameters**	**Main Results**
Kim et al., 2006 [136]	To assess the association between HRV and cognitive impairment in disabled, community-dwelling women aged 65 and older	311 physically disabled, community-dwelling women aged 65 and older	Time and Frequency domain (2-hr ambulatory ECG)	Reduced high-frequency power, indicative of decreased parasympathetic activity, was associated with 6.7 times greater odds of cognitive impairment
Britton et al., 2008 [137]	To investigate the link between decreased HRV and cognitive performance among middle-aged people in the general population.	5375 UK males and females. mean ages (55,61)	Time and Frequency domain (5 min supine resting ECG)	No consistent associations were found in men or women.
Shah et al.,2011 [110]	Is HRV associated with memory performance in Middle-Aged Men	416 middle-aged male twin mean age 55	Frequency domain (24-hr ambulatory ECG)	Lower frequency spectra of HRV are associated with verbal, but not visual, learning and memory.
Frewen et al., 2013 [138]	To assess the relationship between HRV and cognitive performance, in older adults.	4,763 participants mean age (61.7 $\pm$ 8.3) , (55 %) female.	Time and Frequency domain (two 5-min supine resting ECG)	Reduced HRV is significantly associated with lower cognitive performance among older adults aged 50 and older.
AlHazzouri et al., 2014 [139]	To determine the cross-sectional association between HRV and cognitive function in a cohort of elderly Mexican Americans.	869 Mexican Americans (mean age, 75 years; 59% women)	6 minutes supine ECG.	Reduced HRV is associated with worse performance in general cognitive function

Table 2.8: A brief review of research examining HRV and cognitive performance.

Title	**Objectives**	**Participants**	**HRV Parameters**	**Main Results**
Mahinrad et al., 2016 [140]	To examine the cross-sectional and longitudinal relationships between 10-second HRV and various areas of cognitive performance among older people at risk of cardiovascular disease.	3583 participants (mean age 75). 3.2 year follow-up	Time domain (10 seconds supine ECG)	Lower baseline HRV was linked to worse performance in reaction time. Individuals with lower HRV experienced a greater decrease in processing speed over the follow-up period.
Alhazzouri et al., 2017 [115]	To investigate the longitudinal association between HRV and cognitive performance among middle-aged individuals	2118 participants (57.7 % female, 42.2 % Black) with a mean age (45.3) years.	Time domain (10-s supine resting ECG)	lower SDDN is associated with worse executive function among middle-aged adults.
Schaich et al. 2020 [141]	To investigate the relationship between HRV and cognitive performance in a multi-ethnic cohort of aging adults.	3018 participants; mean age (59.3) years	Time domain (10-s supine fasting resting ECG)	Higher HRV is generally associated with better cognitive performance in this multi-ethnic cohort of aging adults

2.3 Summary

The primary question of this thesis is how suitable wearables are for detecting early cognitive impairment. As has been shown, wearables are already widely used in research projects as a potential tool for monitoring the elderly population and identifying initial signs of the development of MCI and/or dementia itself. Wearables have been used for the continuous monitoring of physical activity, which can provide important insights into cognitive decline. Through this review, it is evident that wearables present a valid option for assisting in the diagnosis and management of both dementia and MCI. Wearables evidently can serve many functions, such as assessing cognitive decline, monitoring symptoms, and serving as an assistive technology or cognitive intervention for memory impairment. However, a gap remains in research in this area, whereby comprehensive comparative analysis of datasets and further collection of data on the use of wearables would be useful for improving and expanding the use of wearables in this field and potentially within other patient groups as well.

Digital biomarkers are a data type that has been digitally captured and used as health and disease indicators. Resting heart rate, HRV, accelerometery, electrodermal skin activity, and skin temperature, for example, can all be used to determine an individual's infection status or predict whether or not they will become infected following exposure. As a result, employing wearables to detect biomarkers may be the first step in recognising illnesses before symptoms appear. Several studies have investigated various biomarkers for application in diagnosing and assessing neurodegenerative disease and MCI using wearable and sensor solutions. Moreover, many wearable devices measure HRV, which is a well-established indicator for autonomic function, with a higher HRV indicating more robust autonomic regulation.

Part III

Exploration

CHAPTER 3

Detecting Autonomic nervous system reactions using HRV: A pilot Study

In this chapter, we investigated the reliability of the state-of-the-art wearable sensing devices in detecting autonomic nervous system reactions to stress, and the associations between cognitive performance and HRV in young healthy participants. The pilot study discuss result from employing the CorSense devices to collect sensing data. Then, we evaluate the data, and present the results. Last, a discussion of the findings is presented.

Aging populations pose a considerable challenge for health systems. As the world's old population grows, so does the demand for healthcare services. Wearable technologies are a promising solution that offer continuous, objective, non-invasive monitoring to elderly. Physiological and autonomic biometrics data such as heart rate, HRV, blood pressure, and body temperature, as well as sleep, blood oxygen saturation, and physical activities, are the most frequently measured data using wearable sensors. Some evidence [142] promotes the use of HRV measurement as a method for measuring cardiovascular autonomic function in ANS studies. Multiple studies suggest that irregularities in cardiac rhythm associated with autonomic dysfunction may be related to cognitive im-

pairment.

Wearables can continuously monitor HRV as a measure of neurovisceral integration and ANS balance/imbalance during everyday activities, offering insights into a variety of situations, including activities of daily life, preventive medicine, and behavioural assessments, to aid in continuous clinical care. HRV has been presented as a realistic and reliable quantitative marker of ANS activity in response to stress. It sheds light on humoral, neuronal, and neurovisceral processes in health and illnesses of the brain, body, and behaviour. However, it has not been properly addressed in the digital age. Consequently, this chapter focuses on the first research question: How suitable are current state-of-the-art wearable devices to be applied for detecting HRV changes and its association to cognitive performance in everyday setting?

3.1 Study Aim and Hypotheses

The purpose of this study was to explore the suitability of wearable devices in terms of collecting sensing data to examine the involvement of the ANS in cognitive functioning. We evaluated the ANS reactions before, and during a cognitive challenge. Then, we assessed the influence of the cognitive stressor on HRV. We examined the relationship between HRV and cognitive function in young adults using wearable sensors in order to evaluate the reliability of wearable sensors in detecting changes in HRV.

The aims of this study were:

1. To assess the reliability of wearables devices in capturing the differences in HRV before, during, and after a cognitive challenge.
2. To assess the correlation between short-term HRV, using wearable based device, and cognitive performance on multiple cognitive tests.

Regarding the, the first objective following sub-hypotheses are derived:

- Hypothesis 1-0: There are no differences between HRV before and during the cognitive challenge, induced by mental stress.
- Hypothesis 1-1: There are differences between HRV before and during the cognitive challenge, induced by mental stress.

Regarding the, the second objective following sub-hypotheses are derived:

- Hypothesis 2-0: There is no relationship between cognitive performance and HRV.
- Hypothesis 2-1: There is a relationship between cognitive performance and HRV.

3.2 Design of the study

Independent Variables (IV)

1. Cognitive challenge
   We used CNS Vital Test Signs test battery that has been proven to increase the Sympathetic Nervous System (SNS) activity producing measurable physiological responses. This is to test the first objective that sensing devices are able to identify changes in physiological signals such as HRV induced by stress.

Dependent Variables (DV)

1. Autonomic measure (HRV)
   HRV is a measure of the ANS activity. HRV was measured using CorSense HRV monitor, a wearable device that uses pulse detection using a gold-standard 500 hertz multiwave sensor array. RR interval data of the HRV was exported using the EliteHRV app.

2. Cognitive Performance
   Cognitive performance was assessed using CNS Vital Signs (CNS-VS) (CNS Vital Signs LLC, Morrisville, NC). The CNS-VS is a computer-based neuropsychological battery that includes various tests to evaluate different types of cognitive domains including attention, memory, and executive functioning. In the study, we employed the basic test of the CNS-VS of the neurocognitive status. The test we used consists of seven neuropsychological tests that produce results in 11 cognitive domains. Time needed to complete the total battery is approximately 30 to 40 minutes.

3.2.1 Participants and procedure

We have recruited 10 healthy young participants from Queen Mary University of London (mean age=28.6 years, SD=2.50, age range=20–33; 5 males, 5 females) via university mailing lists. All subjects were instructed to abstain from alcohol, caffeine, and exercise for 24 hours before measurements. Prior to the study, participants were introduced to the experiment, and the study rationale. They were given the consent form to sign and a demographic questionnaire to fill in. Participants were seated with no music background and natural lighting in the room. HRV was measured using CorSens which is a finger-based device. We put on sensors and tested recording accuracy. Then, we recorded baseline HRV for 6 minutes. We analysed only the last 5 minutes for stabilization purposes. We determined 5 minutes based on the recommendation by the guidelines of

the European Society of Cardiology and the North American Society. After that, participants started to perform the test tasks. Data were downloaded and saved for each participant. A general overview of the procedure is shown in 3.1. Ethical approval was obtained from Queen Mary Ethics of Research Committee (QMREC2188). All participants provided written informed consent prior to study completion.

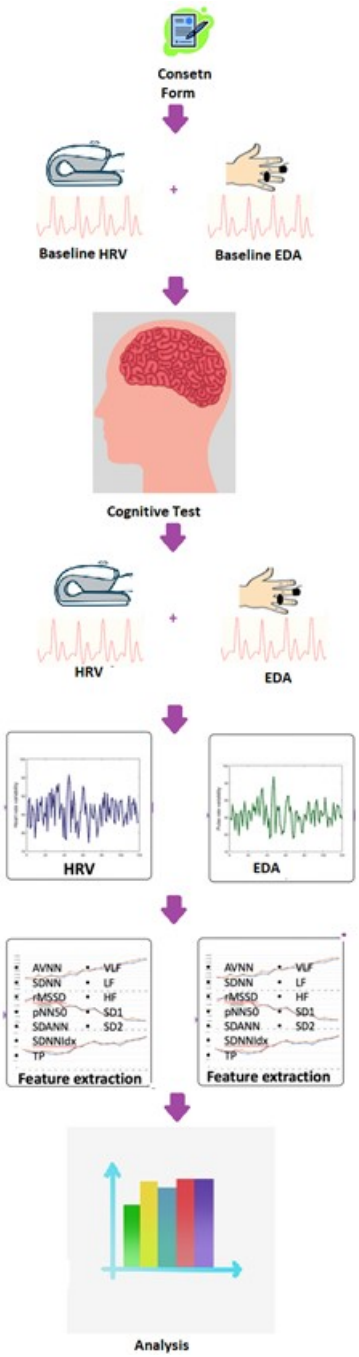

Figure 3.1: Steps of the Proposed Experiment

3.2.2 Data Collection and management

Physiological data in form of HRV was collected using CorSense HRV monitor devices.

Heart Rate Variability

Analysis of HRV is widely used as a standard non-invasive powerful tool for assessing autonomic nervous functions. Its sensitivity to both physiological and psychological changes has popularized its use. For this study, we collected short term HRV using Elite HRV CorSense (Figure 3.2). Participants were asked to slip their finger in the device for 6 minutes before, during and after the test. We used both time and frequency domain for the HRV analysis. Both time domain and frequency domain HRV indices have been found to provide useful information on ANS modulation in studies. For example, time domain metrics of standard deviation, coefficient of variance, and mean successive difference, have a positive correlation with vagal tone.

Figure 3.2: Corsense Placement

3.3 Results and Analysis

Data sets were exported and artifacts in RR interval data were removed with standard elite HRV app. The RR interval sets were analysed using Kubios HRV 2.2 for time, and frequency domain. Kubios HRV is a well-recognized software and most commonly used for electrocardiogram analysis. It supports other data formats such as RR and IBI. For the analysis of this study, we considered only the HRV measurement that is reliable for short term measurement since we only recorded 5 minutes of HRV. From the time domain, we considered Mean RR, STDRR, RMSSD, PNN50 (%), and from the frequency domain we considered (LF/HF ratio), LF (Hz), HF (Hz), LF (log), HF (log), LF (normalized.) HF (normalized).

Objective One

Paired samples t-test was used to assess differences between HRV before and during the cognitive challenge. Different HRV indices were examined in order to determine which components changed significantly under stress. The results are in 3.1. The result showed a significant statistical difference in the normalized HF and LF/HF parameters (P <0.05). Hence, we used these two measurements to test for correlation with different cognitive domains.

Table 3.1: Paired samples T-tests

Heart Rate Variability (HRV)	P-VALUE	t-value
Mean RR	0.9647	0.045
STDRR (ms)	0.2247	−1.303
RMSSD (ms)	0.6775	−0.430
Lower Frequency (LF)	0.5222	0.666
High Frequency (HF)	0.2082	1.356
Very Low frequency (VLF)	0.6713	0.439
High Frequency normalised (HFnu)	0.02607	2.659
LF/HF	0.02868	−2.601

The power of the normalized HF component is considered as an index of modulation of the parasympathetic branch of the ANS, and likewise, the LF/HF ratio has been widely employed as an HRV index of sympathovagal balance between the 2 branches of the ANS. From the boxplot below we can clearly see that during the cognitive test, HF has decreased which implies that parasympathetic activity has decreased. These results suggest that the decrease of parasympathetic activity is associated with stress related to the cognitive task.

Figure 3.3: High Frequency before and during the cognitive test

On the other hand, the increase in LF/HF ratio could mean an increased activity of the SNS. Our findings suggest that increased sympathetic associated with the cognitive task can be captured using wearable devices 3.4.

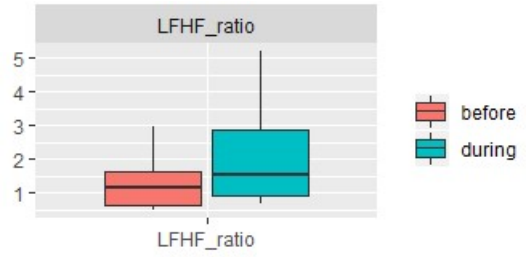

Figure 3.4: LF/HF before and during the cognitive test

Objective Two

The second objective was to assess the correlation between cognitive performance and HRV. As mentioned above, for the cognitive performance we used a computerized battery known as CNS Vital Signs. It consists of 7 tests that assess different cognitive domains: verbal and visual memory, finger tapping, symbol digit coding, the Stroop test, a test of shifting attention, and the continuous performance test. Based on these tests, seven cognitive domain scores were calculated: memory, psychomotor speed, processing speed, reaction time, complex attention, cognitive flexibility, executive functioning, and also the neurocognition index (NCI), a global cognitive measure. Each participant completed all seven tests.

Normality tests

Generally, the Q-Q plot (quantile-quantile plot) are used to check for normality visually. The Q-Q plots below indicate normal distribution of our variables of interest. Figures 3.5and 3.6show QQ plots for some of the cognitive tests.

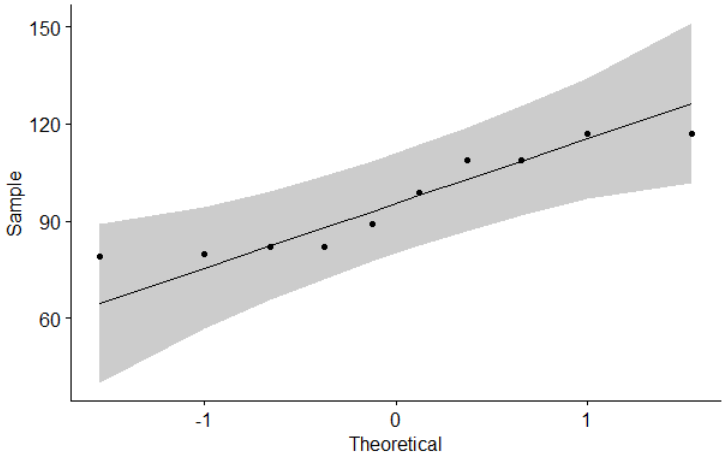

Figure 3.5: QQplot for composite memory

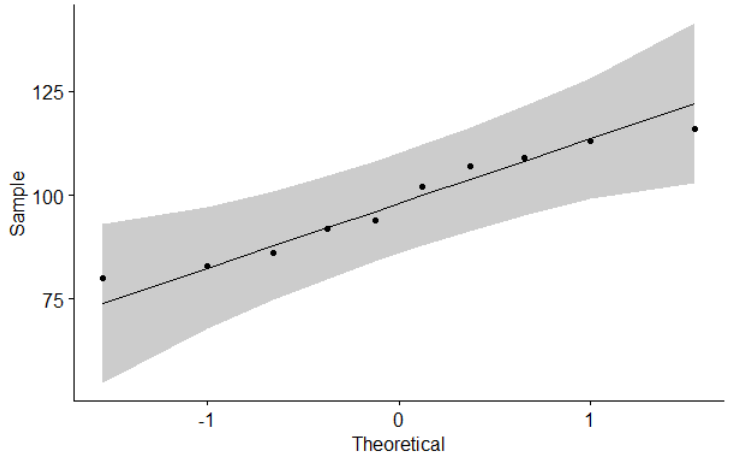

Figure 3.6: QQplot for Complex attention

Most of the plotted points are well distributed on the line indicating that the cognitive test variable was normally distributed.

Shapiro-Wilk W Test:

We also used Shapiro-Wilk W test to assess normality. All cognitive tests were normally distributed (p-value >0.05) (Table3.2).

Table 3.2: Shapiro-Wilk normality test for different cognition Domains

VARIABLE	P-VALUE
Composite memory	0.06431
Psychomotor Speed	0.2245
Reaction Time	0.1396
Executive Function	0.538
Processing Speed	0.843
Cognitive Flexibility	0.3764
Complex Attention	0.5099

Pearson's correlation test was used to identify a relationship between cognitive performance and HRV. We evaluated associations between HRV and different cognitive tests at baseline and during the test. Results show no significant correlation for each parameter, at either time point. Table 5.3 shows the result of the associations between HRV and seven different cognitive test scores.

HRV has been widely used as a biomarker to yield some insights into the activi- ty of the ANS associated with stress. The majority of previous research has assessed the association between HRV and cognitive function in a cross-sectional and older adult setting. One of the studies on aging showed a cross-sectional relationship between HRV (measured using SDNN and frequency domain parameters) and performance on the Montreal Cognitive Assessment

Table 3.3: Pearson's correlation test for the association between HRV and different cognitive domains

		Baseline		During test	
HRV	Cognitive test	P-Value	Correlation	P-Value	Correlation
HFnu	Composite memory	0.945	−0.025	0.167	−0.473
LF/HF	Composite memory	0.924	0.0349	0.242	0.407
HFnu	Psychomotor Speed	0.830	−0.078	0.220	−0.425
LF/HF	Psychomotor Speed	0.609	0.185	0.189	0.452
HFnu	Reaction Time	0.769	−0.107	0.216	−0.429
LF/HF	Reaction Time	0.602	0.188	0.252	0.400
HFnu	Executive Function	0.187	0.454	0.877	0.056
LF/HF	Executive Function	0.148	−0.491	0.780	−0.102
HFnu	Processing Speed	0.589	0.195	0.584	−0.198
LF/HF	Processing Speed	0.640	−0.169	0.586	0.197
HFnu	Cognitive Flexibility	0.193	0.449	0.999	0.0004
LF/HF	Cognitive Flexibility	0.169	−0.471	0.906	−0.043
HFnu	Complex Attention	0.136	0.506	0.974	0.012
LF/HF	Complex Attention	0.119	−0.525	0.846	−0.070

(MOCA), a test of global cognitive domain [138]. To date, most studies showed changes of HRV in response to stress induced by several methods. Particularly, low parasympathetic activity, which is characterized by a decrease in the HF and an increase in the LF. In short, higher HRV has been associated with better cognitive performance, and a lower HRV has been associated with decreased performance on cognitive tests. However, the association between HRV and cognitive performance in young healthy cohort is still mostly unexplored.

The aim of this study was to evaluate the reliability of wearables devices in capturing the differences in HRV before, and during a cognitive test, and to assess the relationship between short-term HRV, using wearable-based device, and cognitive performance on multiple cognitive tests. This is a pilot study to verify the feasibility of implementing the same setting but for MCI and dementia patients. Even though the study was conducted on healthy participants, we needed to present evidence of wearable capabilities and their capacity to identify variations in physical data in healthy participants. Our first hypothesis suggested that participants' HRV would be affected by stress, particularly a reduction in some HRV parameters, and that this reduction could be captured using wearable sensors. To test the above-mentioned hypothesis, we used paired samples t-test to compare HRV before and during the cognitive challenge in the sample study. The result showed the reliability of wearable in detecting changes in the ANS through differences in HRV.

Our second hypothesis proposed that there is an association between short-term HRV, using wearable-based device, and cognitive performance on multiple

cognitive tests in young healthy participants. However, we did not find any significant association between HRV and the cognitive performance, at either time point. This finding potentially could be due to the limited number of participants since our study was based only on 10 young participant. Future research should consider our limitations mentioned above using different and larger sample size. In conclusion, findings from the current study suggested that wearables can be a reliable tool in detecting changes in HRV induced by stress.

3.4 Conclusion and Takeaways

In this section, we utilised wearables in order to identify difference in heart rate variability before and during the cognitive tests. We found significant differences in some HRV parameters before and during a cognitive task. This finding suggest that wearables can be used to monitor HRV and are able to detect difference during in HRV induced by stress. However, this study showed that there was no relationship between cognitive performance and HRV. This could be due to the very limited number of participants or a true lack of association, as several studies demonstrated no relationship between HRV and cognitive function in middle-aged men and women.

Part IV

HRV in Individuals with Dementia

CHAPTER 4

Association between cognitive performance and HRV in individuals with dementia

This chapter extends the findings from the earlier exploratory chapter. Here, we discuss experiment design and findings of ultra-short term (10 sec) HRV measures from the UK Biobank, and the association with cognitive function in patients with dementia.

4.1 Overview and Related Work

Dementia is a neurological disease that leads to deterioration in cognitive function, which impairs memory, social interaction, and daily tasks[27]. Cognitive functioning comprises multiple mental abilities which underlie how people learn, think, solve problems, and make decisions. It is a general term that describes several domains including executive function, memory, and attention. The neurodegenerative disease can range from mild to severe, and its progression may lead to the development of autonomic dysfunction. Autonomic dysfunction develops when the nerves that regulate involuntary and unconscious actions such as heart rate, and blood pressure, are damaged. Furthermore, autonomic dysfunction was found to be 6 times more common in people with mild cognitive impairment (MCI) than in people without cognitive impairment [135]. While HRV declines with age, it is an indication of autonomic dysfunction when it declines rapidly [143].

HRV is normally calculated using long-term (24 hours) or short-term (< 5 min) ECG recordings. Long-term measurements can provide detailed information during different physical states such as activity and rest. Despite the advantages of long-term measurements, they are time-consuming, expensive, and require special expertise which might limit their application. Conversely, measuring HRV from a 10-second ECG recording is more practical and easier to apply in daily practice. It has been suggested that a 10-second HRV may predict 5-minute cardiac vagal tones accurately [144] and has a comparable predictive value for cardiac mortality in older participants [145].

An association between cognition and HRV has been shown in large groups of seniors as well as smaller samples of people with MCI and dementia [130; 141; 102; 146; 147; 148]. From this perspective, HRV can be a promising physiological correlate of cognitive function. Low HRV is an indicator of autonomic dysfunction and has been associated with worse cognitive function [149]. In contrast, people with higher HRV levels have greater control over a variety of cognitive domains including memory [139], the executive function [138], and faster processing speed [140]. The association between HRV and autonomic dysfunction in dementia patients is still debatable, with some research finding a significant difference between dementia and control groups [136; 128] and others finding non-significant results [150]. However, the identification of biomarkers that could help identify disease development in the pre-clinical stage should allow for earlier intervention and possibly prevent the occurrence of clinical unfavourable phenomena [129]. Consequently, we looked at cross-sectional and prospective relationships between HRV and cognitive performance in a group of older adults.

The hypotheses of this study are as follows:

Hypothesis 1 (H1): Measures of HRV amongst dementia patients will be lower relative to age-matched control participants.

Hypothesis 2 (H2): There is a strong positive association between HRV and cognitive function among older group.

4.2 Study design

UK Biobank is a large-scale biomedical database and research resource with over 500,000 participants recruited during years 2006–2010 from around the UK. Participants were asked to come to an assessment centre to fill out a computer-based questionnaire about their lifestyle, general health, and medical history. Other measures taken include weight, height, blood pressure, blood and urine samples. In 2014, data such as imaging and resting 12-lead ECG data were collected. The first 4,000 participants' data was released at the end of 2015

which increased to 25,000 participants by the middle of 2018. By 2022, 100,000 people will have been screened, with 10,000 of them having repeat scans 2–3 years later [151].

4.3 ECG Data

44,446 ECG data files were downloaded from the UK Biobank. Each file contains information about the participants such as ID, date and time of the observation and the raw data of the 12-lead ECG signal at rest,. Raw ECG data were stored in XML files (Extended Markup Language). We developed a python script to read the XML files, perform signal processing in order to extract the important features such as QRS complex and then HRV features as explained in figure4.1.

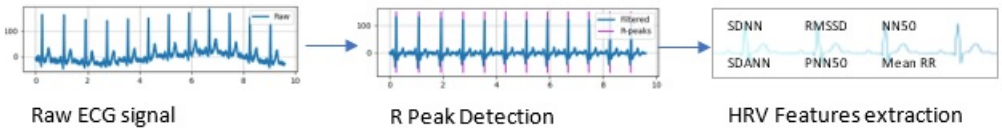

Figure 4.1: Data Processing

4.3.1 Detection of R Peaks and RR Intervals

The accurate extraction of R peaks and RR intervals is a significant stage in the acquisition of the HRV data. The higher the accuracy of R peak identification, the lower the error in the R–R interval time series and subsequent HR variability analysis. Therefore, R peaks must be correctly identified in the ECG data, and any missing or incorrect peaks must be corrected. Additionally, ECG signals can be affected by different forms of noise and artifacts during the recording process [152]. This may influence the signal quality which impacts the process of QRS detection process [153]. Several methods have been proposed for improving QRS and R-wave detection [154]. We have used Pan and Tompkins algorithm [155], this algorithm is the most commonly used method to extract the QRS complex from the ECG signals.

The purpose of the pre-processing stage is to improve the overall quality of the ECG signal so that it can be analysed and measured more precisely. In Pan-Tompkins algorithms, a number of steps are needed for QRS detection such as filtering data for noise removal, a derivative operation to detect the high slopes that differentiate the QRS complex from other waves. The signal is then squared to obtain positive values, emphasising large differences between the QRS complexes and supressing all the small differences coming from other

waves, and then moving window integration [152]. The algorithm process is presented in Figure 4.2. RR intervals are defined as the time elapsed between two successive R waves of the QRS complexes of the ECG signal. Therefore, after the detection of the R peaks, we now can convert the peaks index to intervals time series (RR) by finding the difference between RR intervals.

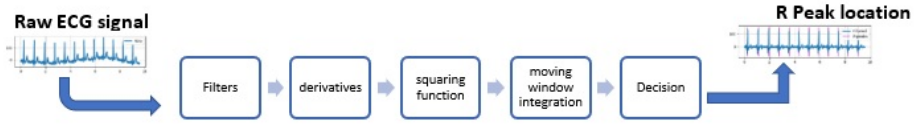

Figure 4.2: The Pan-Tompkins algorithm

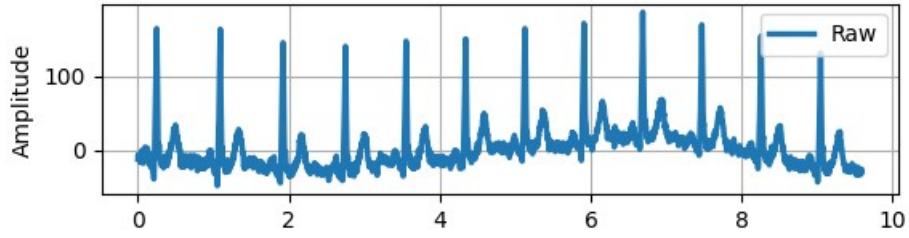

Figure 4.3: Raw ECG before the data processing

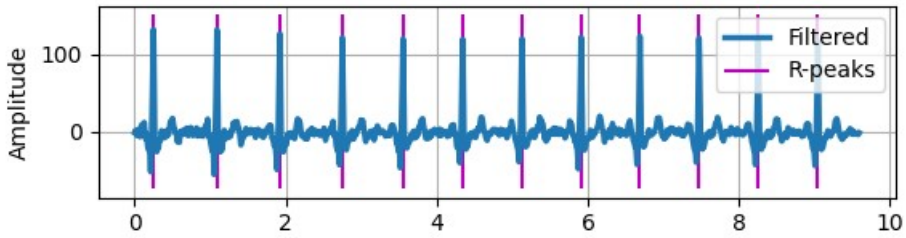

Figure 4.4: R peaks Detection after the data processing

4.3.2 HRV analysis

HRV is the variation in the time interval between each heartbeat. HRV is recognised as a significant biomarker of the activity of autonomic function and as one of the most significant methods of analysing the activity of the autonomic nervous system (ANS). HRV analysis can be calculated from ECG in three main ways: time-domain (statistical measures), frequency- domain (also known as spectral analysis), and non-linear metrics. As the duration of ECG recording can influence HRV analysis, the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996)

established a set of gold standards in terms of ECG durations. Duration of HRV measurements can be 24 hours, short-term (5min), or ultra-short-term (< 5min) [117].

However, more recent studies have challenged the 5 min gold standard with a shorter duration of ECG recordings such as 10s, 30s, and 60s. Munoz et al.[156] recently investigated the reliability of ultra-short and short HRV recordings in a large population (N = 3,387). The authors evaluated ultra-short 10s, 30s, and 120s recording using time-domain indices (SDNN and RMSSD) and compared them with the 5min gold standard measurements. They concluded that a recording of 120s is considered an accurate measure of RMSSD. Moreover, even the standard ECG duration (single 10s) yielded an accurate RMSSD measurement. For SDNN, the authors recommended either a 30s or multiple 10s ECGs. Therefore, and due to the short duration of the ECG recordings (10 seconds), we used the RMSSD of the time-domain indices. Time domain values are calculated directly from the measurement of RR intervals.

4.3.3 Reliability of our data processing method

We compared the accuracy of the HRV metrics calculated through Kubios software to the HRV metrics calculated with our method. The latter achieved a 99.6% accuracy compared to the Kubios method. Details can be found in Table 4.1.

Table 4.1: Time Domain Parameters

PARAMETER	Unit	Kubios software	Our work
Mean RR	(ms)	801	801
Mean HR	(bpm)	75.00	74.97
Min HR	(bpm)	73.01	72.64
Max HR	(bpm)	78.00	77.92
SDNN	(ms)	19.5	19.64
RMSSD	(ms)	10.3	10.5

Among available ECG data, we found 18 patients with dementia files. There were more than 41,938 ECG files for healthy controls. In order to analyse this unbalanced dataset, we adapted the bootstrapping technique, which is a re-sampling technique used to estimate statistics on a population by sampling a dataset with replacement. We sampled 18 observations 40,000 times and then computed the overall mean and variance of these observations while controlling for age and gender. Then we sampled 18 random participants from that distribution. We assumed normality since we know that repeated sampling for large data set i.e., 40,000 would result in a normal distribution by the Central Limit

Theorem.

4.3.4 Participants

HRV recordings were carried out in 18 participants with dementia (M = 65.09, SD = 9.22) and 18 healthy participants (M= 65.64, SD = 7.0). Of the UK Biobank participant included, 76.1% were identified as male.

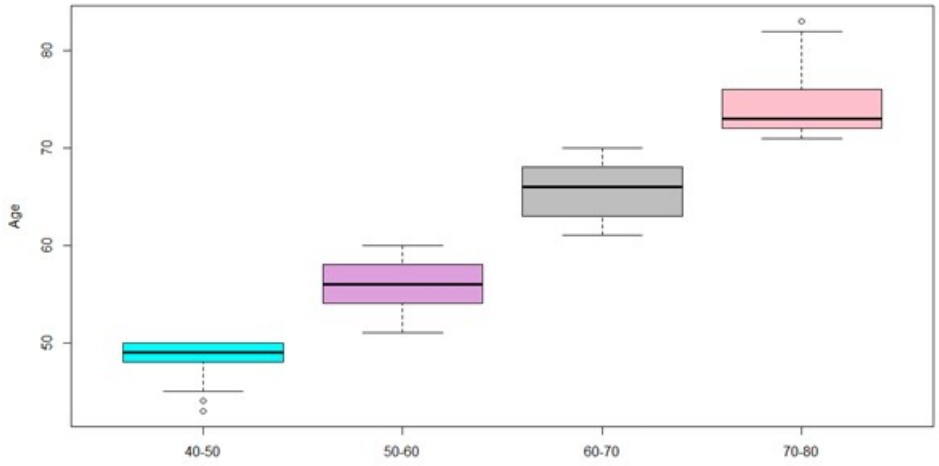

Figure 4.5: Age distribution

4.4 Statistical Analysis

A statistical power analysis was performed for sample size estimation, using the G*Power software [157]. A total sample of 18 people would be needed to detect large effects (d =.93 with 85% power for an independent-groups comparison with alpha at .05. Similarly, Quintana [158] recommended a minimum sample size of 18 to achieve a large effect size with a statistical power of 85% based on a meta-analysis of more than 250 HRV effect sizes. Therefore, our proposed sample size of N= 18 should be sufficient to test hypothesis 1 of this study. To test hypothesis 2 of the study, multiple logistic regression was used to model the associations between HRV and cognition by calculating odds ratio (OR), which quantifies the strength of the association between HRV and cognition, and 95% confidence intervals (CI). All statistical analyses were performed using R statistical software (version 1.2.5019; R Foundation for statistical computing, Vienna, Austria).

4.5 Results

Two HRV parameters were included to assess the difference of HRV values between dementia and healthy controls. An independent-samples t-test was conducted between HRV (RMSSD) in both groups, patients with dementia and healthy control. As predicted, there was a significant difference in RMSSD between the control group (M=5.06, SE=0.11) and the patient group (M=3.94, SE=0.33); t(24)=3.1, p= 0.004. These results suggest that the patient group have lower HRV (RMSSD) values than the control group. Next, another independent-samples t-test was conducted between HRV (SDNN) in the control group (M= 122.6, SE=0.19) and the patient group (M= 110.77, SE=0.34); t(26.9)=0.3, p= 0.73. There was no significant difference between the groups in the SDNN parameter.

Table 4.2: Time Domain Parameters

control RMSSD	patient RMSSD	control SDNN	patient SDNN
5.121456435	5.673804	141.2748	213.77
4.397651966	3.176803	72.3624	23.88
4.413328127	2.373975	73.38738	9.62
5.264274745	1.534714	161.8136	3.48
5.368560263	5.275253	178.7765	190.72
5.302251527	5.031875	167.787	136.13
4.837586384	5.807301	108.2116	302.56
5.634988531	2.030776	231.0695	18.31
5.220581636	4.319087	155.2159	78.53
4.599310986	3.178054	86.85706	33.33
3.570377903	4.804758	20.87584	115.92
5.510579494	6.579015	204.9147	423.11
4.998709062	2.791778	125.8209	10.62
5.014998347	6.173119	127.7642	287.16
5.446556167	2.376764	192.671	8.49
5.400756739	2.645465	184.3811	22.59
5.309865004	4.549446	169.0121	89.37
5.437438825	3.386422	190.9903	26.21

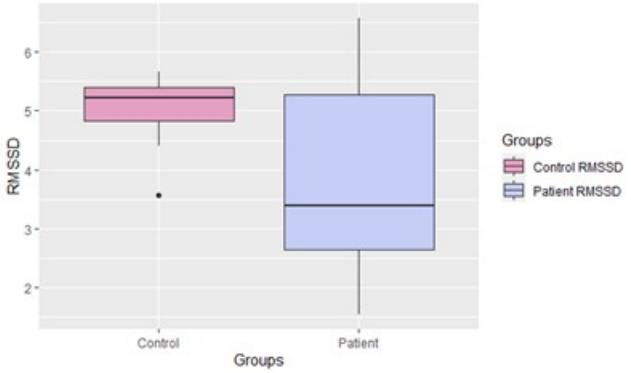

Figure 4.6: HRV(RMSSD) feature in dementia and control groups

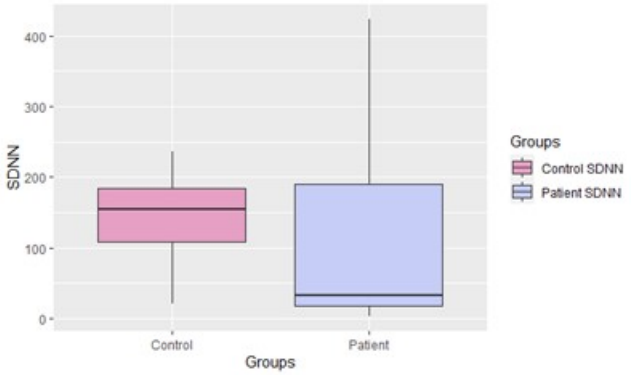

Figure 4.7: HRV(SDNN) feature in dementia and control groups

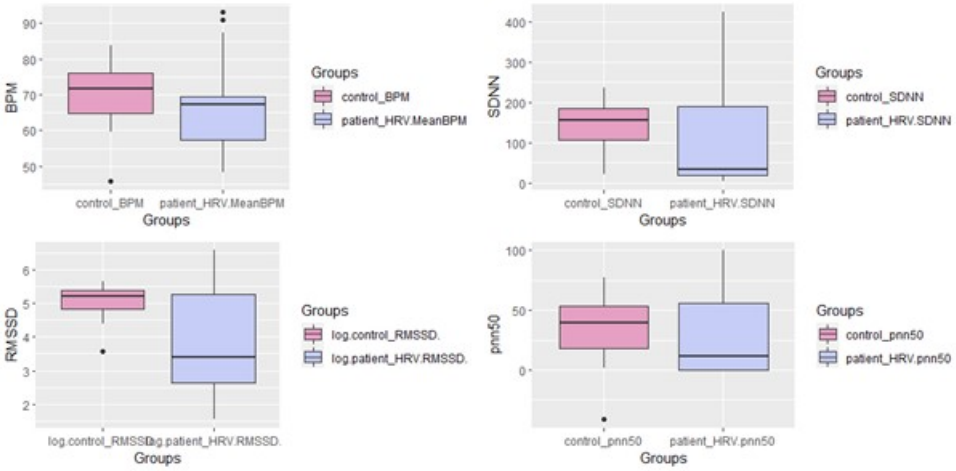

Figure 4.8: Boxplots of sampled control variates for each of the HRV featuers

4.6 Logistic regression analysis and Odds Ratio

We created a variable called ispatient that takes values of 0 or 1 to indicate the absence or presence of dementia, respectively. Logistic regression was used to analyse the relationship between the predictor variables: age, gender, RMSSD and mean RR. The results indicated that RMSSD are significant predictors of dementia. The other three predictors age, gender, and mean RR were not significant predictors of dementia. We evaluated the odds ratios (ORs) of the HRV indices for the likelihood of being a patient with dementia. For RMSSD, the odds ratio was 0.086 (95% CI 0.007- 0.676, p ¡ 0.05) meaning that, we expect to see 8.6% with higher odds of dementia prevalence for every one unit increase of RMSSD.

4.7 Discussion

The overall objective of this study was to test the hypothesis that reduced HRV is associated with prevalent cognitive impairment in patients with dementia. We analysed HRV from short-term ECG data in the UK Biobank. An independent-samples t-test was conducted between HRV (RMSSD) first in

both groups, patients with dementia and healthy control. Results showed a signif- icant difference in RMSSD between the control group (M=5.06, SE=0.11) and the patient group (M=3.94, SE=0.33); t(24)=3.1, p= 0.004. These results suggest that patients with dementia have lower HRV(RMSSD) values than the control group. Logistic regression was performed to analyse the relationship between the predictor variables: age, gender, RMSSD and mean RR, and the odds of being a patient with dementia. Findings revealed that RMSSD and dementia are correlated and that people with higher RMSSD have increased risk of developing dementia. A one-unit increase in RMSSD was associated with an increase in likelihood of being a dementia patient of 0.086 (P<0.05).

The degree of the correlation differed between HRV metrics, suggesting that one HRV measure may be a stronger predictor of cognitive decline than others. RMSSD, an indicator of short-term fluctuations in heart rate mediated by parasympathetic activity, was found to be more closely related to cognitive impairment than SDNN, a measure of long-term fluctuations in heart rate caused by sympathetic and parasympathetic nervous system activity. The findings of this research are consistent with previous studies showing decreased parasympathetic activity in patients with Alzheimer's disease. [198; 136]. Decreased HRV indexes was found to be associated with all types of dementia when compared to controls [159; 136].

4.8 Conclusions and Takeaways

In this study, we used the UK Biobank data to study the appropriate ultra-short term HRV parameters measures to detect cognitive decline in patients with dementia. We used ECG data to calculate R peaks and find the RR intervals. Later, we calculated time-domain HRV parameters. We performed several statistical analyses to investigate the reliability of employing HRV as a biomarker to detect dementia. RMSSD showed a significant difference between dementia patients and control group. Moreover, the findings of logistic regression analysis demonstrated a consistent association between lower HRV, with higher odds of being a patient with dementia.

CHAPTER 5

Machine Learning Approach to Identify Individuals with Dementia Using HRV

In this chapter, we discusses the findings of the use of machine learning classifiers to predict cognitive performance in individuals with dementia.Then, we evaluated the data, and presented the results. Lastly, a discussion of the findings is provided.

5.1 Overview and Related Work

Cognitive function is a broad term that applies to multiple mental abilities involved in knowledge acquisition, information manipulation, and reasoning. Cognitive functioning comprises multiple cognitive domains, such as memory, language, attention, and executive functions [160]. Proper cognitive functioning is a vital component of performing everyday activities. Various aspects can influence the physiological decline of cognitive functions, or in a specific domain, such as aging process and neurodegenerative diseases [161; 162]. Cognitive functioning deteriorates in the presence of autonomic dysfunction [104; 132] . Within this perspective, HRV can be a promising physiological link of cognitive function.

Several studies have investigated the association between HRV and some cognitive domains, such as executive function, memory, attention, language and cognitive domain in general. An executive function and global cognitive func-

tion are the most researched domain of HRV [163]. A correlation between HRV and global cognitive performance was reported with low HRV related to poorer performance [139; 140]. Moreover, several research have investigated the correlation between executive functions and HRV [164; 140; 165]. Lower HRV was associated with lower performance on activities requiring executive functioning. Other cognitive domains such as memory, language, attention, and processing speed were investigated as well. research works investigated the association between HRV and memory where Individuals with higher HRV had better capability to control over memory and a better skills to suppress unwanted memories [139; 166]. According to Frewen et al.[138] lower HRV is associated with lower language performance. The same can be found in attention [167] and processing speed [141]. Low HRV was associated with worse performance in specific cognitive domains.

Machine learning (ML) has been proven useful and reliable in many applications and has been successfully used in numerous classification problems. In healthcare, the most common use of machine learning algorithm is to predict what treatment protocols are likely to be effective on a patient based on various patient variables and the treatment context [168]. It has been used in a number of other applications such as image and speech detection, and stock market trending. During the past few decades, machine learning techniques have been increasingly applied to assist medical diagnosis because of their classification capability. ML has proven reliable and shown its usability in a variety of disease diagnoses. In cardiovascular disease, machine learning has played a significant role in the detection and prediction. Qibin et al. [169] introduced a basic but highly predictive method in which both wavelet transform and autoregressive modelling were used to classify ECG. Later, they used ECG features for the classification of one of five common arrhythmias using a Support Vector Machine (SVM) machine learning algorithm with a Gaussian kernel. This method achieved test set classification accuracies of 100%. Moreover, machine learning have been utilized in several cancer classification research such as breast cancer [170] [171][172], lung cancer [173] [174][175], prostate cancer [176].

Furthermore, machine learning techniques were used for the Identification of Cognitive Tasks using physiological parameters such as HRV, and Electrodermal Activity (EDA). Posada-Quintero et al. [177], tested four machine learning classification tools: k-nearest neighbor classifier (KNN), support vector machines (SVM), decision trees, and discriminant analysis (DA) to classify the cognitive task a participant is performing based on the participant's physiological reactions (HRV, EDA). These classifiers reached an accuracy of 66%, 62% 62% respectively.

The general aim of this study is to use machine learning models for the Iden-

tification of Cognitive performance based on heart rate variability. Particularly, this study tries to explore classification models based on the differences and similarities in the effects of different cognitive task have in the HRV.

Hypothesis 1 (H1): We hypothesize that machine learning techniques could be used as a predictor of cognitive performance using Heart rate variability.

5.2 Methods

5.2.1 HRV Data

XML files were generated by the Cardio Soft Version 6 system which includes ECG information at rest were downloaded from UK Biobank. Standard 10-second ECG recordings were obtained. We developed software based on the most widely algorithm proposed by Pan and Tompkins [155] to detect the R peaks of every heartbeat of the ECG signal. To derive the time domain parameters we used statistical methods; the Root Mean Square of the Successive Differences (RMSSD) and the standard deviation of normal-to-normal R-R intervals (SDNN) in the 10-second ECG recording period.

5.2.2 Cognitive Data

At the UK Biobank assessment centre, participants completed a 15-minute computerised battery to assess their cognitive function. The battery was produced for this UK Biobank study and it did not require supervision by researchers[16]. In 2014, participants completed online assessments in their own homes. Brief descriptions of the tests are provided below. Most of these tests are computerised versions of well validated cognitive tests [178], whilst the tests of reasoning and reaction time are novel to UK Biobank.

1. Trail Making Test (TMT) A and B:tests used to assess cognitive flexibility, processing speed, and executive functions. These tests were introduced in follow-up tests in 2014-2015. For TMT A, participants were asked to connect numbers consecutively. For TMT B, tests were similar but participants were also asked to connect letters and numbers by alternating between these in an ascending sequence (1-A, 2-B, 3-C.. and so on). We used the time taken to complete these tests in our analysis.

2. Fluid Intelligence Test: a test used to assess verbal and numerical reasoning. Participants were given 13 questions (multiple choice) and had two minutes to complete as many as possible. In our analysis, we used the number of questions answered correctly within two minutes.

3. Symbol Digit Substitution Test: a test used to assess processing speed, also introduced at follow-up testing at home in 2014-2015. This test involves matching numbers to symbols. The number of accurate symbol-number matches made in 60 seconds was used in our analysis.

4. Numeric Memory Test :a test used to assess working memory. Participants were shown a two-digit number for a brief period of time. The number then disappeared, and later, participants were instructed to enter the number in reverse order. Each time the participant remembered the digits in the reverse order correctly, this two-digit number became one digit longer. We used the maximum number of digits correctly remembered in the reverse order for our analysis.

5. Reaction Time: UK Biobank developed a Go/No-Go test to evaluate reaction time. A video demonstration was provided to participants before to the start of the test. Participants were shown two cards with symbols on them side by side on the screen for each trial. The two cards either had matching or different symbols on them. When the cards matched, participants were told to push a button-box on the desk in front of them as quickly as possible. When the cards were different, the participant was to do nothing until the cards disappeared and a new pair appeared after a short interval.The score is the mean time, in milliseconds, to press the button-box

6. Tower Rearranging: an altered version of One-touch Tower of London test. The test was utilised to assess planning abilities, which are frequently considered as a component of executive function. Participants were given a display (display A) with three pegs and three different coloured hoops hung from the pegs. Another display was located beneath Display A. (display B). Display B contained three pegs and the same three coloured hoops as display A, but the hoops were set in different locations.The participant's job was to calculate the number of steps required to make display A seem like display B. The number of moves necessary for each item could be anywhere between one and six. The score was the number of items answered correctly in 3 minutes

5.3 Statistical Analysis

We used Heart Rate Variability (HRV) signals to predict the performance of the cognitive test of different cases. The variables we used as a predictors are:

Time Domain parameters, Age, BMI, smoking, and Alcohol intake frequency. We considered 7 cognitive tests for each case, namely:

Table 5.1: Cognitive Tests

Test	Field
Trail Making A	Duration to complete numeric path trail
Trail Making B	Duration to complete alphanumeric path trail
Fluid Intelligence	Fluid intelligence score
symbol digit substitution	Number of symbol digit matches made correctly
Numeric Memory	Maximum digits remembered correctly
Reaction Time	Mean time to correctly identify matches
Tower Rearranging	Number of puzzles correct

To predict the performance of each test, we categorized the performance of each test to have a classification problem. We considered two different cases. First, two categories of poor and high performance. Second, three categories of poor, mediocre, and high performance. To convert the scores to categorized labels, we used the percentiles of each test score so that the number of samples in all categories is equal and the classification is balanced. Moreover, we only included participants older than 65 which resulted in around 13000 samples.

5.4 Machine Learning Models

We used SKLearn library for our analysis. In particular, we used Linear support vector machine (SVM), k-Nearest neighbours (KNN), Linear Discriminant Analysis (LDA), Decision Trees, Random Forest, and Extra Trees. Before feeding these models with the data, we normalized the data with standardscaler, i.e., we made the features zero-mean and unit variance. In order to evaluate the results, we used 10-fold cross-validation. This means that we split the data to training (90%) and testing set (10%), train the model on the training set and find the accuracy (and other metrics on the test set). We repeat the explained process (splitting, training, and testing) 10 times by considering another 10% of the data as the test set. In the end, we will have 10 test accuracy for each trial. The mean of these results gives us a good estimate of the performance of the models, and the standard deviation of these results gives us an estimate of the reliability of the results. Below are the accuracy (max accuracy reached of 10 folds) of different models:

Table 5.2: Max accuracy of 10-fold cross validation for the case of 3 categories.

	SVM	KNN	LDA	DT	RF	ET
Trail making A	0.55	0.5	0.58	0.83	0.58	0.67
Trail making B	0.67	0.58	0.55	0.45	0.55	0.58
Fluid intelligence	0.57	0.62	0.62	0.43	0.69	0.50
Symbol digit substitution	0.82	0.55	0.73	0.58	0.55	0.55
Numeric memory	0.75	0.64	0.55	0.64	0.64	0.75
Reaction time	0.62	0.43	0.50	0.43	0.57	0.50
Tower rearranging	0.64	0.42	0.58	0.42	0.58	0.64

Table 5.3: Max accuracy of 10-fold cross-validation for the case of 2 categories

	SVM	KNN	LDA	DT	RF	ET
Trail making A	0.82	0.73	0.91	0.75	0.83	0.64
Trail making B	0.82	0.64	0.73	0.82	0.75	0.73
Fluid intelligence	0.77	0.77	0.77	0.71	0.79	0.64
Symbol digit substitution	0.73	0.73	0.75	0.64	0.67	0.82
Numeric memory	0.55	0.67	0.58	0.75	0.82	0.73
Reaction time	0.79	0.57	0.71	0.71	0.79	0.64
Tower rearranging	0.73	0.82	0.82	0.67	0.73	0.73

5.5 Discussion

This study sought to evaluate the possibility of machine learning techniques to predict the cognitive performance based on ECG recordings. We tested the performance of KNN, SVM, LDA, DT, RF and Extra Trees machine learning methods. In our analysis, we used supervised learning since we are training a subset of the data from the known classes and evaluating them on the other data along with a prediction. The predictive model was assessed based on max accuracy reached of 10 folds. We categorized the performance of each test considering two different cases. First, two categories of poor and high performance. Second, three categories of poor, mediocre, and high performance. The performance of the well-established machine learning algorithms achieved satisfactory results ranging from 75 to 91

When categorising cognitive performance into 3 categorise, the DT and SVM have reached maximum accuracy of 82%, and 83%, in detecting the Symbol digit substitution test and Trail Making Test A performance respectively. Additionally, SVM and LDA have reached maximum accuracy of 73%, and 75%, in detecting the Symbol digit substitution test and numeric memory test performance respectively. Whilst, when categorising cognitive performance into 2 categorise, Linear discriminant analysis has reached a maximum accuracy of 91%, in detecting the Trail Making Test A performance. Then, SVM and RF reached a maximum accuracy of 82% and 83% in classifying Trail Making Test

A performance. RF and ET reached a maximum accuracy of 82% in predicting the performance of Numeric memory test and the Symbol digit substitution test.

Classifiers reached a high accuracy in detecting TMT A and B, symbol digit substitution, and numeric memory test which is a widely used test to assess executive function (EF), processing speed, and working memory. Several studies showed that poor performance on measures of executive function, such as the trail making tests indicate impairment in EF [179]. Furthermore, Trail making test was used along with wearable technology as a tool to differentiate cognitive impairment participants among older adults, including those with MCI and AD [38]. In fact, several studies have noted that executive function is impaired in the prodromal stage of AD [180] and MCI [181]. Moreover, higher performance on measures of processing speed, and working memory were associated with higher HRV levels[166] and processing speed [140].

5.6 Conclusions, and Takeaways

In this study, we used UK Biobank data to investigate the relationship between HRV parameters and cognitive performance from different cognitive domain. We employed well-established machine learning classifiers to predict the cognitive performance. Results showed that ML was able to to estimate cognitive performance using HRV data. The results indicated that high HRV was associated with better performance on tasks involving executive function, processing speed, and working memory.

Part V

HRV in Individuals with MCI

CHAPTER 6

Association between cognitive performance and HRV in individuals with MCI

This chapter sheds light on the use of wearables for identifying individuals at higher risk of Dementia. We investigated whether wearable sensors can offer reliable, non-invasive techniques to identify MCI patients from healthy controls by measuring heart rate variability (HRV) as a novel physiological biomarker.Further analysis was performed to test the association between HRV parameters and cognitive status controlling for both age and gender. Lastly, a discussion of the findings is presented.

6.1 Overview

Mild Cognitive Impairment (MCI) is a stage of cognitive decline that occurs between the expected cognitive decline associated with healthy aging and the decline seen in dementia. Individuals with MCI experience memory loss or other cognitive domain losses such as language deficits whilst they still maintain their ability to independently perform in daily living activities. MCI is recognized as an important public health problem as a dementia risk[182]. The rate at which those diagnosed with MCI progress to dementia is 3 to 5 times higher than for those with normal cognition [183; 184] with 12% rate of annual progression in the general population and up to 20% in populations that are at higher risk [182].

Dementia is still diagnosed primarily on clinical signs. Biomarkers, on the other hand, are being increasingly recognised as having a significant role to play[185]. Biomarkers and digital biomarkers for dementia can be a promising approach for early-stage pathological diagnosis of dementia since they help objectively assess pathological sequences and disease progression.

Heart rate variability (HRV) is the measure of variations in the time between each heartbeat. This variation is controlled by the autonomic nervous system (ANS). HRV is considered as a valid and reliable diagnostic tool of autonomic regulation, including activation of the parasympathetic and sympathetic nervous systems [186]. Both systems are important for modulating many vital functions, including respiration and cardiac contractility. Low HRV is associated with emotional dysregulation, worse cognitive performance and is a well-established biomarker of cardiovascular disease [143]. HRV analysis provides an accurate, real-time, and non-invasive way to assess autonomic functioning and as such has been widely used in clinical research.

Conventionally HRV is obtained using one of the two widely used methods to measure the cardiac cycle which is electrocardiography (ECG), and photoplethysmography (PPG). For years, ECG has been used as dominant cardiac monitoring and to detect any abnormalities. However, until now, ECG haven't been improved to the point where they can offer the user with flexibility, portability, and convenience. Whilst. PPG is a non-invasive tool uses light-based technology to measure the volumetric variations of blood circulation. PPG has proven to be a viable alternative to traditional HR monitoring when measured at rest [187].The usage of PPG sensors has increased due to non-invasiveness, ease of use, cost effectiveness, and it can be easily integrated into wearable wrist and finger-worn devices [188][189]. PPG sensors are typically attached to the fingers because of the large amplitude that may be achieved as compared to other places. However, adopting PPG-based monitoring approaches can have some limitations such as inaccuracy in tracking PPG signals during everyday routine activities and light physical exercises. In fact, many studies have demonstrated that PPG – based devices are accurate and reliable for HRV during resting conditions [190][191]. Specifically, PPG signal or pulse rate variability (PRV) acquired from the finger were the most similar to heart rate variability [192].

An association between HRV and cognitive function has been demonstrated in large cohorts of older patients as well as in smaller samples of subjects affected by dementia [146]. The first study to establish a correlation between HRV and cognitive functions emphasized changes in HRV based on the type or complexity of the cognitive task [193; 194]. On the basis of this work, several theories were developed to explain the link between HRV and cognitive functioning including the Neurovisceral Integration Model [104], which suggests that the brain areas

engaged in cognitive and emotional functions are also involved in the regulation of autonomic function.

Within this perspective, HRV can play a significant role as a non-invasive and real-time accurate way to assess autonomic regulation. Several studies have demonstrated the predictive value as well as the clinical application of the HRV as a biomarker. Reduced HRV is considered to be a predictor for general mortality [195] and cognitive performance [149]. Furthermore, higher HRV was found to be associated with better cognitive performance, and a lower HRV has been associated with cognitive impairment [102]. Thus, measurement of HRV may add important information to an assessment of older adults' cognitive function.

The present study will use off-the-shelf HRV monitor devices to assess whether real-time measures of HRV can be used as an early indicator of cognitive decline in individuals with MCI who still have intact cognitive abilities relative to healthy controls. We hypothesise that HRV indices will be lower among individuals with MCI relative to healthy controls. If these patterns emerge, it may be possible to identify biomarkers that could help in the detection of the disease in the preclinical stage which could facilitate an earlier intervention and early access to medical treatments to slow down the progression of the disease[196].

6.2 Related Work

Our previous pilot study [25], demonstrated the feasibility of using wearables to assess relationships between autonomic and cognitive functioning. Here we recruited 10 (five males and five females) healthy young participants (M age=28.6 years, SD=2.50). We wanted to prove that wearable and sensors devices have the ability to identify and record physical data and do so reliably. A statistically significant difference was observed in the frequency-domain HRV measure HFnu measured prior to the Stroop test and that measured during it. The reduced HFnu during the test indicates the decreased parasympathetic activity during stress. Moreover, the LF/HF ratio significantly increased throughout the test implying an increase in the relative predominance of sympathetic nervous system activity during the test.

6.3 Methods and Analysis

6.3.1 Participants

A statistical power analysis was performed for sample size estimation, using the G*Power computer software [157]. A total sample of 18 people would be needed

to detect large effects (d =.8 with 85% power for an independent-groups comparison with alpha at .05. Participants were 21 individuals with MCI and 21 healthy controls (MAge=72.95 years, SD=5.86, Range=62–87; 14 male 28 female) recruited from Join Dementia Research (JDR). JDR is a service managed by the National Institute for Health Research in partnership with Alzheimer's Society, Alzheimer's Research UK, and Alzheimer Scotland. It allows people to register their interest in taking part in dementia research. JDR has showed benefits in terms of increased research recruitment efficiency. It facilitated access to research for both public and researchers[197]. Since its inception in early 2015, JDR has more than 50,000 volunteers and there have been over 60,000 enrolments onto dementia studies, that's an increase of 12,000 in 2022 only. More than 1750 researchers from 296 National Health Service, universities, and research institutions have registered. [198].

Participants were eligible for the present research if they were aged 60-90 and had a diagnosis of MCI (for the MCI group). Exclusion criteria included a diagnosis of a neurological condition or a Mini-Mental State Examination Score (MMSE)<24. Participants with current alcohol or substance misuse, a history of cardiovascular conditions including stroke, ischemic attack, and other types of irregular rhythm disturbances, including atrial fibrillation and other arrhythmias were also excluded. Ethical approval was obtained from Queen Mary Ethics of Research Committee (QMERC20.210) B. All participants provided written informed consent prior to study completion. A copy of consent form, participant's information sheet, and questionnaire can be found in the appendix B.

Figure 6.1: Age and Gender distribution of the participants

6.3.2 Data Collection

Data collection including questionnaire and HRV was carried out in a quiet room, between 8:30 a.m. and 12:00 p.m. since HRV can be affected by changes in circadian rhythm, hormonal shifts, and acute stressors throughout the day. Subjects were asked to eat a light breakfast and were asked to abstain from

smoking and drinking any caffeine-containing beverages including tea and coffee for 2 hours prior to the assessments, and to refrain from drinking alcohol in the 12 hours prior to assessments. HRV was assessed for 6 minutes at rest, comprising a 1-minute stabilization period followed by 5 minutes of actual readings, in line with the recommendations of the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology [107]. included in the models.

We used the CorSense finger-worn device which has been proven to be a very accurate consumer-grade HRV monitor. The CorSense has been internally validated with accuracy equivalent to a 5-lead ECG/EKG, the gold standard for HRV detection, with less than 3% variation across multiple subjects with differing skin tones. CorSense measures heart rate variability through pulse detection using a gold-standard 500 hertz multiwave sensor array that conveniently and comfortably slips over participant's finger. We have used Elite HRV Smartphone Application app to read the data and Kubios HRV 3.3.1 (Kubios Oy, Kuopio, Finland) software to analyse the data [199; 200].

6.3.3 Statistical analysis

Numerical data were expressed as mean ± standard deviation (SD) and median with interquartile range (IQR). Categorical data were expressed as frequency and percentages. The significance of difference of numerical data between two groups was assessed using parametric unpaired t-test or non-parametric Wilcoxon rank sum test based on the fulfilment of unpaired t-test assumptions (normality and equal variances). The significance of differences in categorical variables between groups was assessed using Chi-square test or Fisher's exact test. Multiple linear regression models were performed to assess the association between individual HRV parameter as an outcome and cognitive status as the independent variable, adjusting for age and gender. Age was dichotomized using the median value before being included in the models.

Moreover, we ran a logistic regression analysis using measures significantly different between MCI patients and healthy controls to predict health status of each participant. This model included age, gender, mean RR, ln(SDNN), ln(RMSSD), and ln(HF) as predictor variables, and grouping variable (MCI vs. healthy control) as an outcome variable. We ran a 10-fold cross-validation to compute model prediction accuracy. Individuals were initially classified into MCI/healthy groups based on a threshold of 0.5, which means that all individuals with predicted probability of MCI over 0.5 were classified as MCI patients, and individuals with predicted probability of MCI below 0.5 were classified as healthy controls. Sensitivity and specificity indices were calculated for this

threshold value and receiver operating characteristic (ROC) curve was created for each value of the threshold All statistical analysis was conducted in R software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) [201].

6.3.4 Results

The mean age of MCI subjects was significantly greater than that of healthy subjects (74.9 ± 5.43 vs. 71± 5.75 years). As depicted in Table 6.1, the cognitive status was not associated with gender, smoking status, physical activity, or educational level (p = 0.513, 0.488, 0.739, and 0.564, respectively). Regarding the time domain parameters, the mean RR time was significantly different between healthy and MCI subjects (920 ± 90.2 vs. 898 ± 195.4 ms, respectively). For the time-domain indices, both SDNN and RMSSD were significantly lower in MCI subjects compared with healthy subjects (p = 0.014 and 0.004, respectively). Of the frequency-domain parameters, only HF showed a statistically significant difference between the two groups (p = 0.055). Differences in other indices, including VLF, LF, and LF/HF ratio, between healthy and MCI subjects were not statistically significant.

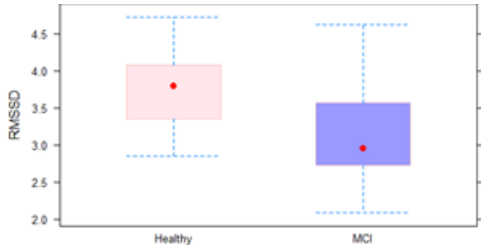

Figure 6.2: RMSSD in MCI and controls group

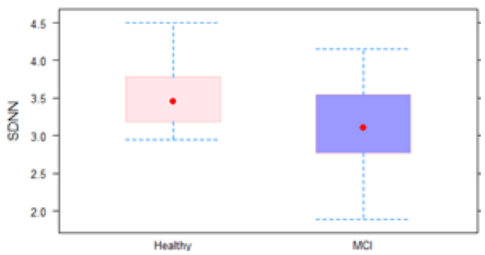

Figure 6.3: SDNN in MCI and controls group

Different linear models were built to test the association between HRV parameters as dependent variables and cognitive status as the independent variable controlling for both age and gender. Cognitive status was significantly

Table 6.1: Pearson's correlation test for HF nz and composite memory

	Healthy	MCI	p-value
	n = 21	n = 21	
Age, years			
Mean (SD)	71 (5.75)	74.9 (5.43)	0.029a
Median (IQR)	71 (66-74)	76 (72-77)	
Gender, n (%)			
Female	15 (71.4%)	13 (61.9%)	0.513b
Male	6 (28.6%)	8 (38.1%)	
Smoking status, n (%)			
Non-smoker	21 (100%)	19 (90.5%)	0.488c
Smoker	0 (0%)	2 (9.5%)	
Physical activity, n (%)			
Not active	6 (28.6%)	7 (33.3%)	0.739b
Active	15 (71.4%)	14 (66.7%)	
Education level, n (%)			
School	4 (19%)	6 (28.6%)	0.564b
Undergraduate	8 (38.1%)	5 (23.8%)	
postgraduate	9 (42.9%)	10 (47.6%)	
Mean RR, ms			
Mean (SD)	920 (90.2)	898 (195.4)	0.639d
Median (IQR)	933 (886-978)	873 (760-1003)	
SDNN, ms			
Mean (SD)	37.6 (18.8)	26.5 (15.8)	0.014 e
Median (IQR)	31.6 (24.2-44)	22.3 (15.8-34.5)	
RMSSD, ms			
Mean (SD)	46.1 (23.4)	30.5 (25.7)	0.004e
Median (IQR)	44.4 (28.3-59)	19.1 (15.2-35.4)	
VLF, ms2			
Mean (SD)	40.1 (46.4)	56.2 (68.7)	0.485e
Median (IQR)	22.5 (12.7-54.9)	28.8 (16.4-78.6)	
LF, ms2			
Mean (SD)	477 (594)	289 (242)	0.672e
Median (IQR)	187.2 (106.7-622.6)	213.5(121.4-419.7)	
HF, ms2			
Mean (SD)	450 (461)	310 (544)	0.055e
Median (IQR)	310.7(117-741)	151.4(64.4-264.3)	
LF/HF			
Mean (SD)	1.3 (1.06)	1.91 (1.66)	0.229e
Median (IQR)	1.03 (0.53-1.64)	1.6 (0.77-2.54)	

a Unpaired t-test, b Chi-square test, c Fisher's Exact test, d Welch Unpaired t-test, e Wilcoxon rank sum test. IQR: interquartile rang, SD: standard deviation, ms: milliseconds

associated with ln(SSDN) and ln(RMSSD) but was not significantly associated with mean RR after adjusting for sex and age. The MCI subjects had approximately 35% and 43% reduction in SDNN and RMSSD, respectively, compared to healthy subjects controlling for age and gender. Out of the frequency domain parameters, cognitive status was only significantly associated with ln(HF) after adjusting for gender sex and age. The MCI subjects showed approximately 58% reduction in HF compared with healthy subjects (p=0.012).

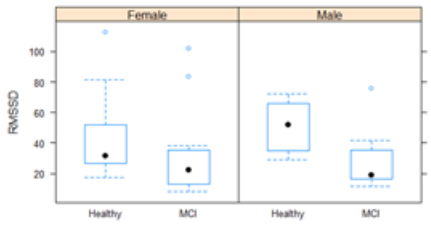

Figure 6.4: RMSSD in MCI and controls group

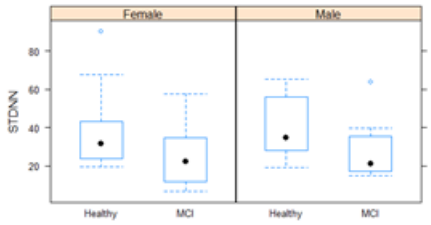

Figure 6.5: SDNN when controlling for age and gender

Prediction accuracy for the logistic regression using 10-fold cross-validation was 76.5%. Specificity of the full model was 0.8571, while sensitivity was 0.8095. Highest accuracy of the model was achieved at a threshold of 0.5. ROC curve showing classification performance at values of all thresholds is presented in 6.6. We use the ROC curve to find classification threshold that has the best sensitivity and specificity at the same time. All points in the curve are different classification thresholds. The one where both sensitivity and 1-specificy are the highest at the same time is our best threshold, in this case is 0.5.

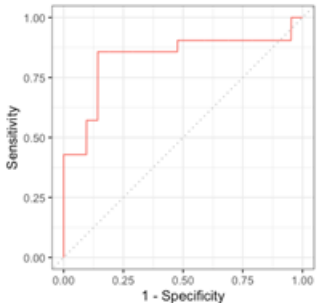

Figure 6.6: ROC curve for every value of classification threshold.

6.4 Discussion

Several studies have investigated different biomarkers in order to diagnose and assess neurodegenerative disease and MCI using biosensors. However, these biomarkers are not ideal solutions for healthcare systems, because they are expensive, time-consuming, and invasive [202]. Furthermore, several attempts have been made to develop biomarkers for the diagnosis of MCI [203; 204]. Yet, there is still considerable scope for improvement in terms of accessibility, reliability, and validity of these biomarkers. To our knowledge, only one study has investigated the feasibility of using biosensor device in patients at risk for dementia. The participants were divided into three groups: 24 healthy controls, 6 had subjective cognitive deterioration, and 3 were amyloid-positive (one with pre-clinical AD, one with pre-clinical Lewy-Body Dementia, and one with mild cognitive impairment)[192].

In this study, we explored differences between HRV in MCI group and in healthy controls, as measured using a PPG sensor. We investigated the feasibility of employing sensors to distinguish between MCI participants and healthy participants. Our primary hypothesis was supported as we observed significant differences between subjects with MCI and cognitively normal controls. Conventional time-domain and frequency-domain measureshave been used for HRV analysis in this study. There was a significant difference in three HRV indices (RMSSD, SDNN and HF) between the two groups. Our findings show reduced HRV indices, suggesting lower parasympathetic activity is associated with MCI participants. This suggeststhat the autonomic dysfunction represented by HRV is detectable in baseline conditions using PPG sensors. Our findings demonstrate that real-time measures of HRV could be used as an early indicator of cognitive decline in individuals with MCI. These findings could be valuable to researchers and clinicians considering using HRV measurement for evaluating neurodegenerative disease in a large population.

Overall, the individual regression results and logistic regression analysis show that RMSSD, SDNN, and HF measures can be used to reliably distinguish MCI patients from healthy controls. Average accuracy of 76.5% is high and a classification threshold of 0.5 yields high sensitivity and specificity. Area under the ROC curve shows that the test has a very good diagnostic accuracy [205]. Previous studies have shown that MCI is related to a dysregulation and changes in HRV [130][206]. This is related to a dysfunction of the autonomic nervous system. Altered function of the autonomic nervous system is also related to worse cognitive performance in the absence of dementia [102]. This knowledge has the potential to contribute to the diagnosis of MCI and other cognitive deficits. However, it has not been applied this way before. Our study is the first one to show that using biosensors to measure HRV can be relatively reliably to distinguish cognitively normal healthy controls from MCI patients. Because HRV can be measured in a matter of minutes, the knowledge that we present here might be particularly useful and, in the future and provided that more studies on the topic are conducted, contribute to a battery of tools used to diagnose MCI.

This study also has limitations that are worth mentioning, the study included a sample of predominantly white older adults (more than 81% of the participants are white), so our findings may not apply to other populations. Furthermore, we had a majority of female participants, which may have prevented us from detecting differences in HRV due to gender. However, gender differences in HRV have been reported to disappear after the age of 50 years [207]. Moreover, the HRV measured from the participants who were already diagnosed with MCI and it's worth mentioning that HRV can be considered as a biomarker for already-diagnosed MCI and that does not necessarily imply that it's a useful biomarker for as-yet-undiagnosed MCI. Further, it is known that the within-subject variability in short-term measured HRV (5-15min) could be very high [208]. In fact, the coefficient of variation for such measurements can vary between 1-100%. There are several factors that might influence intraindividual HRV reliability, such as stress, taking part in a pharmacological intervention, or belonging to a clinical population [208; 209]. On the other hand, short term HRV measurements have a number of advantages, as they can be conducted quickly and are relatively easy to analyze, but they can also be performed in a highly controlled environment. This could alleviate some of the concerns related to high within-subject variability. Other than that, strategies exist to improve HRV reliability, such as reminding individuals to avoid irregular respiration [210], or using specific measures that are less prone to individual variability in HRV, such as time-domain measurements, as opposed to frequency-domain measurements [211], or taking HRV measures at rest. Given that HRV is less reliable in clin-

ical populations, using measures to improve such reliability in MCI patients is especially important and could improve the sensitivity, specificity, and accuracy of distinguishing MCI patients from healthy controls. Finally, since HRV reliability is specific to a measured population, further studies in patients with MCI need to be conducted that would aim specifically at investigating reliability of HRV measurements in this population.

6.5 Conclusion

Overall, our study demonstrated that healthy participants have higher HRV indices comparedto older adults with MCI using sensors technologies. SDNN, RMSSD, and HF were significantly lower in MCI subjects compared with healthy subjects. Findings obtained in our study have clinical importance with regard to using HRV wearable-based data in order to predict MCI. It was a control study and limited and therefore further studies would be needed but this is a very good indication that HRV PPG sensors technologies have potential as a non-invasive early marker to detect those at higher risk of having MCI. Future studies should extend these findings by including individuals with Alzheimer's disease to investigate whether HRV could be a useful diagnostic screening tool at MCI stage of dementia by following up with the participants and identify MCI patients who underwent HRV testing at baseline, and who developed dementia. Moreover, more studies are needed to evaluate the predictive value of HRV in the progression of cognitive decline and how this links to the likelihood of dementia conversion.

CHAPTER 7

Machine Learning Approach to Identify Individuals with Mild Cognitive Impairment Using HRV-Wearable Based Data

The previous chapter has revealed that employing wearable sensors can offer reliable, non-invasive techniques to distinguish MCI patients from healthy controls. In this chapter, we are interested in the use of machine learning models for early identification of MCI by employing wearable-based data. We employed conventional machine learning classifiers and ensemble techniques to help identifying individuals at higher risk of MCI. We discuss how machine learning can aid an early diagnosis of MCI.

7.1 Overview

Machine learning (ML) has increased the possibilities of remote monitoring and diagnosis using the data from wearable devices. The ML techniques involve various steps such as pre-processing, feature selection, training on the labelled dataset, and testing to verify its accuracy and competency. Several studies utilized wearables and other sensing technologies for monitoring older people's daily activities and identify behavioural changes. These studies showed that contin-

uous monitoring in smart environments helps an early detection of functional impairments [24]. Recent research has shown that machine learning algorithms can accurately classify images of AD, MCI, and healthy people [212; 213; 214].

Machine learning can offer a significant help in neurodegenerative disease research, including detecting the onset of the disease [215; 216; 217], measuring it's severity [217; 218], and improving differential diagnosis between MCI and AD and between dementia sub-types [219; 220; 221]. ML has been used with different data including neuroimaging [216; 217; 222; 223], HRV [177; 22], speech and eye tracking [224; 225], and genetic data [226; 227]. Numerous biomarkers have been suggested to assist practitioners in verifying the diagnosis of dementia related to AD; these biomarkers, such as tau PET, however, are not ideal alternatives for healthcare since they are costly, time-consuming, and invasive [28]. Lately, there have been several attempts to establish a biomarker guideline for the diagnosis of MCI [203], but there are still areas for improvement in terms of accessibility, reliability, and validity of these biomarkers.

Digital biomarkers have emerged as an interesting new tool for developing and supporting precision medicine and aiding clinical trials as digital devices have begun to be integrated into the medical scene. Theses biomarkers are physiological and behavioural data that are collected by digital devices such as wearables. The collected data are used to explain, impact, and predict health outcomes. Wearables offer non-invasive, continuous, and real-time health monitoring of targeted biomarkers. Furthermore, COVID-19 has increased the necessity for remote assessment in older persons, who are at higher risk of infection and are urged to employ social distancing measures in particular, but the importance of dementia diagnosis and treatment has not changed. Wearable devices can collect physical, emotional, and chemical data such as heart rate and vital sign, electrodermal activity, tears, saliva, or sweat. Several studies are using wearable sensors along with other devices (home-based devices, smartphones) to remotely assess neurophysiological, motor, functional, cognitive and affective digital biomarkers in disorders such as AD and epilepsy [228; 229].

At present, it is unclear whether employing wearables and sensing technologies for detecting changes in autonomic function is a cost effective and reliable technique to test individuals at risk for AD. Moreover, it is unknown if using sensors may hold promise for monitoring longitudinal changes over time in individuals at risk of cognitive deterioration. The goal of our study is to investigate if utilizing wearables and sensing technologies to gather HRV data in people at risk for dementia is feasible, and if these physiological data might be linked to cognitive function. We propose a machine learning approach for predicting MCI from healthy controls. Indeed, there is a tremendous opportunity to leverage machine learning technologies in the healthcare industry. However, it is one of

the most complex fields [230] and one of the most challenging, especially in the areas of diagnosis and prediction [231].

7.2 Methods

7.2.1 Participants

Participants were 21 individuals with MCI and 21 age-matched healthy controls (mean age = 72.95 years, SD=5.86, Range=62–87; 14 male 28 female) recruited from Join Dementia Research (JDR). JDR is a service managed by the National Institute for Health Research in partnership with Alzheimer's Society, Alzheimer's Research UK, and Alzheimer Scotland. It allows people to register their interest in taking part in dementia research. JDR has showed benefits in terms of increased research recruitment efficiency. It facilitates access to research for both the public and researchers [197] [217]. Since its beginning in early 2015, JDR has more than 50,000 volunteers and there have been over 60,000 enrolments in dementia studies, which is an increase of 12,000 in 2022 only. Participants were eligible for the present research if they were aged 60-90, and had a diagnosis of MCI (for the MCI group). Exclusion criteria included a diagnosis of another neurological condition or a Mini-Mental State Examination c (MMSE) score ¡ 24. Participants with current alcohol or substance misuse, a history of cardiovascular conditions including stroke, ischemic attack, and other types of irregular rhythm disturbances, including atrial fibrillation and other arrhythmias were also excluded. Ethical approval was obtained from the Queen Mary Ethics of Re- search Committee (QMERC20.210). All participants provided written informed consent prior to study completion.

7.2.2 Pre-processing and Feature selection

Data were processed before training. Categorical values were encoded into a bi- nary variable. Continuous variables were log-transformed and normalised. Feature selection was performed to automatically select a subset of features that is most relevant to the task, reduce the dimensionality of feature space and computation time, as well as to enhance the accuracy of optimization methods by ignoring redundant, irrelevant or noisy features [252]. Irrelevant features can be a noise and degrade the performance of a classifier. By reducing the dimension of the features this risk can be mitigated. Therefore, Sequential Forward Selection (SFS) was performed in order to determine the best feature subset to gain the highest classification accuracy. Stratified 10-fold cross-validation was conducted for each classifier. Stratification ensures that the proportion of samples

for each class is preserved in the fold during the cross-validation. The following metrics were used: accuracy, sensitivity, and specificity.

First, each model was cross validated on features splitted between frequency (VLF, LF, HF, LFnu, HFnu, LF/HF) and time domain (MeanRR, SDNN, RMSSD). Secondly, training was conducted using features with time and frequency domain combined and with best accuracy at dimension size k at 17 (all features), 8, 4, and 1. The selected features based on SFS results at k=8 were (age, SDNN, RMSSD, VLF, LF, HF, LFnu, smoker), at k=4 (MeanRR, SDNN, VLF, smoker), and at k=1 (MeanRR), respectively. The dimension was reduced using Sequential Forward Selection (SFS) as explained above. We used Conventional machine learning classifiers were used for the study. The chosen classifiers were Multi-layered Perceptron (MLP), K-Nearest neighbours (KNN), Decision tree (DT), Random Forest (RF), Latent Discriminant Analysis (LDA), Support Vector Machine (SVM), and Logistic Regression Model (LRM).

7.3 Results

The results of the classifiers trained on time and frequency domain features are shown in table 7.1. The classifiers struggled to learn from frequency-domain features. The majority of the classifiers scored lower than baseline (random) of 50% (Fig. 7.1). On the other hand, the classifiers were able to perform better using time-domain features. With an accuracy of 72%, a sensitivity of 86.7%, and a specificity of 58.3% the best results were achieved using Support Vector Machine (SVM). The combination of the two domains was hypothesised to improve the performance of the classifiers. The results can be seen in Table 7.2. All methods had an improved accuracy compared to time-domain features alone, except for SVM which had the same result as the frequency domain. The single model with the highest accuracy was Latent Discriminant Analysis, with an accuracy of 73.5%, sensitivity of 81.7%, and specificity of 66.7%, at k=4 for the number of dimensions. Interestingly, most of the classifiers performed best at feature dimension size of k=4 (Figure 7.2),demonstrating the positive effect of conducting feature selection. The features selected at k=4 were ('MeanRR', 'SDNN', 'VLF', 'smoker'). The selected features were indeed a combination of time and frequency domain, which shows the importance of using both domains. Moreover, it is known that smoking increases the risk of having dementia. The selection of smoking indicators aligns with this fact. Area under curve (AUC) for receiver operating characteristics (ROC) curve for each model compared between time features, frequency features, and time-frequency combined features can be seen in Appendix B. Finally, an ensemble model was created using the top four classifiers (MLP, SVM, LDA, LRM) at k=4. The ensemble model had

the best overall accuracy with 80% accuracy, 86.7% specificity, and 71.7%. The confusion matrix shows the actual predicted values using this model. The model gives 35 correct predictions and 8 wrong predictions with 80% accuracy Fig. 7.2.

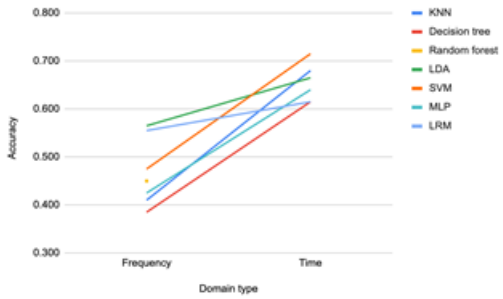

Figure 7.1: Accuracy of classifiers trained with frequency vs. time domain features.

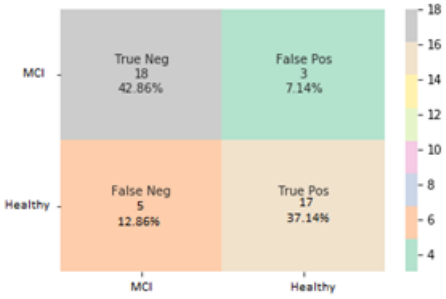

Figure 7.2: The confusion matrix of ensemble model at 4 features.

7.4 Discussion

Machine learning can offer a significant help in neurodegenerative disease, including detecting the onset of the disease [117; 216; 217], measuring its severity [217; 218], and improving differential diagnosis between MCI and AD, and between dementia subtypes [219; 220; 221]. ML have been used with different data including neuroimaging [216; 217; 222; 223], HRV [177; 22], speech and eye tracking [224; 225], and genetic data [226; 227]. Numerous biomarkers have been suggested to assist practitioners in verifying the diagnosis of dementia related to AD; These biomarkers such as tau PET, however, are not ideal alternatives for healthcare since they are costly, time-consuming, intrusive, and radiational [28]. Lately, there have been several attempts to establish a biomarker guideline for

Table 7.1: 10-FOLD CROSS VALIDATION RESULTS

Accuracy

	KNN	DT	RF	LDA	SVM	MLP	LRM
Frequency Domain	0.41	0.39	0.45	0.57	0.48	0.43	0.56
Time Domain	0.68	0.62	-	0.67	0.72	0.64	0.62

Specificity

	KNN	DT	RF	LDA	SVM	MLP	LRM
Frequency Domain	0.45	0.5	0.5	0.667	0.550	0.350	0.600
Time Domain	0.95	0.617	-	0.663	0.867	0.667	0.583

Sensitivity

	KNN	DT	RF	LDA	SVM	MLP	LRM
Frequency Domain	0.400	0.500	0.433	0.483	0.433	0.517	0.533
Time Domain	0.417	0.617		0.717	0.583	0.633	0.667

Table 7.2: 10-fold cross validation results for each classifiers at different feature dimension after using SFS

Accuracy

	KNN	DT	RF	LDA	SVM	MLP	LRM	Ensemble
K=17	0.650	0.535	0.635	0.640	0.550	0.575	0.640	0.665
K=8	0.690	0.550	0.590	0.655	0.715	0.645	0.680	0.725
K=4	0.605	0.685	-	0.735	0.655	0.705	0.730	0.800
K=1	0.595	0.560	-	0.570	0.640	0.665	0.570	0.595

Specificity

	KNN	DT	RF	LDA	SVM	MLP	LRM	Ensemble
K=17	0.683	0.517	0.717	0.717	0.683	0.617	0.633	0.717
K=8	0.667	0.550	0.667	0.650	0.717	0.650	0.700	0.750
K=4	0.750	0.650	-	0.667	0.700	0.700	0.667	0.867
K=1	0.683	0.567	-	0.700	0.767	0.767	0.700	0.817

Sensitivity

	KNN	DT	RF	LDA	SVM	MLP	LRM	Ensemble
K=17	0.650	0.550	0.567	0.583	0.450	0.550	0.667	0.583
K=8	0.733	0.550	0.533	0.667	0.733	0.650	0.667	0.667
K=4	0.467	0.717	-	0.817	0.617	0.717	0.800	0.717
K=1	0.533	0.567	-	0.467	0.533	0.567	0.467	0.883

the diagnosis of MCI [28], but there are still areas for improvement in terms of accessibility, reliability, and validity of these biomarkers. We believe that ML-based predictive models using wearable sensors will improve our understanding of MCI and dementia and provide a more accurate and precise definition of it.

Our study demonstrated the performance of supervised machine learning methods in predicting dementia patients using HRV features. We evaluated several ML classifiers using both time- and frequency- domain features. Our investigation showed that among ML-based classification algorithms, SVM classifier outperformed the other algorithms with an accuracy of 73.5% in predicting MCI patients. SVM is one of the most commonly used supervised classifiers in the field of pattern recognition and has been widely adopted in many neurodegenerative disease [232]. Furthermore, an ensemble model was created using four classifiers (MLP, SVM, LDA, LRM) to improve the robustness and accuracy of the classification model. The accuracy of the ensemble model had the best overall accuracy with 80%, 86.7% specificity, and 71.7% sensitivity. By using the ensemble model, sensitivity, specificity, and overall accuracy has improved which indicates that he ensemble-based classifier performs better than individual classifiers.

Our research yielded two significant findings about HRV. The first is that HRV indices measured using wearable devices could be a potential biomarker in the early diagnosis of MCI. The use of wearable devices may eventually help clinicians and researchers to detect autonomic dysregulation associated with early dementia pathology in a non-invasive and cost-effective manner. The second finding is that ensemble ML conventional classifiers can boost performance even with a small dataset of 42 patients. We demonstrated, using supervised machine learning techniques, that HRV data collected via a wearables could be a potentially reliable approach to monitor cognitive changes associated with preclinical dementia. The results are promising as it showed the performance of conventional machine learning methods in predicting dementia patients using Heart Rate Variability (HRV) features.

Recently, machine Learning methods have shown efficacy in the field of HRV analysis [233; 234]. In this work, we only tested a very shallow network approach (multi-layer perceptron), so it will be interesting to use a much deeper network, although, more data will be crucial for the successful training of such a model. Furthermore, different methods for ECG signal processing have been proposed. Some work used data from adjacent epochs in predicting the label of the current epoch [234]. As feature engineering is crucial especially for conventional machine learning methods, more complex algorithms to improve signal processing can be useful [235].

7.5 conclusion

In this research work we have investigated a new approach for the automated classification of MCI from HRV wearable-based data. Our findings are of clinical importance with regards to assisting practitioners in diagnosis of MCI. We have used both conventional and ensemble classification models to distinguish patients with MCI from healthy controls based on HRV indices collected using wearable device. Further studies with a larger sample size and longer follow-up period are required to investigate this relationship further and to expand upon these preliminary findings. This may assist in explaining the potential of wearables and sensing technologies in the early identification of MCI and dementia in general.

Part VI

Conclusions and Future Work

CHAPTER 8

Conclusions

The potential of wearable and physiological sensing technologies was investigated in this dissertation to answer the question: How suitable are wearables and sensing technologies for detecting cognitive impairment in people with MCI using HRV? The key research contribution of this thesis which advance the state-of-the-art in employing wearables to monitor and detect cognitive impairment using HRV parameters are presented below. The research questions are discussed in light of the findings of previous studies.

8.1 Summary of contributions

This thesis has investigated wearable sensing techniques towards assessing cognitive function in patients with MCI and dementia. In the pilot study, cognitive function was assessed by means of HRV monitored by wearable technologies. In the second part of the thesis, HRV was assessed in patients with dementia. The data used in this study were accessed through the UK Biobank. Here, we confirmed the association between HRV and cognitive function in patients with dementia. In the third part of the thesis, we assessed the feasibility of using wearables in detecting cognitive decline in MCI patients.
As mentioned previously in section 1.3, detailed descriptions of methods and results can be found in the corresponding chapters. What follows is a summary of our contributions to the field:

What is the current state of the art in wearable technologies for persons with MCI and dementia?

This question was addressed in Chapter 2,We presented a comprehensive overview of the investigations to date into the use of wearable technologies to support people living with MCI and with dementia and the resulting benefit to their wellbeing. We assessed the role of wearables in three broad categories: in the assessment of dementia symptoms, their role as an assistive technology, and their role as a cognitive intervention. We also reviewed the use of wearables in combination with non-wearable technologies and the potential to monitor multiple parameters at once using a single wearable. We detailed the limitations of wearable technologies, identified the unmet needs and challenges in the implementation of wearables-based interventions, and proposed the required next steps to improve the outcomes of people living with dementia using wearable technologies. Overall, we have presented an up-to-date and comprehensive review of current research in the field of wearable technologies and dementia. In addition to reporting the range of possible uses for wearables to detect and monitor cognitive change and behavioural and psychological symptoms, this review provided a discussion of current wearables that support cognitive interventions in dementia. This work is an important contribution in to understanding of how wearables can support the needs of people living with dementia and their caregivers.

What is the reliability of wearables devices in capturing the differences in HRV before, during, and after a cognitive assessment? Is there a significant correlation between HRV derived from wearables and cognitive performance?

This question was addressed in Chapter 3, we conducted a pilot study to address the above research questions. The main focus of our research was to investigate whether HRV features derived from wearable devices could be utilised to distinguish different levels of stress. Moreover, we investigated the association between short-term HRV measured using wearable-based device and cognitive performance on multiple cognitive tests. We discussed how data obtained from sensors can be used to assess ANS reactions. The hypothesised observations were partly confirmed, and statistical differences were shown in HRV before and during the cognitive test. We concluded that wearable and sensing technologies could be used as a reliable tool to monitor HRV and are able to detect difference in HRV under different stress conditions. However, the study did not show a relationship between cognitive performance and HRV in our sample. This could be due to the very limited number of participants (n=18) or due to the study sample characteristic – young and healthy participants. Our findings

are consistent with results from similar studies [236].

Will measures of HRV amongst patients with dementia be lower relative to healthy controls? How strong is the association between HRV and cognitive function among older groups?

This question was addressed in Chapter 4. The data used in this study were accessed through the UK Biobank. We firstly developed a python script to read the ECG files, perform signal processing, extract the important features such as QRS complex, and finally extract HRV features. Later, we compared the accuracy of our HRV metrics to the one calculated through Kubios software. Our method achieved a 99.6% accuracy comparing to the Kubios method. Findings of the study showed that reduced HRV was significantly associated with cognitive impairment in dementia patient. Specifically, groups of patients with dementia had lower HRV(RMSSD) values than the control group. Overall, the results are consistent with earlier research that investigated the relationship between HRV and cognitive function in patients with dementia. Decreased HRV indexes were previously associated with all types of dementia [237; 238; 146; 239] .

What is the feasibility of using wearable biosensor devices for assessing physiological changes associated with MCI?

This question was addressed in Chapter 6, Here, we investigated the feasibility of employing a wearable device to distinguish between participants with MCI and healthy controls using HRV. Our primary hypothesis was supported as we observed significant differences in subjects with MCI compared to cognitively normal controls. Conventional time-domain and frequency-domain analyses have been used for HRV analysis in this study. There was a significant difference between the two group on three HRV indices (RMSSD, SDNN, HF). Our findings showed reduced HRV indices, suggesting lower parasympathetic activity in participants with MCI. Overall, individual regression results and logistic regression analysis showed that RMSSD, SDNN, and HF measures can be used to reliably distinguish MCI patients from healthy controls. Average accuracy of 76.5% was high and a classification threshold of 0.5 yielded high sensitivity and specificity.

8.2 Future work

Despite potential benefits of wearables in healthcare, significant challenges and important limitations remain and prevent the widespread adoption and further use of wearable technology in medical practice and in dementia studies. one of the main limitations is the lack of standards and regulations. Therefore, a standard protocol in evaluating wearables should be proposed since current studies use different sets of activities, algorithms, or approaches in assessing the function of wearables in the management of dementia.

Studies on user acceptance, ease of use, user interface, physical design and structure of wearables can also be conducted to evaluate how people living with dementia perceive the use of wearables. Additionally, surveys on how people living with dementia perceive their needs and how they imagine bridging the gap in wearable technology can be carried out to ensure the patient voice is heard. Larger population studies and clinical trials on the use of wearables are also encouraged to gain broader understanding of the advantages of using wearables in the management of symptoms and in preserving cognitive function among people living with dementia.

One area investigated by just one research group [13] is the potential to use wearable devices to stratify patients diagnosed with dementia into one of the four subtypes of dementia. With the understanding that each of these subgroups has a different and distinct clinical manifestation, correct subtyping could ensure the most appropriate care is provided for each individual. It would be useful to investigate further the use of wearable devices for this purpose in tandem with general monitoring of various selected parameters as discussed.

This work serves as a starting point in studying the feasibility of using wearables to detect cognitive decline. Future studies should include individuals with Alzheimer's disease to investigate whether HRV could be a useful diagnostic screening tool at the MCI stage of dementia. This could be done in the UK Biobank by identifying MCI patients with available HRV data who later developed dementia.

Part VII

Appendix and Bibliography

Appendices

APPENDIX A

Appendix

The following pages contain material used during the MCI study (Chapter 4). The material comprises:

1. Ethics approval letter
2. Consent form (sample export)
3. Participant Information Sheet
4. Participant Questionnaire

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Research Ethics Administrator
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c/o Dr Akram Alomainy
School of Electronic Engineering
and Computer Science
Queen Mary University of London
Mile End
London

18th September 2019

To Whom It May Concern:

Re: QMREC2188 - Detecting Autonomic nervous system reactions using HRV and EDA: A Pilot study.

I can confirm that Eaman Alharbi has completed a Research Ethics Questionnaire with regard to the above research.

The result of which was the conclusion that the proposed work does not present any ethical concerns; is extremely low risk; and thus does not require the scrutiny of the full Research Ethics Committee.

Yours faithfully

Mr Jack Biddle – Senior Research Management and Governance Officer

Queen Mary
University of London

Consent form

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: Detecting Autonomic nervous systeme reactions using HRV and EDA: A Pilot study

Queen Mary Ethics of Research Committee Ref: _____

Thank you for considering taking part in this research. The person organizing the research must explain the project to you before you agree to take part.

If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time. If you are willing to participate in this study, please circle the appropriate responses and sign and date the declaration underneath.

Statement	**Circle a response**
I agree that the research project named above has been explained to me to my satisfaction in verbal and/or written form	YES / NO
I understand that if I decide at any other time during the research that I no longer wish to participate in this project, I can notify the researchers involved and be withdrawn from it immediately	YES / NO
I have read both the notes written above and the Information Sheet about the project, and understand what the research study involves	YES / NO
I agree to take part in the study, which will include use of my personal data	YES / NO

Participant's Signature:_____ Date: _____

Investigator's Statement:

I _____ confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the volunteer and provided a copy of this form

Information Sheet

Queen Mary University of London

Information sheet

Detecting Autonomic nervous systeme reactions using HRV and EDA: A Pilot study

We would like to invite you to be part of this research project, if you would like to. You should only agree to take part if you want to, it is entirely up to you. If you choose not to take part there won't be any disadvantages for you and you will hear no more about it. [If appropriate: Choosing not to take part will not affect your access to treatment or services in any way].

Please read the following information carefully before you decide to take part; this will tell you why the research is being done and what you will be asked to do if you take part. Please ask if there is anything that is not clear or if you would like more information.

If you decide to take part you will be asked to sign the attached form to say that you agree.

You are still free to withdraw at any time and without giving a reason.

Purpose of the Study

The purpose of this study is to examine the involvement of the Autonomic nervous system in cognitive functioning. We want to evaluate the autonomic nervous system (ANS) reactions before, during and after the cognitive challenge. Then, will try to assess the influence of the cognitive stressor on Heart Rate Variability and EDA. We will check if there is a relationship between stress and cognitive function.

Study Layout

Preparation:

Before we equip you with the sensors, we will ask you to fill out a pre-study questionnaire. This

questionnaire contains questions about your demographics (age, gender), smoking behaviour and fitness level (since those are factors which can influence your heart rate readings).

In preparation for the study, you will be equipped with the sensors we use during the experiment.

There is a wrist-worn wearable (Apple Watch) which will be placed at your non-dominant arm. In addition, you will slip CorSense onto your finger. Furthermore, you will be asked to wear a ring that has a Galvanic Skin Response Sensor from Moodmetric.

All those sensors will be shown and explained to you beforehand.

Study:

The experiment will be conducted once and once you volunteered you will be assigned a time slot. The researcher will be in the room with you throughout the experiment for the instructions and any questions.

Baseline/Relaxed Recording: You will be asked to sit in front of a screen for 5 minutes. This enables us to collect a sensor sample in a relaxed state.

Test Condition: You will be asked to take a cognitive test. It is comprised of seven tests: verbal and visual memory, finger tapping, symbol digit coding, the Stroop Test, a test of shifting attention and the continuous performance test.

At the end of the study, the sensors will be removed.

Time Commitment
The study will last around 60- 70 Minutes including introduction, preparation, and removal of the sensors in the end.

Data Sharing
All the information that we collect about you during the course of the study will be kept strictly confidential. You will not be able to be identified or identifiable in any reports or publications. Any data collected about you in the online questionnaire will be stored on a password-protected hard drive. Data collected may be shared in an anonymized form to allow reuse by the research team and other third parties. These anonymized data will not allow any individuals or to be identified or identifiable.

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information, sheet to keep and be asked to sign a consent form.

If you wish to contact the responsible research team, please email Eaman Alharbi:

e.alharbi@qmul.ac.uk

If you have any questions or concerns about the manner in which the study was conducted please, in the first instance, contact the researcher responsible for the study. If this is unsuccessful, or not appropriate, please contact the Secretary at the Queen Mary Ethics of Research Committee, Room W117, Queen's Building, Mile End Campus, Mile End Road, London or research-ethics@qmul.ac.uk

Demographic Data and Assessment of Influential Factors

1. Age: ----------

2. Gender:
   - ☐ male
   - ☐ female
   - ☐ non-binary
   - ☐ I prefer not to

3. What is the highest degree or level of school you have completed? If currently enrolled, the highest degree received.
   - ☐ No schooling completed
   - ☐ Nursery school to 8th grade
   - ☐ Some high school, no diploma
   - ☐ High school graduate, diploma or the equivalent
   - ☐ Some college credit, no degree
   - ☐ Trade/technical/vocational training
   - ☐ Associate degree
   - ☐ Bachelor's degree
   - ☐ Master's degree
   - ☐ Professional degree
   - ☐ Doctorate degree
   - ☐ Others:_____

4. Employment Status: Are you currently…?
   - ☐ Employed for wages
   - ☐ Self-employed
   - ☐ Out of work and looking for work
   - ☐ Out of work but not currently looking for work
   - ☐ A homemaker
   - ☐ A student
   - ☐ Military
   - ☐ Retired
   - ☐ Unable to work
   - ☐ Others:_____

5. If you are an employee, how many years of experience do you have
   - ☐ 0-4
   - ☐ 5-9
   - ☐ 10 -14
   - ☐ More than 15 years

6. how much sleep do you get each night, on average?
   - ☐ Less than 6 hours
   - ☐ 6-9 hours
   - ☐ More than 9 hours

7. How would you describe your general health?
   - ☐ Excellent
   - ☐ Good
   - ☐ Fair/Poor
   - ☐ I prefer not to tell

8. How would you describe your general physical activity:
   - ☐ Low Physical Activity(Walking)
   - ☐ Moderately Physical Activity(carrying light loads, bicycling at a regular pace, or doubles tennis)
   - ☐ High Physical Activity(heavy lifting, digging, aerobics, or fast bicycling?)
   - ☐ I prefer not to tell

9. How much time do you usually spend on physical activity?
   - ☐ _____ hours per day
   - ☐ _____ minutes per day
   - ☐ Don't know/Not sure

10. What is your current cigarette smoking behavior (including hand-rolled cigarettes)?
    - ☐ Daily smoker (at least one cigarette per day, disregarding religious fasting)
    - ☐ Occasional smoker (less than one cigarette per day)
    - ☐ Ex-smoker of cigarettes
    - ☐ Non-smoker of cigarettes
    - ☐ I prefer not to tell

APPENDIX B

Appendix

The following pages contain material used during the MCI study (Chapter 6). The material comprises:

1. Ethics approval letter
2. Consent form (sample export)
3. Participant Information Sheet
4. Participant Questionnaire

Queen Mary, University of London
Room W117
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Queen Mary University of London
Mile End Road
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Research Ethics Facilitators
Tel: +44 (0)20 7882 7915 / 6947
Email: research-ethics@qmul.ac.uk

28/05/2021

Dr Akram Alomainy
School of Electronic Engineering and
Computer Science
Queen Mary University of London

Cc: Eaman Alharbi

Dear Dr Alomainy and Mrs Alharbi,

Re: QMERC20.210 - Association between HRV and Cognitive performance using wearable technologies.

The research ethics application for the study detailed above has been reviewed by the Queen Mary Ethics of Research Committee (Supplementary Panel).

I am pleased to inform you that, based on the information provided, the above study has been **approved.**

Date of Approval: 28/05/2021

Approval End Date: The approval is valid for 3 years.

The application was approved subject to the following **conditions:**

Extensions Amendments:

If you propose to make an amendment to the research after approval or extend the study beyond the date of the approval expiry date given above, the Research Ethics Facilitators (research-ethics@qmul.ac.uk) should be contacted. The Facilitators will provide guidance about the notification required, the type of amendment and the process to be followed for further approval.

Annual Progress Report:

Annual Progress Reports must be submitted to research-ethics@qmul.ac.uk on the 12-month anniversary of the QMERC's approval letter and every year after that, until study completion.

Generic Approvals:

Where generic research ethics approval is granted, the responsible academic staff member should lead the review of the approval on the 12-month anniversary of the QMERC's approval letter to ensure there has been no significant changes and submit an Annual Progress Report to the QMERC. If significant changes are identified, a new generic ethics application should be submitted, but if not, the existing approval will remain and be renewed every three years.

Adverse Events:

In case of any unexpected or adverse events or deviations from the proposed protocol as per the original QMERC application, please contact the Research Ethics Facilitators at research-ethics@qmul.ac.uk within 5 days of the event.

Final Report:

When your study has finished, an End of Study Notification Form should be submitted to the QMERC at research-ethics@qmul.ac.uk (within 90 days of study completion).

Covid-19:

Approval for study issued as above but all aspects are subject to the QMERC temporary procedure in light of COVID-19 pandemic and the government advice on restrictions. As such, elements that involve face-to-face interaction or overseas travel must regularly check for, and follow, the latest guidance.

We wish you the best for your research.

Yours faithfully,

Mantalena Sotiriadou

Research Ethics Facilitator, on behalf of the Queen Mary Ethics of Research Committee

29/10/2020 v 0.1

Queen Mary University of London

Consent Form

Title of Research Study: Association between HRV and Cognitive performance using wearable technologies

Principal Investigator: Dr. Akram Alomainy

Queen Mary Ethics of Research Committee Ref: [QMERC20.210].

Thank you for your interest in this research.

Should you wish to participate in the study, please consider the following statements. Before signing the consent form, you should initial all or any of the statements that you agree with. Your signature confirms that you are willing to participate in this research, however you are reminded that you are free to withdraw your participation at any time.

Statement	**Please initial box**
1. I confirm that I have read the Participant Information Sheet dated 29/10/2020 version v 0.1 for the above study; or it has been read to me. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to stop taking part in the study at any time without giving any reason and without my rights being affected.	
3. I understand that my data will be accessed by the investigator.	
4. I understand that my data will be securely stored in password protected hard drive and in accordance with the data protection guidelines of the Queen Mary University of London until the graduating of the researcher in fully anonymized form.	
5. I understand that I can access the information I have provided and request destruction of that information at any time prior to the end of this year 2020. I	

understand that following to that date I will not be able to request withdrawal of the information I have provided.	
6. I understand that the researcher will not identify me in any publications and other study outputs using personal information obtained from this study.	
7. I understand that the information collected about me will be used to support other research in the future.	
8. I agree to be contacted about other research studies in the future.	
9. I agree to take part in the above study.	

Participants should read Queen Mary's privacy notice for research participants which contains important information about your personal data and your rights in this respect. If you have any questions relating to data protection, please contact Data Protection Officer, Queens' Building, Mile End Road, London, E1 4NS or data-protection@qmul.ac.uk or 020 7882 7596.

Participant name	Date	Signature
Name of person taking consent	Date	Signature

I Eaman Alharbi, confirm that I have carefully explained the nature, demands and any foreseeable risks (where applicable) of the proposed research to the participant and provided a copy of this form.

Principal Investigator (or Supervisor for student projects)
Akram Alomainy
a.alomainy@qmul.ac.uk

Student Investigator (if applicable)
Eaman Alharbi
e.alharbi@qmul.ac.uk

Queen Mary University of London

Participant Information Sheet

Study title

Association between HRV and Cognitive performance using wearable technologies

Version number and date

0.1 29.10.2020

Researcher's name

Eaman Alharbi supervised by Dr. Akram Alomainy

Queen Mary Ethics of Research Committee reference number: [QMERC20.210]

Invitation paragraph

We would like to invite you to be part of this research study, if you would like to. You should only agree to take part if you want to, it is entirely up to you. If you choose not to take part, there won't be any disadvantages for you, and you will hear no more about it.
Please read the following information carefully before you decide to take part; this will tell you why the research is being done and what you will be asked to do if you take part. Please ask if there is anything that is not clear or if you would like more information.
If you decide to take part, you will be asked to sign the consent form to say that you agree.
You are still free to withdraw at any time and without giving a reason.

What is the purpose of the study and what would taking part involve?

The purpose of this study is to examine whether measuring heart rate variability (HRV) with wearable devices and sensors can be used to predict the cognitive performance.

Preparation:

Before we acquire Heart rate measurement (HRV), we will ask you to fill out a pre-study questionnaire. This questionnaire contains questions about your coffee consumption, smoking and alcohol behaviour since those are factors which can influence your heart rate readings).

In preparation for the study, you will be asked to sanitize your hand as a precautious procedure due to covid-19. Then you will slip your finger onto CorSense device, and the ECG device.

Study:
If you decide to take part, the researcher will arrange for an appointment at Queen Mary University of London at time convenient to you.
Baseline Recording: You will be asked to sit comfortably in a quiet room for 6 minutes. This enables us to collect a sensor sample in a relaxed state.

Time Commitment
The study will last around 15 Minutes including introduction, preparation, and removal of the sensors in the end.

Why am I being invited?

You are being invited to participate in this research study because you are over the age of 50 and healthy or suspect to have Mild Cognitive Impairment (MCI).
You should not take part in this study if you have Significant cardiac problems, Pacemaker fitted or High blood pressure.

Do I have to take part?

This participant information sheet has been written to help you decide if you would like to take part. It is entirely up to you, you should only agree to take part if you want to. If you do decide to take part you will be free to withdraw at any time without needing to provide a reason, and with no penalties or detrimental effects.

What are the possible benefits of taking part?

Taking part in the study will support this PhD research that aims to further our understanding of associations between Heart rate Variability (HRV) and Cognitive function and how these finding can be used in detecting cognitive performance and might work as a biomarker in helping with Dementia research.

What are the possible disadvantages and risks of taking part?

We don't anticipate having any risks by participating in this experiment.

Expenses and payments

This study is unpaid.

What information about me will you be collecting?

We will be collecting Heart rate variability along with demographic information such as Age, Gender, education, smoking and alcohol consumption since those are factors which can influence your heart rate readings. Join Dementia will provide us with information such as the Mini–Mental State Examination (MMSE) test score.

How will my data be stored and who will have access to it?

Your data will be kept strictly confidential and will be stored in fully anonymised format. You will not be able to be identified or identifiable in any reports or publications. Any data collected about you will be stored on a password-protected hard drive and only the researcher will be able to access it.
Data Protection Policy
Information/Data Governance Policy – DG14 – Storage of information

When and how will my data be destroyed?

Your data will be erased through hard drive formatting upon graduating with PhD degree.

How will my data be used and shared?

The results of this study will be part of the PhD thesis that is connected to this research project. Results will be mentioned in a future conference or journal paper publication. All data is stored locally in an anonymised form and will not be accessible for or shared with others.

Research Data Access and Management Policy

Under what legal basis are you collecting this information?

- Queen Mary University of London **processes personal data** for research purposes in accordance with the lawful basis of 'public task'.

- Please read Queen Mary's privacy notice for research participants containing **important information about your personal data and your rights** in this respect.

- **If you have any questions** relating to data protection, please contact Queen Mary's Data Protection Officer, Queens' Building, Mile End Road, London, E1 4NS or data-protection@qmul.ac.uk or 020 7882 7596.

What will happen if I want to withdraw from this study?

You can withdraw from this study at any time without providing a reason. Withdrawing will have no disadvantage for you, and you will hear no more about this study. Your data will only be submitted if you complete the study.

Your data will be saved entirely anonymised and is not possible to link the data to a particular person. For this reason, it is however not possible to delete the data entry of a specific person.

What should I do if I have concerns about this study?

- If you have any concerns about the manner in which the study was conducted, in the first instance, please contact the researcher(s) responsible for the study Dr. Akram Alomainy(a.alomainy@qmul.ac.uk) .
- If you have a complaint which you feel you cannot discuss with the researchers then you should contact the Research Ethics Facilitators by e-mail: research-ethics@qmul.ac.uk.

- When contacting the Research Ethics Facilitators, please provide details of the study title, description of the study and QMERC reference number (where possible), the researcher(s) involved, and details of the complaint you wish to make.

Who can I contact if I have any questions about this study?

Dr. Akram Alomainy
a.alomainy@qmul.ac.uk

Eaman Alharbi
e.alharbi@qmul.ac.uk
07305672662

Queen Mary University of London

Surveys and Data Collection

Study title

Association between HRV and Cognitive performance using wearable technologies.

Questions

Age:

Gender:

What is the highest degree or level of school you have completed?

	Yes	No
1. Have you consumed any caffeine beverages in the past two hours?	○	○
2. Have you consumed any alcoholic beverages in the past 24 hours?	○	○
3. Do you usually smoke? If yes, please report the number of cigarettes you smoke on a daily basis.	○	○
4. Have you smoked in the past two hours?	○	○
5. Have you been clinically diagnosed with Mild Cognitive Impairment (MCI)? If yes, please state the year when you were first diagnosed	○	○

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