EXPLORING THE NEURAL CORRELATES OF BALANCE AND EXERCISE IN DEMENTIA

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ਸਤਿ ਨਾਮੁ ਕਰਤਾ ਪੁਰਖੁ ਨਿਰਭਉ ਨਿਰਵੈਰੁ ਅਕਾਲ ਮੂਰਤਿ ਅਜੂਨੀ ਸੈਭੰ ਗੁਰ ਪ੍ਰਸਾਦਿ ॥

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ਆਦਿ ਸਚੁ ਜੁਗਾਦਿ ਸਚੁ ॥ ਹੈ ਭੀ ਸਚੁ ਨਾਨਕ ਹੋਸੀ ਭੀ ਸਚੁ ॥1॥

I stand

on the sacrifices

of a million women before me

thinking

what can i do

to make this mountain taller

so the women after me

can see farther

Legacy – Rupi Kaur (1, p213) .

Abstract

Balance deficits in dementia are linked to increased falls risk, leading to injury, fear of falling, reduced activity, and loss of independence. Exercise based interventions can be useful in reducing falls risk as well as improving balance in older adults with cognitive impairments. The neural mechanisms involved in balance and exercise in this population are not well understood. The National Institute for Health Research (NIHR) funded Promoting Activity Independence and Stability in Early Dementia (PrAISED2) Randomised Controlled Trial (RCT), is trialling a tailored exercise programme aimed to promote activity, independence, and stability in older adults with Mild Cognitive Impairment (MCI) and mild dementia. This trial presented a unique opportunity to pilot a novel Virtual Reality (VR) based balance task and investigate the neural correlates of balance in older adults with MCI and dementia. To do this, I used functional Magnetic Resonance Imaging (fMRI) a non-invasive neuroimaging technique which detects haemodynamic changes associated with neural activity at rest or during experimental tasks.

The aims of this PhD were 1) conduct a systematic review of the effects of exercise on fMRI outcomes in older adults with MCI and dementia 2) pilot a novel virtual reality-based balance fMRI task in both healthy adults and older adults with MCI or dementia 3) explore activation in response to task conditions and the relationship with balance performance in people with dementia 4) explore the relationship between resting state functional connectivity and balance performance.

Through the systematic review, I identified 12 papers from 6 studies that met the inclusion criteria. Intervention duration ranged from 21-24 weeks and included aerobic training, walking, dancing, and mind-body exercises. No study that included people with dementia was found. Exercise interventions appeared to decrease task-related connectivity and activity during motor, memory, attention, and inhibition task but increased connectivity of the dorsal attention network (DAN), hippocampus and posterior cingulate at rest.

I then recruited healthy young adults aged 18-35 to take part in a pilot fMRI study of the VR balance task. Additionally, I piloted this task in a subset of participants recruited from the PrAISED RCT, who were all older adults aged 65 and over with a diagnosis of MCI or dementia. Both groups completed the MRI tolerability questionnaire and provided feedback on task experience. Both healthy volunteers and older adults with dementia scored overall scanner experience as 4/5 for comfortableness. In both groups, I conducted exploratory whole-brain analyses exploring activation in response to each task condition (walking, obstacle navigation and postural instability) and differences in activation between the conditions. Healthy young adults displayed activation in the cerebellum, visual and motor areas. Older adults with cognitive impairments displayed activation in visual and motor cortices across the task conditions.

In the pilot study with the PrAISED participants, I also explored the relationship between task-related activation in response to each condition (walking, obstacle navigation and postural instability) with performance on static and dynamic balance assessments. Static and dynamic balance performance was associated

with activation in motor regions during walking and instability conditions and the anterior cingulate cortex during the obstacle avoidance condition.

In addition to the task fMRI sequence, the participants also underwent a resting state fMRI scan. For the resting state fMRI data, I used a data-driven approach to identify common resting state networks. I explored the relationship between both intra and inter network connectivity with balance performance. Intra network connectivity of the limbic network may be associated with poorer dynamic balance performance whilst inter network connectivity between the visual network and sensorimotor network may be associated with improved dynamic balance performance.

Exercise can alter neural activity and connectivity in people with memory problems, however, future work needs to include people with more advanced dementia. Furthermore, future work should explore the optimal intensity and duration of exercise interventions to be of benefit to the patient. The work presented in this thesis has shown that participants with memory problems can engage with a VR-based task and scanning procedures in this population are well tolerated. VR based balance tasks are a promising technique to be able to improve our knowledge of the neural mechanisms involved in balance dysfunction in dementia, however further work is needed to ensure that the tasks are accessible to people with more severe cognitive impairments and functional limitations. Potential associations of intra and inter network functional connectivity with dynamic balance performance were noted, however, these did not reach statistical significance. Further investigation in larger

samples and study designs with participants with differing severity of cognitive impairments is warranted to explore these interactions further.

Conference presentations

Poster presentations:

Bajwa, R.K., Van der Wardt, V., Harwood, R.H. & Dineen, R.A. Using a virtual reality balance task to explore neural correlates of balance in older adults with dementia: A pilot fMRI study. Poster presentation at British Geriatric Society 23rd International Conference on Falls and Postural stability, September 2022, Nottingham UK.

Oral presentations:

Bajwa, R.K., Armugam, N., Van der Wardt, V., Harwood, R.H. & Dineen, R.A. A systematic review of exercise interventions and MRI outcomes in older adults with dementia or Mild Cognitive Impairment (MCI). Oral presentation at NIHR Nottingham Biomedical Research Centre Musculoskeletal theme virtual conference, January 2021, Nottingham, UK.

Declaration

Except where acknowledged, I declare that this thesis is entirely my own work and is based upon research carried out in the Division of Clinical Neuroscience, Unit 1 Mental health and Clinical Neuroscience, University of Nottingham, between February 2019 and November 2022. The material contained herein has not been presented, or is currently being presented, either wholly or in part of any other degree or qualification.

Rupinder Kaur Bajwa

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- COVID-19. The pandemic brought all my research to a complete stop, and I was never able to resume the work I initially planned. The pandemic has taught me a lot both professionally and personally. Doing a PhD during the pandemic has been a journey, not only professionally, but personally as well. I have learned a lot about myself, and what I value, and I am grateful for the lessons this experience has taught me. As we come out of the pandemic, I will take those lessons with me to build a better future.

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List of abbreviations

ACC	Anterior Cingulate Cortex
AD	Alzheimer's disease
AO	Action Observation
BBS	Berg Balance Scale
BRC	Biomedical Research Centre
CRN	Clinical Research Network
DAD	Disability Assessment in Dementia
DAN	Dorsal Attention Network
DMN	Default Mode Network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DLB	Dementia with Lewy bodies
EEG	Electroencephalogram
fMRI	Functional Magnetic Resonance Imaging
FNIRS	Functional Near Infrared Spectroscopy
FPN	Fronto-Parietal Network
FTD	Fronto-temporal lobe dementia
FWE	Family wise error
GLM	General linear model
ICA	Independent Components Analysis
MCI	Mild Cognitive Impairment
MI	Motor Imagery
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging

NEADL	Nottingham Extended Activities of Daily Living Scale
NHS	National Health Service
NIHR	National Institute of Health Research
NOS	Newcastle Ottawa Scale
PFC	Prefrontal Cortex
PGfAR	Programme Grants for Applied Research
PIVC	Parieto-Insula Vestibular Cortex
PMC	PreMotor Cortex
PrAISED	Promoting Activity Independence and Stability in Early Dementia and Mild Cognitive Impairment
PROSPERO	Prospective Register of Systematic Reviews
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
ROB	Risk of Bias
ROI	Region of Interest
rsfMRI	Resting-state functional Magnetic Resonance Imaging
RSN	Resting State Network
SMA	Supplementary Motor Area
SMN	Sensorimotor Network
SPM	Statistical Parametric Mapping
TAU	Treatment As Usual
tsfMRI	Task-based functional Magnetic Resonance Imaging
TUG	Timed Up and Go
UK	United Kingdom
VaD	Vascular Dementia
VR	Virtual Reality
WHO	World Health Organisation

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Part I: Introduction and Background

1. Introduction

1.1 Background to the problem

Developments in medicine and lifestyle have improved life expectancy across the world, with an average life expectancy of around 73.4 years (2). The World Health Organisation estimated that in 2020 there were around 1 billion people across the world aged 60 and over, projected to double by 2050 (3). In the UK the Office for National Statistics estimated that in 2015, 18% of the population were aged 65 and over, projecting that this will rise to 26% by 2041 (4).

Factors influencing population ageing include increased life expectancy due to declining mortality rates, declining fertility rates and migration (4,5). We are now living longer but may not necessarily be living healthier, as ageing is increase the risk of disease and disability (6,7). In England alone, Age UK estimates that around 7 million people aged 60 and over are living with two or more long-term conditions (8). Forty per cent of adults aged 65 and over have reported that their long-term conditions affect their abilities in activities of daily living and their quality of life (8). Long term conditions associated with ageing include hearing loss, cataracts, back pain, arthritis, chronic obstructive pulmonary disease (COPD), depression, diabetes, heart disease and neurodegenerative diseases (2).

The biological mechanisms involved in ageing are complex. As we age there is a gradual accumulation of molecular and cellular damage, while cell renewal rates slow leading to a general decline in organ function, health, and functional abilities (9–11). The biological changes due to ageing can underpin visual

impairments, hearing loss, memory deficits, slower information processing speed and musculoskeletal changes including decreased bone density, decreased muscle mass and changes in mobility; specifically, balance and gait (2). These age-related changes have been associated with an increased risk of falls and fall-related consequences including fear of falling, reduced activity, loss of independence, falls related fractures and hospitalisation (2).

Ageing is the biggest risk factor for cognitive decline, mild cognitive impairment (MCI) and dementia (12). MCI refers to the prodromal stage of dementia and is characterised by cognitive difficulties that are greater than expected for one's age, but not severe enough to affect daily life (13,14). One or two in every 10 people aged 65 and over in the UK may have MCI (15). MCI increases the risk of developing dementia with estimated progression rates of between 5-15% per annum (16). Dementia is a syndrome of progressive and irreversible loss of cognitive skills which affects daily activities (17). In addition to age, lifestyle factors and genetics can increase the risk of developing MCI and dementia (12,18).

The World Health Organisation ranked Alzheimer's disease and other dementias in the top ten causes of death globally in 2019 (19). In the UK it is estimated there are currently 944,000 people living with dementia (20). According to Alzheimer's Research UK, one in fourteen people aged 65 is at risk of dementia and rising to one in six people in people aged 80 and over (21). The cost of dementia in the UK is estimated to be around £34.7 billion and the cost of unpaid care provided by family members or friends is estimated to be around £13.9 billion (22).

People with MCI and dementia have an increased risk of falling compared to cognitively healthy older people (23,24) and consequently have a higher risk of fractures and poorer outcomes after fractures (25). Falls in older people with memory problems can also lead to loss of independence, fear of falling and a decrease in social, leisure and physical activities (24,26). The increased risk of falls is due to dementia-specific risk factors including type and severity of dementia, cognitive impairments, gait, and balance deficits (24). Falls cost the health service around £2.3 billion each year (27).

1.2 Problem statement

Current interventions aimed at improving balance dysfunction and prevention of falls in healthy older adults have been successful in improving balance and falls risk, however, these interventions appear to have mixed success for older adults with memory problems (28–33). Many of these studies used self-reported outcome measures which may not be sensitive enough to detect more subtle biological changes which may need to accumulate over time to be clinically relevant.

Neuroimaging techniques, particularly functional MRI (fMRI), are non-invasive and able to detect and measure changes in the brain that may not be clinically evident (34). Functional MRI also has the potential to inform the development of disease and treatment-specific biomarkers, providing additional objective outcomes for evaluating the efficacy of complex rehabilitation interventions for people with cognitive impairments.

To date little is known about how underlying brain activity involved in balance is altered in people with MCI and dementia. Research using fMRI tasks to study

neural correlates of balance and postural control in healthy populations, often use still images or get participants to physically do a task and then asks them to imagine it or use a screen to deliver a video (35,36). The tasks often involve complex instructions requiring an ability to retain and learn new information as well as recall instructions and tasks from memory. For older adults with cognitive impairments who may struggle to learn new information and have memory problems, such fMRI tasks are likely to be burdensome. To tackle this issue, a novel virtual reality (VR) based balance task, designed specifically for older adults with cognitive impairments was piloted. Additionally, research using resting-state fMRI investigating balance and exercise-related changes in connectivity in people with MCI and dementia is lacking. To address this knowledge gap, the evidence base for exercise related changes in functional connectivity in older adults with MCI and dementia was systematically reviewed. Resting-state fMRI was used to explore the relationship between the connectivity of resting state networks and balance in older adults with MCI and dementia.

1.3 Aims and objectives

The NIHR Programme Grants for Applied Research (PGfAR) funded Promoting Activity Independence and Stability in MCI and Early Dementia research programme has developed an exercise and functional activity-based intervention, specifically for older adults with cognitive impairments (37). This trial provided a unique opportunity to use functional MRI to study functional connectivity and activity related to balance and exercise in older adults with MCI and mild dementia.

The overarching aim of this thesis was to use the novel VR-based balance task and fMRI to explore the neural correlates of balance and review current evidence available about the neural correlates of exercise in older adults with MCI and dementia. To address this aim, the following objectives were proposed:

1. Conduct a systematic review investigating the effects of exercise interventions on fMRI outcomes in older adults with MCI and Dementia.
2. Trial a novel VR-based balance fMRI task in healthy young adults and older adults with MCI and Dementia.
3. Investigate the relationship between inter and intra network connectivity and physical performance on static and dynamic balance assessments in people with MCI and dementia.

1.4 Thesis structure

This thesis comprises of three parts. Part 1 consists of introductory and background information chapters. Part 2 presents a systematic literature review and the empirical studies conducted along with the results. Part 3 includes a general discussion and key conclusions from the work presented in this thesis.

1.4.1 Part I

In this chapter the aims and objectives of this thesis have been presented and an overview of the thesis structure is provided below.

Chapter 2 is split into three sections. Section 1 provides background information around the mechanics of postural control and discusses the evidence for the role of the cerebral cortex in maintaining postural control in various contexts and the limitation of some of the neuroimaging methods used. This section also looks at

the application of motor imagery and action observation tasks alongside fMRI to explore neural correlates of postural control and introduces virtual reality as an alternative, more accessible technique to explore cerebral activation involved in postural control in more life-like scenarios.

Section 2 of chapter 2 presents key information around the prevalence, risk factors, neuropathology and symptoms of mild cognitive impairment and dementia. This section then focused on executive dysfunction in dementia and explores the link between executive function, postural instability and falls in this population. Finally, section 3 of chapter 2 describes the benefits of exercise in the general population, ageing and dementia. This section also discusses the potential neuroprotective effects of exercise in older populations with and without cognitive impairments. Finally, the section provides an overview of the PrAISED intervention and RCT, around which the work presented in this thesis was conducted.

Chapter 3 describes the principles of the MR signal, fMRI, and fMRI task design. This chapter also discusses both clinical and research applications of MRI and fMRI in dementia.

1.4.2 Part II

Chapter 4 addresses objective 1. In this chapter systematic review methodology was used to identify research studies investigating the effects of exercise on task-based or resting-state fMRI outcomes in older adults with MCI or dementia. Additionally, I conducted a narrative synthesis and presented the findings based on fMRI outcome type; resting state or task based.

Chapter 5 contributes toward addressing objective 2. This chapter referred to the pilot study of the VR balance task in healthy young adults. Survey data on MRI tolerability, task experience and fMRI data collected from piloting the fMRI task in this group is included here.

Chapter 6 also contributes toward objective 2. This chapter comprised of a pilot study of the fMRI task in older adults with MCI and dementia, recruited from the PrAISED RCT. Survey data on MRI tolerability and task experience for this group is included here. Additionally, exploratory whole-brain analysis of task fMRI data collected from the PrAISED cohort is presented. Finally, in this chapter, the relationship between activation in balance related regions of interest and balance assessment performance, and whether executive function mediates this relationship is explored.

Chapter 7 addresses objective 3. This chapter included resting state fMRI data collected from the PrAISED cohort. Independent Component Analysis (ICA) was used to identify components corresponding to large-scale networks. This chapter also explored the relationship between Intra and inter-network connectivity with balance assessment performance.

1.4.3 Part III

Chapter 8 provides an overview of the initial thesis aims and objectives, prior to the COVID-19 pandemic. This chapter also presents an overview of the COVID-19 pandemic, related lockdowns, and restrictions in the UK, the impact on research more generally, the population of interest, as well as the impact on the PrAISED RCT and the initial objectives of this thesis. Recent findings on risk factors for COVID-19-related adverse outcomes, the disproportionate effect of the virus and

pandemic-related restrictions on the patient population of interest are presented and the impact of these on the initial thesis objectives is discussed. Adaptations made to the thesis considering the ongoing pandemic are described and the present thesis aims and objectives are summarised. The key findings from the previous chapters are summarised and the results are discussed. Finally, this chapter discusses the strengths and limitations of the studies included in this thesis, the recommendations for future research and summarises the key conclusions from this body of work.

2. Background

2.1 The role of the cerebral cortex in postural control

Over the last 15,000 years, human beings have evolved rapidly from hunter-gatherers to building villages, towns, and cities and developing complex language systems and social structures. Though perhaps not one of the most glamorous, the most fundamental development of human evolution, beginning around 4 million years ago, was that of bipedalism. Humans have evolved to use bipedalism as the primary form of movement, this involves standing upright, walking, and running (38–40). To execute these forms of movement, balance or postural control is required. Being able to regulate and maintain balance whilst standing, walking, or running is key to being able to engage in activities of daily living (40).

The term balance is often used in association with postural control and stability. In line with Newton's first law of motion, the mechanical definition of balance is the state of an object when the forces acting upon it are zero (41). The ability of an object to be able to balance in a static situation depends on the position of the centre of mass (COM) or centre of gravity (COG) and the area of the base of support (BOS). If the COG falls within the BOS, then the object is balanced. If the COG, falls outside of the BOS, then the object is unbalanced. Stability or instability is related to the amount of displacement of the COG or external force that can be applied before an object becomes unbalanced. If an object is unable to withstand greater displacements of COG or greater amounts of external force, then it is said to be unstable (41).

The human body has a relatively high COG and a very small BOS. When the COG falls outside of BOS, humans have an innate ability to anticipate or detect a threat to stability and use muscular activity to counteract the effects of gravity and prevent falling, this is referred to as postural control. Postural control is defined as one's ability to maintain their centre of gravity within their base of support during quiet standing or movement (41). Static postural control involves maintaining COG over BOS during a fixed position such as sitting or standing (38). Dynamic postural control involves maintaining postural stability during movement such as walking or running by transferring the COG forward over the BOS with each step or anticipating and controlling brief moments of instability such as during running (42).

2.1.1 Mechanical models of postural control

Postural control can be divided into three main areas of activity: (i) maintenance of posture e.g., sitting or standing, (ii) voluntary movement between postures (going from sitting to standing) and (iii) reacting to external disturbance or perturbations (e.g. slips or trips) (41). Postural control strategies can be either predictive, reactive or a combination of both (40,41). Reactive strategies are employed in response to unexpected perturbations such as slip, trip, or push, whilst predictive strategies are employed when postural instability is anticipated or planned.

There are two groups of movement strategies used to regain and maintain balance; fixed support strategies and change in support strategies (see Fig. 2.1(43,44).) Fixed support strategies, refer to the ankle or hip strategy and involve keeping the feet in place. The former is based on the inverted pendulum

model which views the body as one large link that rotates around the ankle joint. The ankle strategy is employed to respond to a low level perturbation such as sway, which involves adjustments from ankle joints and muscles to bring COG back within the centre of the BOS. The latter, the hip strategy is employed for larger and faster perturbations. This strategy involves knee and hip joints and surrounding muscles to regain balance control and prevent a fall (43). Change in support strategies involves stepping or reaching to maintain balance. The stepping strategy is used when perturbation causes COG to be displaced from BOS. It involves stepping out to increase BOS so that the COG remains within the BOS and balance is restored. The reaching strategy involves reaching out to try and bring the COG back within the BOS (43).

Biomechanical explanations of postural control such as the inverted pendulum model view the body as a single link and explain postural control as a series of reflexes in response to perturbations (38). This view is limited in its explanation of postural control during stance and locomotion and does not consider that a body moves more like a multi-link structure, where each component is able to move to some degree (45). It also fails to acknowledge the role of neurophysiological and multisensory systems.

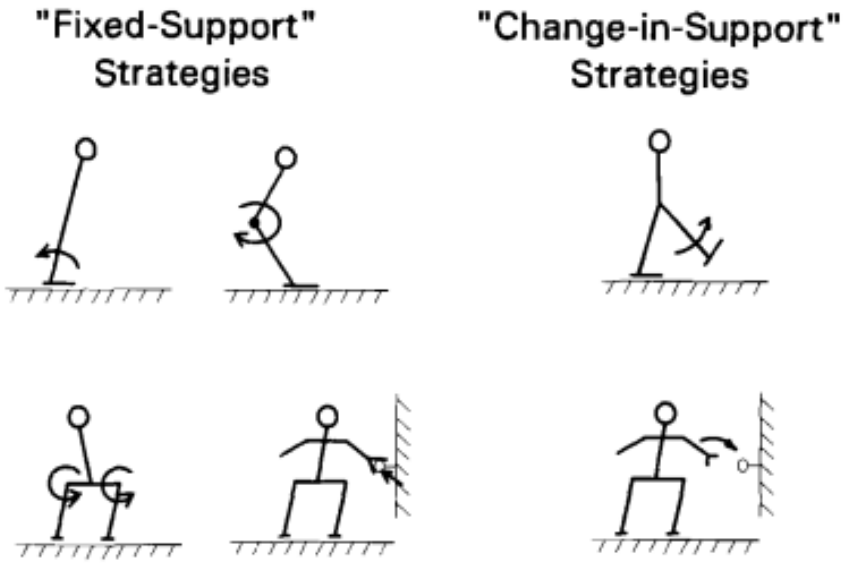

Figure 2. 1 Diagram of support strategies from Maki and McIlroy (1997)

2.1.2 Multisystem integration in postural control

Postural control during static and dynamic movements can become more effective with practice (41), therefore postural control is not solely a reflex but is more of a motor skill involving the integration of multisensory (visual, vestibular, somatosensory) information to produce appropriate motor outputs in response to gravitational and environmental forces (43,46,47). The central nervous system (CNS), made up of the spinal cord and brain, acts as the central hub, integrating sensory input to assess postural stability and generate motor output to maintain, anticipate or react to threats to postural stability (40,42,46,48).

2.1.3 Role of the cerebral cortex in postural control

2.1.3.1 Indirect evidence

Previously postural control was thought to be an automatic process or a reflex, controlled by the spinal cord, brainstem and subcortical structures (49). These explanations of postural control were based on animal studies which found

postural control reflexes to be intact in the presence of spinal and hindbrain injury (50). Humans are bipeds, walking and maintaining an upright posture, thus the animal models were not able to capture the complexity involved in human postural control and gait (51–53).

Studies in humans with brain lesions or brain injury have shown that various cortical and subcortical regions play a key role in maintaining postural stability. Studies of patients with traumatic brain injury have observed altered postural control due to the injury (54,55). Repeated concussion has also been linked to postural control deficits (56,57). Studies of patients after a stroke provide further support for the role of the cerebral cortex in postural control (58,59).

Researchers have also applied dual-tasking paradigms to investigate whether increasing cognitive load can alter postural stability in healthy, ageing and clinical populations (60). Dual tasking involves completing two tasks simultaneously, for example walking while talking or completing a cognitive task such as counting backwards in threes whilst walking. Dual or multi-tasking increases attentional demands as both tasks compete for resources. When the demand for resources outstrips available resources the performance of both tasks is impaired. This can manifest as walking more slowly, counting more slowly or making errors whilst counting (61,62).

As we age our postural control abilities and the ability to switch our attention effectively to meet multiple task demands at the same time begins to decline. Studies exploring the effects of dual-tasking on postural stability have found altered postural control in healthy younger and older adults, as well as older adults with Parkinson's disease, MCI and dementia (61,63,64). In dual-tasking

situations that involved a mental and walking task, older adults displayed changes in various gait characteristics including gait speed and cadence (62,65). These studies indicated maintaining postural stability requires the integration of motor and cognitive networks, further evidencing the of role of cerebral cortex in postural control (66).

Postural instability is a part of normal ageing and a common symptom in neurodegenerative diseases such as Parkinson's disease and dementia. Ageing is associated with brain atrophy within the caudate, cerebellum, hippocampus and prefrontal areas (67). Neuropathology relating to neurodegenerative diseases such as dementia is also present across the cerebral cortex (68). A systematic review by Khaya et al. (69) explored brain activity during balance in age-related neurodegenerative conditions. They found older adults with and without neurodegenerative diseases displayed increased activation of the prefrontal cortex during dual tasking compared to younger adults. These findings provide further evidence that the cerebral cortex plays an important role in maintaining balance.

2.1.3.2 Direct evidence

The application of neuroimaging and neurophysiological techniques such as functional near-infrared spectroscopy (FNIRS) and electroencephalography (EEG) have provided direct evidence of cortical involvement in postural stability (70). Studies using balance tasks with differing degrees of complexity and postural control demand have found that as the task complexity or postural demands increase, activity within frontal, parietal, central and occipital regions is increased (71–73). Goel et al. (74) used transcranial magnetic stimulation (TMS)

to create a virtual lesion within the supplementary motor area and explore changes in balance abilities. They reported the group who underwent TMS showed increased low gamma activation in the anterior cingulate, cingulate gyrus and posterior parietal regions and the increased activation across these regions increased in line with task complexity. These findings indicate that the frontoparietal regions may be part of a network that is able to inform postural response strategies to perturbations or balance challenging tasks.

FNIRS has been used to explore changes in haemodynamic activity during balance challenging tasks. Chen et al. (75) found increased haemodynamic activity within the prefrontal cortex during walking with and without obstacle navigation or walking while talking with and without obstacle navigation in older adults. Increased activity in PFC was noted during walking while talking, with and without obstacle navigation, compared to walking conditions. Additionally, older adults with slower gait showed increased PFC activity during both walking and walking while talking with obstacle navigation compared to without obstacle navigation (75).

2.1.4 Exploring functional neural correlates of balance using action observation, motor imagery and fMRI

2.1.4.1 Motor imagery

Motor imagery is a mental task that involves imagining a motor-based movement or action, without physically engaging in the execution of a task (76–78). It can involve imagining a movement from memory or imagining the future execution of movements. Motor imagery involves activating brain regions involved in the planning and execution of a movement whilst voluntarily inhibiting motor

output. Mechanisms of motor imagery are explained by the motor simulation theory (78). According to this theory, actions are held in a covert stage where they are mentally simulated (76). Imagined and executed actions share motor representation of an intention to act, however in motor imagery the intention to act is not converted into motor output (76,77). Neuroimaging studies have found that motor imagery and motor execution share common neural pathways (36,79). Activation-likelihood estimation meta-analysis found that motor imagery recruits a frontoparietal network as well as subcortical (basal ganglia, putamen, pallidum) and cerebellar regions (80). A more recent systematic review and meta-analysis also found motor imagery recruited a frontoparietal network, and motor imagery tasks recruited more brain regions that are often involved in the actual movement (81).

2.1.4.2 Action observation

Action observation involves observing someone else perform an action or behaviour. The mirror neuron system plays a key role in action observation (82). Rizzolatti et al. (83), first discovered mirror neurons when investigating grasp response in macaques. They found the premotor cortex was activated both when performing a motor task and when observing the motor task being performed. The mirror neuron system is associated with understanding the actions and emotions of others, as this system can invoke similar responses internally to what the individual observes in others(82,83). Mirror neurons play a key role in observational learning and imitation(76,82). Similar to motor imagery, action observation tasks also recruit the frontal, parietal and motor regions (81,84,85).

2.1.4.3 Current applications of motor imagery and action observation

Motor imagery and action observation have been applied to a variety of contexts including sports performance, Parkinson's disease, and stroke rehabilitation (86–92). Motor imagery and action observation have been used to study neural activity during motor control tasks and whole-body movements such as walking, standing, running, and balancing/postural control using imaging techniques such as EEG and FNIRS (93). FNIRS and EEG have enabled researchers to uncover the potential role of cerebral regions in maintaining balance. These neuroimaging techniques are portable and enable researchers to study near to real-time changes in cerebral blood flow and brain activity during balance tasks. However, these techniques have poor spatial resolution and can only measure activity a few centimetres deep into the cortex.

In comparison, fMRI has superior spatial resolution and can acquire a whole brain volume image in under 2 seconds. However, fMRI is sensitive to movement and MRI scanners are not portable machines, which means it is not possible to use this type of imaging during actual movement or balance tasks. Task fMRI involves completing mental tasks such as the Stroop test whilst undergoing an fMRI scan and have been widely used to study brain activity involved in a range of cognitive processes. Task fMRI combined with motor imagery is one-way researchers can overcome movement limitation issues of MRI scanners (36).

Researchers have begun to employ motor imagery and action observation principles to create balance and whole movement-based tasks that do not require motor output whilst in the MRI scanner, allowing the use of fMRI imaging to explore neural correlates of limb movements, whole body movements such as

gait and postural stability (35,94). Studies using these tasks often require participants to practice the task in real life prior to undergoing an MRI scan and then imagining themselves completing the same task whilst in the scanner (36,95,96). Some studies have combined these tasks with plantar simulation platforms, to enable the simulation of perturbations to challenge postural control (97,97–99).

2.1.4.4 Limitations of motor imagery and action observation tasks

Motor imagery tasks often involve recalling a complex movement from the memory of completing the task prior to the scan, or generally from memory of completing the task in day-to-day life. Action observation can often be used in conjunction with motor imagery and these tasks can involve observing an image or video prompt of the task and trying to recall it from memory. Motor imagery tasks are also combined with gait or balance simulation platforms. The types of tasks usually involve complex instructions that the participant needs to learn, retain, and recall when in the scanner. For older adults with memory problems, learning and retaining new information, combined with memory impairment means these types of tasks are likely to be not achievable and burdensome. Developing new types of tasks that are less burdensome for older adults with memory problems is needed to be able to explore the neural correlates of balance in a population where postural instability can lead to falls and falls related adverse outcomes. The use of virtual reality (VR) technology to create an immersive experience may be more accessible and engaging for people with memory problems and is discussed in more detail in the next section (see 2.1.6).

2.1.5 Virtual reality as an alternative to motor imagery and action observation

2.1.5.1 What is virtual reality?

VR is a popular technology amongst gamers and is becoming popular in medicine, healthcare education and research (100,101). VR involves interacting with a computer designed virtual reality environment. There are three types of virtual reality simulations, non-immersive, semi-immersive or fully immersive. Non-immersive VR environments involve interacting with a virtual environment whilst sitting in a physical space. Examples of non-immersive virtual reality include video games using consoles such as the PlayStation, Nintendo Wii, and Xbox. Semi-immersive virtual reality gives the users a perception of a different environment whilst they are still in their real-world surroundings. This type of VR is often used in education and training such as cockpit simulators used for pilot training. Fully immersive virtual reality is the most realistic simulation of a virtual environment of the three types of VR. It usually involves wearing goggles or a headset and headphones, to create a more immersive sensory experience, which transports the individual to the virtual environment in which they can interact with their virtual surroundings (102).

2.1.5.2 Current applications of virtual reality

VR is being trialled in medical education, to train surgeons and simulate real-life clinical experiences for medical students (100,101,103). VR is being applied in research environments to understand health, and behaviour and develop novel interventions for a range of conditions. VR has also been used to study pain perception. A recent study found that VR was able to alter pain perception in paediatric burns patients (104). VR has also been used in psychiatry practice and

research to treat a range of conditions including phobias, depression, eating disorders and post-traumatic stress disorder (102,105).

VR based interventions have been trialled in rehabilitation settings for stroke and Parkinson's disease. Stroke rehabilitation RCTs have reported improvements in upper limb function in response to VR based therapy (102,106). A meta-analysis of VR therapy for upper limb rehabilitation in stroke also reported significant improvements in recovery of upper limb function (107). VR training for cognitive rehabilitation in stroke has resulted in significant improvements across various cognitive domains, including memory, executive function, and visuospatial skills (108). In Parkinson's disease, VR therapy has been successful in improving outcomes for balance and gait deficits (109). VR has also been used in cognitive training interventions to improve cognitive impairments in people with MCI and dementia (110,111)

Neuroscience research is increasingly using VR to study neural correlates of behaviour, cognition and social interactions (112,113). VR can create virtual environments that are highly realistic while retaining high levels of experimental control (114). Furthermore, VR may simulate a brain response in the virtual environment that is like what would occur in the real world, while brain activity is being monitored via imaging methods such as fMRI (112,114,115).

VR may be able to provide an alternative to motor imagery and action observation tasks (116). fMRI studies have found that VR tasks may engage more of the sensorimotor systems compared to simple stimuli and be able to overcome the issue of individual differences observed in motor imagery ability and neural activation (112,117). Additionally, for older adults with cognitive

impairments, VR tasks may be easier to comprehend and engage with compared to motor imagery and action observation tasks which often have complex instructions, requiring participants to rely on remembering task instructions and movements.

2.2 Dementia, executive function, and postural control

The term 'dementia' has its origins in Latin and means a 'state out of mind' (118). The notion of cognitive decline in the elderly and dementia has been around for centuries and was acknowledged within Ancient Egyptian, Greek and Roman civilisations (119). Dementia is a syndrome of chronic and progressive deterioration of cognitive abilities which interferes with daily life (120). There are estimated to be around 200 different types of dementia. In the UK the most common types of dementia are Alzheimer's disease accounting for 60 to 70% of cases, vascular dementia accounting for 15 to 20% of the cases and mixed dementia (a combination of Alzheimer's disease and vascular dementia) accounting for 10 to 15% of the cases (121).

2.2.1 Risk factors for cognitive decline and dementia

In addition to ageing, research has identified various risk factors which may increase one's risk of developing dementia. Pre-existing health conditions such as heart disease, stroke and depression have been linked to an increased risk of dementia in later life (12,122). Specific cardiovascular risk factors such as hypertension, hyperlipidaemia, type 2 diabetes and obesity have also been shown to increase the risk of dementia (12,18,122). In addition to health, lifestyle factors may also contribute to dementia risk. Research has shown that poor diet, sedentary lifestyle, smoking, increased alcohol consumption, reduced

social engagement and level of education may all contribute to increased risk of cognitive decline and dementia (12,18,122). Genetics can also increase the risk of dementia. Several gene variants increase the risk of certain dementia subtypes. For instance, the Apolipoprotein (APOE) e4 allele has been associated with an increased risk for AD (18). Recent work has shown that area-level deprivation and ethnicity are also associated with dementia risk, with those from more deprived areas in the UK or from black or south Asian communities at higher risk of developing dementia compared to those from a white background (123).

2.2.2 Preclinical dementia and MCI

2.2.2.1 Preclinical dementia

The preclinical stage of dementia is when disease pathology is present, but no symptoms are present or detectable. This stage of dementia is usually only identified and used in research settings to track disease progression. Some studies have highlighted that the preclinical stage of dementia can be detected up to 10 years before the onset of clinically measurable symptoms (124).

2.2.2.2 Mild Cognitive Impairment

Mild Cognitive Impairment is characterised by noticeable cognitive decline, worse than expected for the individuals' age but not severe enough to disrupt activities of daily living (13,14,125). It is estimated between 5-15% of people living with MCI go on to develop dementia each year (16). There are two subtypes of MCI: amnestic and non-amnestic. For the former, memory deficits are a key feature, where this is the only complaint, it is often referred to as single domain amnestic MCI. Where the memory deficits are accompanied by other cognitive deficits such as executive dysfunction and attention, then it is referred

to as multiple domain amnestic MCI. For the latter, non-amnestic MCI, memory is usually preserved and cognitive decline is noted in one (single domain) or multiple (multiple domain) areas (14,126). The underlying pathology of amnestic MCI is often due to Alzheimer's disease, whereas vascular dementia, frontotemporal lobe dementia and dementia with Lewy bodies pathology may cause non-amnestic MCI (14,126).

Mild cognitive impairment is sometimes referred to as pre-dementia or the prodromal stage of dementia. Though it is important to note that not all people diagnosed with MCI experience the progression to dementia. A cohort study followed a group of older adults with MCI over a 7 year period and found 53% of participants enrolled in the study had non-progressive MCI, whilst 35% of participants had reverted back to normal cognition (127). Studies using fMRI to explore differences in functional connectivity in progressive and non-progressive MCI have noted differences in activation of dorsal and ventral pathways as well as altered connectivity in key regions such as temporal cortices, inferior parietal lobule and occipital gyrus in people with progressive MCI when compared to those with stable MCI (128,129). A more recent cross-sectional study comparing functional connectivity in default mode network, frontoparietal network and sensorimotor network in those with progressive MCI, non-progressive MCI and healthy controls found reduced connectivity in default mode network and FPN in those with progressive MCI but not in non-progressive MCI (130). These studies suggest that there may be differences in MCI neuropathology between those who go on to develop dementia and those who do not which may skew the outcomes of imaging studies and intervention

efficacy outcomes as those with non-progressive MCI may not possess the same underlying pathology and experience the same deterioration of symptoms as those with progressive MCI,

2.2.3 Neuropathology

2.2.3.1 Alzheimer's disease

Alois Alzheimer, a German Psychiatrist and Neuropathologist was the first to discover what we now call Alzheimer's disease (AD). He conducted a post-mortem histological examination of the brain of a woman with early-onset dementia and discovered microscopic lesions caused by plaques and neurofibrillary tangles (NFTs), widely recognised as hallmarks of Alzheimer's disease (68,131). Since Alois Alzheimer's discovery in the early 1900's research has identified the formation of extracellular plaques as a result of pathological accumulation of beta-amyloid proteins and intracellular NFTs are a result of pathological accumulation of tau protein (68,131). These plaques and NFTs lead to the loss of neurons and synapses leading to structural changes and loss of functional connectivity. The structural, functional, and chemical changes occurring due to the accumulation of the proteins in the brain, give rise to the symptoms of cognitive and functional decline seen in AD (68,131).

Braak and Braak (132,133) conducted a post-mortem study examining amyloid deposits and neurofibrillary changes in brains of individuals with and without dementia. Through this study, the researchers noted that the spread NFTs appeared to follow a predictable pattern, which led to the development of the Braak and Braak staging system of AD related changes (132,133). In stages 1-2 lesions are usually noted in the trans-entorhinal regions, including the

subcortical nuclei and locus coeruleus, extending out to the entorhinal regions. In stages 3-4, lesions from stage 2 become more severe and lesions begin to develop in the neocortex of the fusiform and lingual gyri. In stages 5-6 the spread of pathology is more diffused across frontal, superolateral and occipital regions, reaching primary and secondary neocortical areas (133,134) (see figure 1).

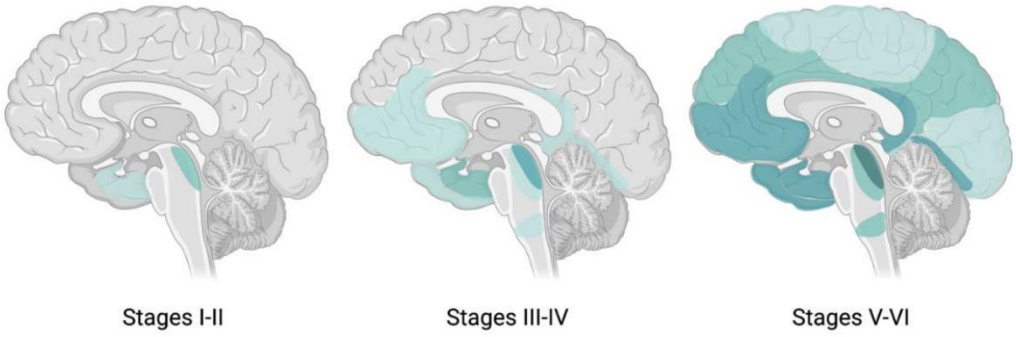

Figure 2. 2 Braak and Braak staging of AD pathology from van Oostveen et al. (2021).

2.2.3.2 Vascular dementia

Vascular Dementia (VaD) is characterised by cerebrovascular lesions caused by a range of disorders and degeneration of blood vessels in the brain including atherosclerosis, small vessel disease, and cerebral amyloid angiopathy. Atherosclerosis is the degeneration of medium and larger cerebral arteries and can lead to a range of infarcts. Small vessel disease refers to the degeneration of small cerebral arteries and can lead to microbleeds. Cerebral amyloid angiopathy involves deposits of amyloid beta proteins in the blood vessel walls, affecting cerebral blood flow and causing ruptures of blood vessels, microbleeds and micro-infarcts (135). Risk factors for VaD include hypertension, high cholesterol, diabetes, obesity, and physical inactivity (135,136).

2.2.3.3 Fronto-temporal lobe dementia

First described by Pick in 1982 and once referred to as Pick's disease, fronto-temporal dementia encompasses a spectrum of disorders including behavioural variant FTD, semantic and non-fluent primary progressive aphasia (137). In FTD, atrophy occurs in the frontal and temporal lobes, whereas in AD cerebral atrophy is more widespread (137).

2.2.3.4 Dementia with Lewy bodies

Key pathological features of dementia with Lewy bodies (DLB) include the accumulation of proteins forming Lewy bodies within brain cells and the discolouration and depigmentation of the substantia nigra and locus coeruleus (68).

2.2.3.5 Diagnosing dementia type

In the UK, to diagnose dementia, The National Institute for clinical excellence (NICE) guidelines advise that a full history of symptoms should be sought from the individual and someone close to the individual. Neuropsychological assessments should be administered to assess cognitive abilities and a neurological examination, and where appropriate, structural imaging (see section 3.3) should be used to rule out reversible causes of cognitive decline (138). NICE also advise that further testing to diagnose dementia subtype should only be considered when knowing the dementia subtype would affect disease management. Further testing can include a verbal episodic memory assessment when Alzheimer's disease is suspected. Cerebrospinal fluid testing for tau or amyloid beta can also be conducted to check for Alzheimer's disease. Additionally, FDG-PET or perfusion SPECT imaging can be used to distinguish

between Alzheimer's disease, fronto-temporal dementia and dementia with Lewy bodies (138). For vascular dementia, MRI should be used to support diagnosis (see section 3.3).

2.2.4 Symptoms of dementia

2.2.4.1 Non-cognitive symptoms

Nearly all people living with dementia will experience behavioural and psychological symptoms to some degree during the course of the disease, however, symptom presentation will differ between individuals, type and severity of dementia (139,140). Behavioural and psychological symptoms of dementia or neuropsychiatric symptoms can include low mood, depression, anxiety, aggression, agitation, irritability, apathy, disinhibition, delusions, hallucinations and changes in sleep or appetite (140,141). These symptoms can increase distress and lead to a poorer quality of life for both the person with dementia and their carer and have been associated with increased carer burden (140,142).

2.2.4.2 Cognitive symptoms

Cognitive symptoms of dementia vary between individuals and dementia subtypes. Memory impairments are usually the first and the most commonly reported symptom and present as being unable to learn and retain new information, also referred to as episodic memory impairment (143). In addition to episodic memory, impairments have also been noted in working memory and semantic memory (143,144). Impairments in visuospatial skills have also been noted in dementia and can manifest as difficulties in the perception of objects in space or being able to navigate to a familiar location such as home (143,144).

Other symptoms of dementia include aphasia, apraxia, agnosia, and executive dysfunction (17). Poorer performance on executive function measures have been associated with poorer balance and slower gait speed in healthy older adults (145,146). Symptoms of executive dysfunction, a key feature of dementia, are of interest to the work presented in this thesis as research has found a link with increased postural instability (147). Research exploring the link between executive dysfunction and postural instability in dementia is discussed in more detail in the next section (see 2.2.6).

2.2.5 Executive function

2.2.5.1 What is executive function?

Executive function (also referred to as executive control or cognitive control) refers to a set of top-down processes such as attention, problem-solving, planning, reasoning, organisation, emotion, and self-regulation. We rely on these skills every day to learn, work and manage daily life (148,149). There are three core areas of executive function: working memory, cognitive flexibility and inhibitory control (148,149).

2.2.5.2 Assessment of executive functions

A wide range of neuropsychological tests have been developed to assess different cognitive abilities underpinning executive function and are routinely used in research and clinical practice. Tests such as the forward and backward digit span test, CORSI block test, and CANTAB spatial span test are used to assess working memory abilities (148,150). The Stroop task, Erickson flanker task and go-no-go tasks measure inhibitory control (148). Cognitive flexibility can involve 'thinking

outside the box' and can be assessed using verbal or semantic fluency tests, Wisconsin card sorting task and task switching tasks (148).

2.2.5.3 Executive dysfunction in dementia

Executive function undergoes rapid development during childhood, peaking in early adulthood and beginning to decline in later life (151). Working memory abilities, planning, cognitive flexibility and inhibitory control abilities begin to decline from 30-40 years of age and continue to decline with age (18,151–153). Changes in executive function abilities that are worse than expected for an individual's age and severe enough to affect functional abilities are a core feature of dementia. Deficits in working memory, attention, response inhibition and task switching have been noted in older adults with MCI when compared with healthy controls (154–156). A systematic review and meta-analysis of executive function impairment in MCI found that cognitive flexibility and inhibitory control were impaired in older adults with MCI when compared with healthy controls (157).

The pattern of executive dysfunction may differ based on MCI and dementia subtypes. Brandt et al. (155) investigated whether impairments in specific executive function domains were associated with specific subtypes of MCI. Multi-domain MCI had more significant impairments in planning/problem solving and working memory compared to single-domain MCI participants. Working memory deficits appear to be a common feature of AD and vascular dementia (158). Impairments in attention, response inhibition and set shifting are common in FTD (159). fMRI has also been used to explore differences in neural activation during an attention-based task in patients with AD, DLB and Parkinson's disease compared with healthy older adults. All groups recruited a fronto-parietal-

occipital network during the task. The AD and DLB groups had slower reaction times during incongruent trials and greater activation of fronto-parietal-occipital network compared to those with Parkinson's disease and healthy controls (160).

2.2.5.4 Postural instability, falls and executive dysfunction in dementia

Older adults with dementia are at an increased risk of falls and related adverse outcomes. The increased risk of falls is attributed to dementia specific risk factors including dementia type, severity and increased postural instability. Once thought to be a marker of advanced disease, accumulating evidence suggests the inverse; postural instability is likely to be an early marker of the disease (161,162). Reviews of falls risk factors in the early stages of dementia found impairments in standing balance and postural sway are associated with an increased risk of falls (147,163,164).

Studies have explored the relationship between cognition and postural stability across the spectrum of normal ageing and cognitive impairment in later life. Older adults with MCI were found to display greater postural sway compared to healthy older adults (165). Increasing executive dysfunction and overall cognitive impairment have been associated with deterioration in all measures of balance (166). A prospective cohort study in older adults with mild and moderate cognitive impairment found greater executive dysfunction, increased postural sway and slower reaction times were significantly associated with increased falls risk (167). Those with greater executive dysfunction were 1.5 times more likely to fall (167). Hunter et al. (168) explored the association between executive function, visual acuity and balance in young adults, older adults, and older adults with AD. They found executive function and balance

declined with age, especially in the AD group. Additionally, poorer executive dysfunction was associated with balance control deficits.

2.3 Exercise and dementia

2.3.1 World Health Organisation recommendations

Being active is an essential part of a healthy lifestyle for all ages. The World Health Organisation recommends that adults and older adults should spend between 150-300 minutes per week engaging in moderate-intensity aerobic activity or spend between 75-150 minutes engaging in vigorous intensity activity per week and also spend 2 or more days per week doing muscle strengthening exercise that involve all major muscle groups (169,170). Physical activity is any activity that requires bodily movement and energy expenditure e.g., working, playing, housework, travelling, or engaging in recreational activities. Exercise is a subcategory of physical activity that involves planned, structured and repetitive movements that aim to maintain or improve one more area of physical fitness (171,172).

2.3.2 General benefits of exercise

The benefits of physical activity and exercise in the general population have been well established, from improving emotional wellbeing, mood, self-esteem, mental health and cognition (172–175), to weight management (172,173). Regular exercise can improve physical health such as muscle mass and bone health (176). Regular physical activity can also improve balance and mobility, whilst reducing the risk of falls (177). Leading an active lifestyle can reduce the risk of developing non-communicable diseases such as type 2 diabetes, osteoarthritis, cancer, heart disease, stroke and depression (175,178).

2.3.3 Exercise in later life

An active lifestyle throughout mid to later life can have protective benefits during the ageing process and may delay cognitive decline. A study by Chapman et al. (179) reported improvements in immediate and delayed recall memory performance, perceived exertion and cardiorespiratory fitness in middle aged and older adults assigned to an exercise intervention. Studies of sedentary healthy older adults who embark on an exercise programme have reported small improvements in cognitive function as a result, which suggests lifestyle changes in later life can be beneficial (12).

Exercise and regular physical activity in later life may be associated with lower risk of cognitive decline and developing dementia (174). Longitudinal studies have found that older adults who are physically active show less cognitive decline over two-year and ten-year follow up periods (180). Another large, multinational, longitudinal study (The LADIS study) of older adults with differing degrees of cognitive impairments and differing dementia subtypes explored whether physical activity could impact the progression of cognitive decline and dementia. They reported that physical activity over time was associated with reduced risk for cognitive impairment and dementia (181).

A systematic review of longitudinal studies found physically active people have a lower risk of developing cognitive impairment and have a higher cognitive ability score. The review also reported that low intensity activities such as walking are negatively associated with the incidence of dementia and Alzheimer's disease (174). A meta-analysis investigating the protective effects of physical activity on dementia risk found that physical activity was able to protect against cognitive

decline and all dementia types, with physical activity being most beneficial in protecting against AD (182). Another systematic review found that exercise interventions and increased physical fitness appeared to mostly impact brain structures vulnerable to neurodegeneration (183).

2.3.4 Exercise and dementia

Regular physical activity and exercise may also have benefits for people with MCI or dementia. Several systematic reviews and meta-analyses have investigated the effects of exercise on cognition in older adults with MCI and dementia, revealing mixed findings. One systematic review found no exercise related changes in cognition in dementia (184). Another systematic review reported exercise related improvements in executive function (185). Interestingly the DAPA trial found that participants with dementia who completed a 12-month exercise intervention displayed deterioration in cognitive abilities (28). Exercise may also be beneficial in managing behavioural and psychological symptoms of dementia. A combination of resistance and aerobic exercise was found to significantly improve symptoms of depression in older adults with MCI (186). A meta-analysis found exercise significantly reduced behavioural and neuropsychological symptoms in older adults with dementia (187).

Exercise has been found to have positive effects on functional abilities which are often affected by dementia. MOTODEM, a pilot RCT of a 12-week physical activity intervention for people with mild to moderate AD found the intervention group displayed maintenance of functional abilities, executive function, behaviour, and mood, at 12 and 24 weeks follow up compared to the control group who deteriorated across all outcomes at both time points (32). The FINALEX trial

explored the effects of a long-term group-based and home-based exercise interventions on mobility and physical functioning in older adults with dementia. Compared to both the group and home-based exercise groups, physical functioning deterioration in the control group was significantly faster (29). Another RCT evaluating the effects of a progressive resistance and functional training intervention on gait characteristics found improvements across various gait characteristics including stride time and stride length in the intervention group when compared with the control group (188). A combination of strength and aerobic exercise was also found to improve balance and mobility in older adults with MCI (186).

Several systematic reviews have examined exercise intervention studies in dementia. Generally, exercise-based interventions were found to improve mobility and physical functioning (189). Multicomponent interventions were more effective in improving balance, gait speed and mobility compared to resistance training alone (190). A systematic review and meta-analysis by Lam et al. (191) reviewed the effects of exercise on strength, balance, mobility, and endurance in older adults with cognitive impairments and dementia. Supervised exercise session of 60 minutes, two to three times per week, was found to improve physical function. Meta-analyses revealed exercise improved performance on Berg balance, sit to stand test, timed up and go, walking speed and 6-minute walk test in people with MCI or dementia.

Exercise based interventions may also reduce the risk of falls in older adults with cognitive impairment. The FINALEX trial found that both the group exercise and home-based exercise groups had significantly fewer falls compared to the

control group (29). Several systematic reviews have reported that exercise interventions for older people with and without cognitive impairment are effective in reducing falls, with multifactorial exercise programmes being more effective in people with cognitive impairments (192,193). A review and meta-analysis by Burton et al. (26) found that exercise reduced falls risk by 32%.

Previous RCTs which tested the efficacy of exercise interventions in MCI and dementia have used a range of primary outcome measures including functional abilities, cognition, behaviour and mobility and reported mixed findings (28,29,32,184,184,185,189). The progression of dementia and symptoms of cognition and functional abilities are often slow in the early stages of the disease and the progression pathway highly variable. Thus outcome measures have been shown to have mixed sensitivity based on disease stage and may not be able to detect more subtle changes in the early stages of dementia (194). Additionally, some outcome measures such as functional abilities are self-reported, requiring the ability to recall information which is likely to be challenging for older adults with MCI or dementia (195). Mixed outcomes of exercise based interventions for people living with dementia may be attributable to challenges posed by limitations of outcome measure and the lack of consensus of what constitutes a meaningful outcome (194,195).

2.3.5 Physical activity and brain health

Physical activity can improve brain health and increase neuroplasticity across the lifespan (196). Research has used both structural and functional neuroimaging techniques to study structural and functional brain changes relating to physical activity induced neuroplasticity.

2.3.5.1 Ageing

Physical activity plays a key role in protecting against age related physical, functional, and cognitive decline and dementia. MRI and fMRI have been used to explore structural, functional and connectivity changes in the brain during ageing. MRI studies have shown that whole brain and regional brain volume decreases as we age (18). Physical activity can offset this, slowing brain atrophy. Physical inactivity has been linked to increased medial temporal lobe atrophy, especially within the hippocampus and greater memory dysfunction (197,198). Being physically active in later life has been linked to greater frontal and hippocampal volumes (198,199). Older adults who met WHO's weekly recommendations for 150 minutes of moderate intensity or 75 minutes of vigorous intensity physical activity had greater temporal lobe volumes compared to older adults who did not meet WHO's weekly activity recommendations (200).

The Framingham Study followed a cohort of older adults over a decade to explore the association between physical activity, MRI markers of dementia and risk of dementia. Older adults with the lowest activity levels were 1.5 times more likely to develop dementia. Also, a linear relationship between physical activity levels, whole brain and hippocampal volume was noted, where those with higher levels of physical activity displayed greater whole brain and hippocampal volume compared to those who were less physically active (201).

Exercise interventions may also induce positive effects on brain health in later life. An RCT of aerobic exercise intervention in older adults found at follow-up that the intervention group displayed a 2.12% and 1.97% increase in the left and right hippocampus volume, whilst the control group showed a 1.40% and 1.43%

decrease in hippocampal volume. In addition, the researchers also found that increased levels of physical fitness were associated with greater hippocampal volume (202). An RCT of resistance training in older women found post intervention reductions in white matter lesion volume in the intervention group, compared to the control group (203).

Physical activity in later life can also improve cerebral blood flow regulation, functional connectivity, neural efficiency, and compensatory activation. Post aerobic exercise intervention's increase in cerebral blood flow have been noted in the anterior cingulate and hippocampus in healthy older adults (179,204). An RCT comparing the effects of aerobic exercise and non-aerobic stretching and toning on functional connectivity, found at 6 months into both interventions, increased functional connectivity within the default mode network and frontal executive network, which often display age related changes (205). Liu-Ambrose et al. (206) conducted an RCT of a 12-month long resistance training intervention in older women, examining the effects of the intervention on task related activation, measured using fMRI. At follow up, the resistance training group displayed greater change in task related activation in the left middle temporal gyrus, left anterior insula and the left orbital frontal cortex.

Domingos et al. (207) conducted a systematic review exploring the effects of physical activity on brain structure and brain function in older adults. MRI studies showed that physical activity was associated with larger whole brain volume and larger hippocampal, temporal, and frontal volumes, which tend to be more vulnerable to dementia related pathology. fMRI studies highlighted that physical activity was associated with increased task related activity.

2.3.5.2 Dementia

Exercise and physical activity-based interventions may be beneficial for people with MCI and dementia (see section 2.3.4), however, results still appear mixed. Researchers have begun to apply structural and functional MRI to uncover neural mechanisms of exercise in this population. Cross-sectional studies have found engaging in regular physical activity was associated with greater frontal cortex and hippocampal volume and lower whole brain atrophy in older adults with MCI and mild AD (208–213). Also, regular physical activity was associated with preserved white matter integrity, with lower levels of physical activity being associated with more severe white matter lesions (210,211,214).

Interventional studies have found mixed effects of exercise on the whole brain and regional brain structures. Case-control studies comparing exercise related changes in cerebral grey matter in MCI and healthy controls have reported increased cortical thickness in the bilateral insula, precentral gyri, precuneus, posterior cingulate, inferior and superior frontal cortices in both groups (215) and greater grey matter diffusivity in the left insula cortex in the MCI group compared to healthy controls (216) after 12-weeks of a walking intervention. A 6-month multicomponent exercise intervention was found to have increased hippocampal volume in older adults with MCI and AD (217).

A pilot RCT exploring the effects of moderate intensity exercise intervention on cortical and subcortical structures in older adults with preclinical AD found that the control group displayed cortical thinning in several cortical (frontal, parietal, lingual, temporal, occipital, supramarginal, para hippocampal gyri) and subcortical brain regions (thalamus, putamen, hippocampus, amygdala)

compared to the exercise group (218). Two studies testing a 12-week walking intervention and a 16-week aerobic intervention found no changes in brain volume and cerebral blood flow in older adults with AD (219).

Research has begun to explore exercise induced changes in functional connectivity in the early stages of dementia. Eyre et al. (220) compared the effects of yoga to memory training on functional connectivity in older adults with MCI. Both groups displayed increased connectivity within the default mode network and language network post intervention. This increased connectivity was also associated with improved verbal memory performance in both groups. A recent case-control study studied the effects of a 12-week aerobic exercise intervention on resting cerebral blood flow in older adults with and without cognitive impairment. Post intervention changes in cerebral blood flow in the left insula and anterior cingulate cortex were noted in the MCI group and were associated with improved verbal fluency (221). A multimodal exercise programme for older adults with MCI was found to increase functional connectivity within the pre and post central gyri during a cognitive task and strengthen functional connectivity within regions vulnerable to AD (222). Exercise interventions may increase the capacity for compensatory activation and connectivity in regions that are affected by AD pathology, However, more work is needed to understand the current landscape of the research using functional imaging to measure exercise related changes in functional connectivity and to explore functional changes in older adults with differing degrees of cognitive impairment.

2.3.6 Promoting Activity, Independence and Stability in Early Dementia and Mild Cognitive Impairment (PrAISED)

Promoting Activity Independence and Stability in MCI and Dementia is a National Institute for Health Research (NIHR) Programme Grants for Applied Research (RP-PG-0614-20007) funded research programme which has been running since 2016.

A team of academics, physiotherapists, occupational therapists, rehabilitation support workers, nurses, health psychologists, geriatricians and Patient and Public Involvement collaborators (PPI), have developed a complex intervention for people with MCI and dementia, aimed at promoting activity, independence and reducing the risk of falls (37).

The intervention consists of up to fifty visits from a combination of physiotherapists, occupational therapists, and rehabilitation support workers over a 12-month period. The intervention also involves 150 minutes of activity per week including balance challenging exercises and functional based activities that aim to support independence and improve the individual's community and environmental access. Additionally, the intervention is tailored to the individual's needs, interests, and goals. The PrAISED intervention was designed to be delivered in the participant's home. The intervention has been designed to help people with MCI and dementia to live well for longer, establish positive, healthy habits and prevent crises.

The definitive PrAISED multi-centre RCT opened to recruitment in October 2018, across 5 sites in the UK; Nottinghamshire, Derbyshire, Lincolnshire, Oxfordshire and Bath (223). The RCT recruited 365 participants and carer dyads, from local

memory clinics, local GP practices and the National Institute for Health Research's Join Dementia Research Register. Participants were randomised to the PrAISED intervention or the control group. The control group received standard NHS falls prevention care which consisted of up to 3 visits from a therapist, a falls risk assessment and advice on how to prevent falls.

Inclusion criteria for the multicentre RCT was aged 65 and over, diagnosis of MCI or dementia, MoCA score of 13-25 (inclusive), having a family member or friend who was also willing to act as an informant and take part in the study. Additionally, the participant had to be able to walk without human help, communicate in English, and be able to complete neuropsychological tests. Finally, the participants had to have the mental capacity (as defined by the Mental Capacity Act 2005) to consent to take part in the trial. Participants with a diagnosis of dementia with Lewy bodies, a co-morbidity preventing participation in exercise, being unavailable over the next year due to extended holidays, a planned relocation or having a life-limiting illness of less than 12 months, were not eligible for the trial (223).

The PrAISED RCT was due to close to recruitment in June 2020, however, due to the COVID-19 pandemic and subsequent UK-wide lockdown in March 2020, trial recruitment was suspended until October 2020. Once safe to do so, recruitment across all sites recommenced in October 2020, recruitment was briefly halted again in December 2020, restarting again in January 2021 and concluding in June 2021. During the COVID-19 lockdowns, it was not feasible to deliver the intervention face-to-face. Instead, the intervention was delivered via telephone

or video call. Where this was not feasible, participation was paused until it was safe for therapists to resume face-to-face visits.

Before the COVID-19 pandemic, the PrAISED RCT provided a unique opportunity to use functional MRI to investigate neural correlates of postural control and exercise in people with MCI and Dementia. Participants recruited at the Nottinghamshire and Derbyshire sites for the PrAISED RCT, who consented to be contacted about other studies, were approached about taking part in the MRI sub-study. The MRI sub-study initially involved multi-modal MRI scans within 6 weeks of the PrAISED baseline and follow-up research assessments 12 months later.

2.4 Summary

Section one of this chapter reviewed the evidence base around the role of the cerebral cortex in postural control, drawing upon animal studies, studies from brain injury, stroke, ageing and neurodegenerative diseases as well as dual tasking studies. Studies using neuroimaging techniques such as EEG and FNIRS to measure neural activity relating to balance and the limitations of such techniques were discussed. The utility of fMRI as an alternative neuroimaging method which can address some of the limitations of other widely used neuroimaging techniques were considered. The movement limitations associated with fMRI were highlighted and key studies that have applied motor imagery and action observation techniques alongside fMRI to uncover the neural mechanisms involved in postural control were presented. The potential issues around the accessibility of such tasks for older adults with memory problems were emphasised and virtual reality combined with fMRI was presented as an

alternative technique to explore neural correlates of postural control in older adults with memory problems.

In section two of this chapter the population of interest to this thesis, older adults with MCI and dementia were introduced. An overview of the risk factors for dementia, neuropathology underpinning common dementia subtypes and common symptoms were provided. Executive function, what it is, how it can be assessed, neuroanatomy involved and evidence around the changes due to ageing and dementia were discussed. The literature around executive dysfunction, postural instability and falls in dementia was also explored.

In section three of this chapter, key definitions and recommendations around physical activity and exercise were provided. The general benefits of physical activity and the benefits in later life were presented. The effects of physical activity on mood, cognition, mobility, postural control and falls in older adults with MCI and dementia was also discussed. Current evidence around structural and functional neuroprotective effects of exercise in the ageing process and for those with MCI or dementia was discussed, highlighting the knowledge gap in functional mechanisms for the latter groups. Finally, an overview of the PrAISED research programme, the intervention and the RCT was provided, and how this research programme provided the opportunity to conduct the work presented in chapters 6 and 7.

3. Magnetic resonance imaging in dementia

3.1 The magnetic resonance signal

The atom is the basic building block for all matter in the universe. Most atoms contain protons and neutrons. Hydrogen is the only atom to contain only protons in its nucleus. Hydrogen atoms are one of the most abundant elements in the human body, therefore central to MRI and creating the MR signal. Hydrogen is a single proton nucleus which is why conventional MRI is often referred to as proton MRI. The hydrogen proton creates a small magnetic field due to its spinning motion, which can interact with a magnetic field in a way that enables us to measure and manipulate the magnetic state of these atoms.

Nuclei of hydrogen atoms point in different directions. Applying a strong magnetic field, known as the B_0 field, the hydrogen nuclei will align in parallel or antiparallel to the field. For MRI, a strong magnetic field is formed by a superconducting coil that is always on and cooled by liquid helium. The strength of the magnetic field in an MRI scanner is measured using the unit Tesla. The Earth's magnetic field is around 0.00005 Tesla, in contrast, the magnetic fields of MRI scanners can range from 1.5 to 11 Tesla. A 3 Tesla (3T) MRI scanner is approximately 60,000 times stronger than the earth's magnetic field.

In a strong magnetic field, the aligned hydrogen nuclei will spin (or precess) at a rate known as the Larmor frequency that is proportional to the strength of the magnetic field. The Larmor equation can be used to calculate this:

$$\omega=\gamma B0$$

Where ω= the spin rate of the atom, γ= is the gyromagnetic ratio and B0 = strength of the magnetic field.

The hydrogen nuclei are like spinning tops, precessing at a rate proportional to the magnetic field, but not in phase with one another. A radio frequency (RF) pulse can be applied in line with Larmor frequency to align the precession of the nuclei. The RF pulse does this in two ways, it causes the nuclei to become excited and move away from precession in line with the magnetic field and instead precess in phase or in synchrony with other nuclei. When the RF pulse is removed, the nuclei return to their original direction known as longitudinal relaxation. This process creates a signal which can be measured using a receiver coil, forming the basis of the MR signal which is used in both MRI and fMRI.

Once the RF pulse is complete, we can measure the relaxation processes of the hydrogen nuclei in 2 ways to produce brain images and generate contrast between tissue types. The first is to measure the time taken for the nuclei to fall out of alignment with the B_0 field (longitudinal relaxation) and return to their original alignment with the magnetic field, also known as T1 relaxation time. The second is to measure the time taken for the hydrogen nuclei to fall out of synchrony with one another (transverse relaxation), also referred to as T2 relaxation time. Both T1 and T2 processes although independent of one another, occur simultaneously. T2* is another method of measuring the transverse relaxation of the hydrogen nuclei. This method also considers the inhomogeneities present in the magnetic field caused by different tissue types, changes in blood flow and blood oxygenation.

The location of the MR signal can be identified by carefully applying magnetic fields of varying strengths, in the x, y and z directions. These are known as gradient fields and are created by different gradient coils within the scanner. Gradient fields are added when acquiring the MR signal so that different brain areas have slightly different frequencies. The resultant minor differences in read-out frequencies allow spatial localisation of the MR signal, and hence the construction of a spatially meaningful MR image. Applying gradient fields at different times during the RF pulse sequence in combination with T1 and T2 weighting can create contrasts between tissue types such as grey matter, white matter or cerebrospinal fluid and other tissue properties such as blood oxygen level, which is of importance to this thesis.

3.2 Functional MRI (fMRI)

fMRI (functional Magnetic Resonance Imaging), a derivative of MRI, is a non-invasive neuroimaging technique to study brain activity. Functional MRI exploits the differences between oxygenated and de-oxygenated blood on T2* measurements in brain tissue.

3.2.1 Blood Oxygen Level Dependent (BOLD) effect

The signal that fMRI measures is dependent on changes in blood oxygen levels in the brain and therefore referred to as Blood Oxygen Level Dependent or BOLD signal. The BOLD signal is an interplay between blood volume, blood flow and blood oxygenation, and is of great interest to researchers and clinicians alike as it provides an indirect measure of neuronal activity. The BOLD effect is core to fMRI; both resting state and task related.

The magnetic properties of haemoglobin are moderated by whether it is bound to oxygen or not. Oxygenated haemoglobin is diamagnetic (repelled by a magnetic field) whereas deoxygenated haemoglobin is paramagnetic (attracted by a magnetic field). As neural activity in a particular brain region increases, so does the need for oxygen and other nutrients, in those areas. Neural activity results in localised increased delivery of oxyhaemoglobin which causes small distortions in the magnetic fields, leading to a faster decay of the T2* signal or an increase in the BOLD signal at a local level. fMRI measures the T2* signal as this is sensitive to changes in blood flow and oxygenation.

3.2.2 The Hemodynamic Response Function (HRF)

The change in the MR signal due to a neural event and subsequent changes in blood oxygen level is referred to as the Haemodynamic Response Function (HRF). Increased metabolic demand, due to neural activity, leads to an increase in the supply of oxygenated blood to the active regions. As more oxygenated blood is supplied than consumed, the concentration of deoxygenated blood decreases, leading to an increase in the signal. This increase has an of onset 1-2 seconds after the onset of the neural activity and lasts for around 5-8 seconds after neural activity peaks. After reaching the peak, the BOLD signal decreases below the baseline level, for around 10 seconds, which is referred to as the post stimulus undershoot (see figure 2). This undershoot occurs, due to blood flow decreasing more rapidly than blood volume, resulting in a greater concentration of deoxygenated blood in these active regions. It can take 15-20 seconds for the BOLD signal to return to levels prior to the onset of the neural event.

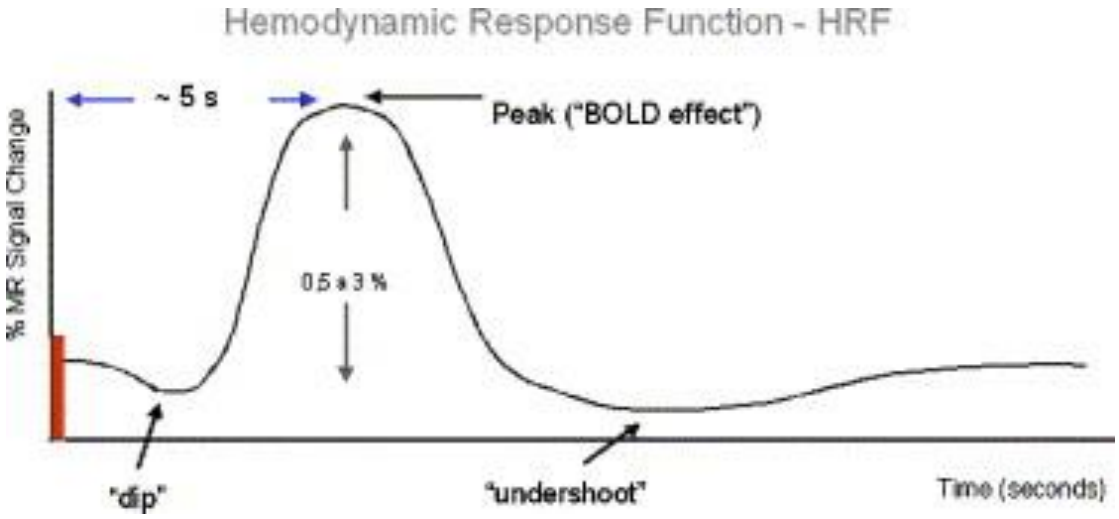

Figure 3. 1 Hemodynamic Response Function (HRF) plot from Amaro & Barker (2006).

3.2.3 Echo planar imaging.

Echo planar imaging (EPI) was developed by Sir Peter Mansfield at the University of Nottingham in the 1970s, for which he later won the Nobel Prize. The EPI method is the fastest method for imaging acquisition, allowing researchers to acquire brain volumes very rapidly with a TR (repetition time) of 2 seconds or under. EPI uses a single RF pulse to capture all the data associated with a single slice of the brain. EPI also applies a series of gradient pulses in alternating directions in rapid succession to capture all slice related data before the onset of the next RF pulse. Due to the long readout times post RF pulse, EPI images are often susceptible to distortions or signal drop out relating to inhomogeneities within the magnetic field, specifically around the nose or ears. Nevertheless, the development of EPI led to the use of functional MRI to study functional connectivity and neural activity at rest and in response to an event or task. fMRI is now a widely used technique by cognitive neuroscientists, psychologists, psychiatrists and in surgical planning (224). More recently fMRI

has also been used to identify functional biomarkers in different disease populations to provide additional outcomes for diagnostic and intervention-based studies (225,226).

3.2.4 Resting state fMRI (rs-fMRI)

Resting state fMRI (rs-fMRI) measures consistent low frequency fluctuations (0.01-0.08Hz). First discovered by Biswal and colleagues in 1995, resting state fMRI has been increasing in popularity over the last 2 decades (227,228). Resting state fMRI involves measuring spontaneous changes in these low frequency fluctuations of the BOLD signal in the absence of a task. This technique is often used to investigate connectivity between brain regions or networks. This essentially means looking at temporal correlations between BOLD signals extracted from two separate regions of the brain. From this researchers infer that these regions may be connected or talking to one another (228–230). Using resting state fMRI to investigate the temporal connectivity of brain regions, has led to the identification of 'resting-state networks' (RSNs).

Resting state fMRI has been widely used in healthy and clinical populations to understand spontaneous fluctuations in BOLD the signal in resting state networks and how the presence of illness related pathology may alter network connectivity (230). rs-fMRI allows researchers to study brain activity in participants who may struggle to understand complex task instructions and complete complex tasks. The lack of a task makes rs-fMRI particularly attractive for patients who may have difficulty with task instructions, such as those with neurologic, neurosurgical, and psychiatric conditions, as well as for paediatric populations (228).

Resting state networks (RSNs) are temporally related and spatially distinct networks of brain regions that correspond to brain regions which work together during a task (231). Research has identified many RSNs of interest including the sensorimotor network (SMN), visual network, auditory network, default mode network (DMN), dorsal attention network (DAN), frontoparietal network (FPN), frontal executive network (FEN) and the salience network to name a few (231). Resting state and task-based fMRI studies have demonstrated disruptions in DMN, SMN, FPN and DAN connectivity in people with cognitive impairments and dementia (232–234).

3.2.4.1 Default Mode Network

The default mode network (DMN) albeit an unexpected discovery, has become an increasingly studied network in both health and disease (235,236). Resting state fMRI studies have identified disrupted DMN connectivity in older adults with MCI and dementia (see section 3.5.2.2). The DMN is usually active when we are not engaged in an external task, thus thought to play a role in self-referential mental activity (237). The anatomical correlates of this network include the posterior cingulate cortex, precuneus, medial prefrontal cortex, inferior parietal lobule, angular gyrus, and hippocampus (229,235).

3.2.4.2 Sensorimotor Network

The sensorimotor network often referred to as the somatomotor network was one of the first RSNs to be discovered by Biswal and colleagues (227). the sensorimotor network is made up of the supplementary motor area, premotor, primary motor, and primary and secondary somatosensory cortices and is involved in the planning and execution of movement (231).

3.2.4.3 Fronto-Parietal Network

The fronto-parietal network (FPN), referred to as the flexible hub of cognitive control, is involved in top down, goal directed processes. It is postulated that the FPN acts as a co-ordinator between other RSNs. Neuroanatomically, the FPN is made up of the dorsolateral prefrontal cortex, the inferior parietal lobule, the middle of the middle temporal gyrus, the dorsomedial prefrontal region, anterior and superior cingulate cortex (231,238).

3.2.4.4 Dorsal Attention Network

The Dorsal Attention Network (DAN) is involved in goal directed attention processes (231). The DAN is a task positive network, meaning it is more active during a task and less active at rest. The DAN consists of the inferior parietal sulcus, frontal eye field, anterior cingulate cortex, and bilateral temporal gyrus. DAN is negatively correlated with the DMN in both task and resting state fMRI studies (229).

3.2.5 Task related fMRI

Task related fMRI involves participants performing a task whilst undergoing an fMRI scan, this allows researchers to measure changes in the BOLD signal and make inferences about the brain regions and neural networks involved in completing the task. For task-based fMRI, experiments are two types of designs: block design and event related design (239).

3.2.5.1 Block design

In block design fMRI experiments, stimuli are presented as blocks also referred to as epochs (230). 1 stimulus per block or epoch is presented and alternated with a different stimulus or rest period. The simplest and most popular block

design in fMRI research, often referred to as A-B 'block' designs, involves presenting the experimental condition (A) followed by a rest period (B), this method can be used to measure the differences in signal between the condition of interest (A) and the rest period (B) (240).

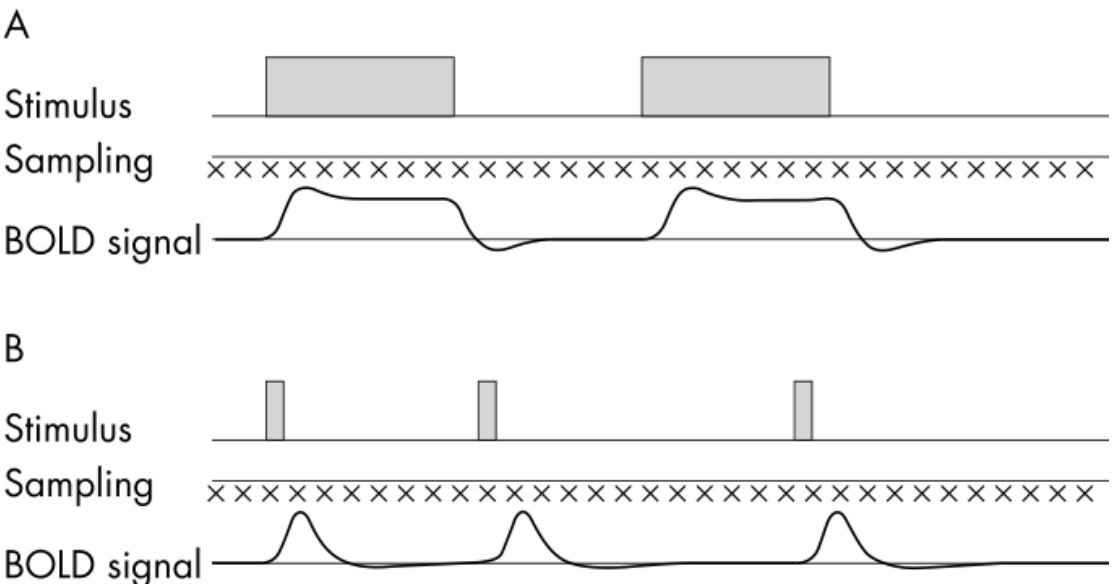

Figure 3. 2 Representation of fMRI block design paradigm (A) and event related paradigm (B) from Matthews et al. (2004).

To ensure that the experimental design is robust, researchers must consider the length of each block. Too short and the BOLD signal may not return to baseline before the onset of the next block, which can make it difficult to measure the true effect of the experimental condition. Too long and participants may become fatigued or bored while completing the task and may start to engage in task unrelated thoughts (240). The optimal duration of a block is between 15-30 seconds in length, the ideal duration depends upon the type of stimuli used (240). This type of design is more suited to measuring if there are changes in activation when the stimuli are present compared to when it is not, however it is

not able to provide information about the characteristics of the HRF in response to stimuli (240). Nevertheless, block design is still a very popular and robust method of presenting stimuli in an fMRI experiment, additionally compared to event related design, block design has increased detection power (240).

3.2.5.2 Event related design

Event related design is used when the research question is interested in studying the characteristics of the HRF response (onset, amplitude) (240). This type of design can also be used to analyse the neural correlates of behavioural responses. Stimuli in this design are made up of short discrete events which are presented in a random order, often interspersed with rest periods. Presentation of stimuli in this type of design is much shorter than in blocked design, with a duration of between 0.5 and 8 seconds (230). The short duration of stimuli and rest periods along with the randomised presentation of conditions means participants are less likely to become bored or engage in unrelated thoughts during the task (230,241). There are a few limitations of event related design that are important to note. This type of design is very sensitive to head movement which may impact data quality and the signal to noise ratio is lower than in block design experiments, having implications for detection power of the task (230).

Task fMRI experiments are often limited to cognitive based tasks as any task involving movement can lead to head motion, introducing movement artifacts into the data and reducing data quality. When designing an fMRI task, it is important to consider the research question and the effect of interest. The block design is more suited to measuring changes in activation in response to stimuli,

whereas event related design is better suited to studying key features of the HRF response (239,242).

Empirical chapters presented in this thesis have used a block design to present a novel video-based motor imagery task designed specifically for older adults with cognitive impairments. The task consists of three conditions, walking, obstacle navigation and postural instability and a rest condition and has been designed to measure neural activation related to balance. More information about the task and duration of the blocks is presented in chapter 5.

3.3 Clinical application of MRI in dementia

The NICE guidelines for the diagnosis of dementia advise that structural imaging should be used to rule out alternative and reversible causes of cognitive decline and as a supporting diagnostic tool to identify dementia subtype (138,243–245).

The following MRI imaging sequences are commonly used by clinicians to aid dementia diagnosis(246):

- T1 weighted – used to measure atrophy. Volume loss within the medial temporal lobe may be indicative of Alzheimer's disease.
- T2 Fluid Attenuated Inversion Recovery (FLAIR) - used to measure white matter hyperintensities (WMH) which are a key feature of small vessel disease underlying vascular dementia (245).
- T2* weighted or Susceptibility Weight Imaging (SWI) – used to measure cortical microbleeds (CMB), which are also indicative of vascular dementia.

3.4 Application of structural MRI in dementia research

3.4.1 T1 weighted MRI

To identify structural markers of MCI and dementia, MRI studies have used T1 weighted sequences to measure whole brain and regional atrophy and cortical thinning in older adults at risk of or diagnosed with MCI and dementia (247). MRI studies have found hippocampal atrophy may be present for up to 10 years before the onset of clinically detectable symptoms (124,248). In the prodromal stage of AD, MRI studies have identified changes in both whole brain and regional atrophy. A systematic review and meta-analysis of structural brain changes in MCI found the rate of whole brain atrophy in individuals with MCI was around 1.02% per year compared to 0.46% in healthy older adults (249).

The medial temporal lobe (MTL) is a key region which consistently shows pathology related changes in the early stages of AD (250). The MTL is made up of several regions including the hippocampus, entorhinal cortex, perirhinal cortex and parahippocampal cortex (231). Several meta-analyses have identified decreases in MTL volume in individuals with MCI and AD (251–253). Studies have also highlighted that MTL atrophy may be able to predict the progression from MCI to dementia (225). Within the medial temporal lobe, one key marker that has been well established and validated through volumetric MRI scans is a reduction in hippocampal volume in the early stages of AD (250). Vijayakumar et al. (254) found a 25% reduction in hippocampal volume in participants diagnosed with Alzheimer's disease, a 21% reduction in hippocampal volume in participants diagnosed with mixed dementia and an 11% reduction in

hippocampal volume in participants with vascular dementia when compared to healthy controls.

MRI has also been used to investigate changes in cortical thickness, sometimes referred to as cortical thinning, in ageing, MCI and dementia. Similar to findings around whole brain volume loss being detectable up to 10 years before the onset of clinically detectable symptoms (124,248), studies have found changes in cortical thickness in brain regions vulnerable to AD several years before the onset of clinically measurable symptoms (255). A case control study comparing cortical thickness between healthy older adults, older adults with MCI and older adults with AD found that the MCI group had cortical thinning in the medial temporal lobe, frontal and parietal areas compared to healthy controls. Between the MCI and AD groups, cortical thinning was present within the temporal lobe and globally across the cortex (256). A longitudinal study reported a 3.2% reduction in overall cortical thickness in patients progressing from MCI to AD. Additionally, regional cortical thinning was most prominent in the medial temporal cortex, inferior temporal gyrus, superior parietal lobule, temporal pole, precuneus and angular gyrus (257).

A detailed review of structural imaging biomarkers in dementia highlighted that MTL atrophy can predict MCI to AD progression with a sensitivity of 73% and specificity of 81% (258,259). Whole brain and hippocampal atrophy are highly sensitive markers of disease progression and are being increasingly used in AD research (225). A review of imaging biomarkers has highlighted that MRI provides excellent anatomical detail as well as a strong grey and white matter contrast (226). This review further highlighted that volume loss within the

prefrontal cortex and hippocampus was accelerated in AD and MCI when compared to normal ageing (226). Cortical thinning within the entorhinal cortex and hippocampus appears to be a highly sensitive measure of structural change in MCI and AD (226).

3.4.2 T2 weighted MRI

T2 weighted Fluid Attenuated Inversion Recovery (FLAIR) MRI sequences have been used to measure white matter hyperintensities (WMH) (245). WMHs are caused by cerebral small vessel disease, representing axonal loss and demyelination of neurons (260). WMHs have been linked to cognitive decline in healthy older adults and adults at risk of MCI and dementia (261). Some studies have found baseline WMHs to be predictive of conversion from cognitively healthy to MCI but not progression of MCI to dementia (262). Other studies have found increases in WMHs in the parietal lobe were predictive of progression to AD in cognitively healthy older adults (263). A review of longitudinal studies investigating association between WMH and cognitive decline found WMHs may be a potential early predictor of dementia, however, the association of WMHs and cognitive decline may be mediated by cognitive reserve, additionally, the location of WMH may mediate the risk of dementia (261). A recent systematic review and meta-analysis investigating the effects of WMHs and the risk of MCI and dementia found that baseline WMHs were associated with a 14% increased risk of developing MCI, a 25% increased risk of AD, and a 73% increased risk of vascular dementia (264).

3.4.3 T2* weighted MRI

T2* weighted Gradient Recall Echo (GRE) or Susceptibility Weighted imaging (SWI) sequences have been used to measure microbleeds (245,246). Cerebral microbleeds are small chronic brain haemorrhages caused by small vessel damage or cerebral small vessel disease (265,266). Cerebral microbleeds have been linked to cognitive decline in healthy older adults and adults at risk of MCI and dementia (245,265,266).

The Rotterdam study, a longitudinal follow up of middle-aged adults over ten years, to explore the incidence of dementia, found that the presence of 4 or more microbleeds were associated with cognitive decline. Additionally, location of microbleeds were associated with dysfunction in different cognitive domains. Lobar microbleeds were associated with decreased performance in executive function and memory, while microbleeds in other brain regions were associated with decreased information processing and motor speed (267). Another study exploring the relationship between microbleeds and cognition in older adults with small vessel disease also found that microbleeds in frontal and parietal lobes were associated with visuospatial and executive function, while microbleeds within the basal ganglia were associated with attention deficits (268).

Romero and colleagues (269) investigated the relationship between cerebral microbleeds and incidence of dementia from participants enrolled in the Framingham heart study. They found that generally participants with cerebral microbleeds had a 1.74 times higher risk of dementia, while participants with deep and mixed cerebral microbleeds had a 3 times higher risk of dementia. A

recent meta-analysis of prospective studies exploring the association between microbleeds and cognitive impairments, found that as the number of microbleeds increased, so did the risk for dementia. This study also found that the combination of deep and mixed microbleeds increased the risk of dementia by 75% (270).

3.5 Application of fMRI in Dementia research

In the last decade there has been an increase in the number of studies applying task related and resting state functional MRI in populations with MCI and dementia. Task related fMRI studies have used a variety of cognitive tasks to investigate alterations in brain activity due to dementia related pathology (271). Resting state fMRI has also been used to investigate changes in functional connectivity of brain networks at rest in the early stages of cognitive decline, MCI and dementia (250).

3.5.1 Task related fMRI

Task related fMRI has been used to investigate the changes in neural activation underlying memory and executive functions in those at risk of cognitive decline or living with dementia. A systematic review by McDonald et al. (272), found that most of the tasks used in fMRI studies with older adults, older adults at risk of cognitive decline and older adults with cognitive impairments measured various cognitive domains including memory, cognitive flexibility, inhibition and cognitive control and attention (272).

Task related fMRI studies have often used case control designs to compare differences in task related activation in people with MCI and dementia to normal ageing. Changes in semantic memory task activation have been noted in people

with AD, with reduced activation in the left temporal occipital cortex compared to healthy controls (273). A longitudinal study explored changes in memory encoding brain activation in older adults who progressed from MCI to dementia, found at baseline and follow up, participants with MCI who went on to develop dementia, displayed increased activation in right supramarginal gyrus and decreased activation in the left hippocampus and pars opercularis when compared to healthy controls (274).

An activation likelihood meta-analysis of case control studies exploring episodic memory task activation found that participants with AD had lower activation in the right hippocampus and participants with MCI had lower activation in the cerebellum during the memory task compared to healthy older adults (233). A co-ordinate based meta-analysis of case control studies of memory encoding and retrieval task activation found older adults with MCI had increased activity in the right hippocampus during memory encoding tasks but decreased activity in the left hippocampus and fusiform gyrus during memory retrieval tasks. Conversely, older adults with AD had increased activation in the precuneus during encoding memory tasks and decreased activity in right hippocampus during retrieval tasks (234).

Executive dysfunction is a core feature of dementia. A case control study using the odd ball paradigm as an fMRI task to explore differences in attention and inhibition control related activity in older adults with MCI and healthy older adults found participants with MCI displayed impairments in episodic memory functioning, object naming and verbal fluency when compared with healthy controls. Additionally in the MCI group, reduced task related activity was noted

in left and right temporal regions, left cuneus, left supramarginal gyrus, anterior cingulate cortex and left middle frontal gyrus (275). The verbal fluency task is widely used to assess cognitive flexibility and to monitor cognitive decline and disease progression in dementia. This task has been used alongside fMRI to explore changes in cognitive flexibility related activation in dementia. Compared to healthy older adults, those with dementia displayed greater activation in the bilateral superior frontal gyrus, inferior frontal gyrus, left supplementary motor area and the right middle frontal gyrus (276). A comparison of working memory activation between healthy older adults and older adults with MCI revealed increased activation in the right insula and the right lingual gyrus in the MCI group (277). Additionally, during the working memory task, a region of interest analysis focusing on medial temporal lobe (often showing signs of atrophy in MCI and AD), revealed greater activation of parahippocampal cortex in participants with MCI when compared to healthy controls (277).

Memory, attention, and executive function-based fMRI tasks have provided useful tools to undercover the changes in brain activity associated with memory and cognitive dysfunction in ageing and cognitive decline. Studies have found both hypoactivation and hyperactivation during cognitive tasks in people at risk of decline, older adults with MCI and older adults with AD. It is important to note that studies using task fMRI appear to be in older adult populations at risk of cognitive decline, older adults with MCI or older adults with mild dementia, very few studies have used task fMRI in older adults with more advanced dementia. Additionally there is little research available that has used task based fMRI to

explore changes in brain activation relating symptoms of altered postural control.

3.5.2 Resting state fMRI

Resting state fMRI has been used to study subtle changes in spontaneous fluctuations in the BOLD signal in specific brain areas and networks such as the medial temporal lobe, hippocampus, DMN, SMN, FPN and DAN, which have been shown to be affected by AD related pathology (226). In addition to this, resting state fMRI has also been used to study functional connectivity and integrity of brain networks which are often affected by dementia related pathologies (278). Researchers have often favoured resting state fMRI over task fMRI as the former is more accessible for those with cognitive impairments as it does not require participants to remember complex task instructions (229).

3.5.2.1 Connectivity of regions vulnerable to AD

Several studies have investigated functional connectivity of the hippocampus. Wang et al. (279), conducted a case control study, examining differences in functional connectivity of hippocampus in participants with mild AD and healthy controls. Compared to healthy older adults, adults with AD displayed altered connectivity of right hippocampus with the medial prefrontal cortex, right cuneus and precuneus, left cuneus, right superior and middle temporal gyrus and posterior cingulate cortex (279). More recent research has explored direct connectivity of the right hippocampus in MCI and AD compared to healthy older adults. Significant differences in functional connectivity of right hippocampus between healthy older adults, those with MCI and those with AD were noted in in the temporal lobe, frontal lobe, and cingulate cortex (280) .

3.5.2.2 Connectivity and integrity of default mode network in dementia

There is increasingly accumulating evidence showing that altered DMN connectivity may be a core feature of AD (281,282). In preclinical stages of AD, connectivity of key brain regions within the DMN appears to be altered (283). Case control studies have highlighted decreased DMN connectivity in older adults with AD when compared to those with MCI and healthy older adults (284,285). A review of changes in functional connectivity found decreased DMN connectivity in AD (286). These findings have been further supported by a meta-analysis of network dysfunction in AD, which found hyperconnectivity of DMN in people with MCI but decreased connectivity of DMN in people with AD (232). Another case control study comparing DMN connectivity between healthy older adults and older adults with MCI reported the converse, decreased DMN connectivity in MCI (287).

Disrupted DMN connectivity, may not be unique to AD. A cross sectional study by Kim and colleagues (288) explored differences in functional connectivity of DMN (and central executive network see section 3.5.2.3) in people with AD, VaD and mixed pathology dementia. Participants with AD displayed decreased functional connectivity within the inferior parietal lobule, while participants with VaD displayed decreased functional connectivity within the medial and superior frontal gyri. In the mixed pathology dementia group, decreased functional connectivity was noted in the posterior cingulate gyri (288). Another case control study found that compared to those with AD, participants with frontotemporal dementia displayed increased connectivity within the DMN (286,289).

A more recent systematic review and meta-analysis explored differences in DMN connectivity between healthy controls and older adults with MCI. This study revealed very mixed findings, with some studies reporting no difference in DMN connectivity between older adults with MCI and healthy controls, other studies reported hypoconnectivity of the DMN, whilst some reported hyperconnectivity. As well as this, some studies reported a mixed effect of both increased and decreased connectivity among different regions within the DMN (290). These studies show that while DMN connectivity is disrupted in dementia, underlying pathology appears to have divergent effects on connectivity within the network.

3.5.2.3 Connectivity and integrity of networks beyond the DMN in dementia

There is emerging evidence that other resting state networks also displayed altered connectivity in MCI and dementia. Case control study design has been widely used to compare differences in functional connectivity of various networks between differing disease severity and normal ageing. Agosta et al. (291) reported that those with MCI had increased connectivity within the executive and salience networks, whereas those with AD had reduced connectivity in FPN when compared with healthy controls (291). Disrupted connectivity of SMN and visual networks has also been noted in older adults with MCI and AD, when compared with healthy controls (292,293). Connectivity of the control network was greater in those with MCI than those with AD (292). Altered connectivity within the dorsal attention, executive and salience networks, and altered connectivity between the dorsal attention and default mode network have also been noted in those with MCI and AD when compared with healthy controls (282,294).

Resting state fMRI and case control study designs have also been used to explore differences in functional connectivity between dementia subtypes. Disrupted connectivity of the central executive network was observed in Alzheimer's disease and vascular dementia and disruption of this network was greater in mixed dementia than single pathology dementia (288). Differences in functional connectivity have been noted between AD and FTD. Those with AD pathology had greater connectivity within the salience network compared to those with FTD and healthy controls, while those with FTD had greater connectivity within the DMN compared to those with AD and healthy controls (289). Differences in functional connectivity have also been noted in AD and behavioural variant FTD. Those with AD displayed altered connectivity within the visual and default mode work whereas those with behavioural variant FTD displayed altered connectivity within auditory and visual networks (295). Additionally, a meta-analysis found increased connectivity of the salience and limbic networks in Alzheimer's disease (232).

3.6 Summary

This chapter has provided an overview of the principles of the magnetic resonance signal which forms the bases for MRI and functional MRI. The principles of echo planar imaging, BOLD signal and HRF, which are core to functional MRI are also summarised. A brief overview of resting state fMRI and various resting state networks, task-based fMRI, and commonly used task fMRI designs is presented. Information around the clinical applications of MRI as a diagnostic tool to aid dementia diagnosis is provided and the use of MRI in research in advancing our understanding of structural brain changes due to

dementia related pathology is discussed. The application of functional MRI (both task based and resting state fMRI) in research settings has been instrumental in identifying changes in brain activity underpinning cognition and changes in functional connectivity in normal aging, cognitive decline, and dementia. This chapter also highlighted how studies using task fMRI in older adults at risk of cognitive decline, older adults with MCI or mild dementia have largely focused on changes in cognition related brain activity. This chapter also drew attention to how fMRI research in dementia to date has largely used resting state fMRI due to the perceived burden of task fMRI. The data presented in chapters 5,6 and 7 were collected using task-based and resting state fMRI sequences to explore neural correlates of postural control in people with dementia, as postural control deficits are key symptom of dementia, with increased falls risk and related adverse outcomes for the individual.

Part II: Research Studies

4. Exercise related changes in functional MRI outcomes in older adults with mild cognitive impairment and dementia – A systematic review.

4.1 Background

Research has identified a link between being physically active, reduced risk of dementia and potentially delaying onset in those at risk. Currently there is no pharmacological treatment available to cure or prevent the onset of dementia (296,297). Lifestyle based interventions such as exercise and physical activity, offer an alternative approach to reducing risk, delaying progression and managing symptoms (297). Previous studies and systematic reviews have shown that exercise interventions may have a positive effect on cognition, falls risk, rate of falls and performance in activities of daily living in people living with MCI and dementia (26,189,298–301). However, results from RCTs evaluating(27,178) efficacy of exercise interventions in this population have yielded mixed results (28,189). For instance the FINALEX trial found that exercise reduced the rate of decline in activities of daily living and reduced falls in people with dementia (29). In contrast the DAPA trial reported no significant differences in performance of activities of daily living or cognition between the intervention and control groups at follow up (28). Variation in duration, frequency and intensity of the exercise interventions and different outcome variables may contribute to the mixed results we see in people with dementia (26,302). Additionally self-reported outcomes and neurocognitive assessment tools may not be as sensitive to exercise related changes as techniques such as neuroimaging, (34).

Exercise has also been shown to increase functional connectivity with various resting state networks as well as improving neural efficiency in various brain regions such as the hippocampus (205,303). fMRI studies of healthy older adults have identified exercise related changes in blood flow and cerebral activation. Burdette et al. (204) investigated the effects of exercise on cerebral blood flow and functional connectivity in older adults at risk of cognitive decline. They found greater connectivity in the hippocampus in the intervention group, compared to the control group (204). Walking and balance exercises have been found to increase functional connectivity within the default mode network, frontal executive network and fronto-parietal network (304). Balance training has also been associated with improved postural stability and a reduction in brain activation in areas related to postural control (305).

Previous reviews summarising evidence on exercise related changes to brain activity and connectivity have used a variety of neuroimaging techniques such as MRI, PET, EEG as well as fMRI (180,306,307). Additionally, these reviews have focused mainly on healthy older adults, though a few have included studies on older adults at risk of cognitive decline or older adults with MCI (180,303,308). As older adults with memory problems have a higher risk of falls and immobility (24,26,309), and exercise interventions may be beneficial in reducing the risk of falls, fMRI studies have the potential to inform us about changes in brain activity and connectivity in response to therapeutic interventions. This in turn may allow better screening of interventions for impact on intermediate outcomes (such as task-related and resting state fMRI) prior to embarking on expensive and labour-intensive clinical trials. Additionally, fMRI measures may also provide further

information for refinement or tailoring of interventions in terms of the types of activities, dose, or duration of therapy.

The purpose of this study was to conduct a systematic review of current evidence around the effect of exercise interventions on resting state functional connectivity and task-related functional activity, as measured by fMRI, in adults aged 65 and over with MCI or dementia.

4.2 Method

This systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (ID CRD42020152444) and conducted in line with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (310).

4.2.1 Search strategy and study selection

Search strategy was informed by previous relevant reviews on exercise intervention for older adults and functional MRI (24,26,189,232,300,311). The search strategy was also reviewed by experts in the field (RD, RH and VvDW) and by subject librarian (see Appendix A for search strategy).

MEDLINE, Embase, PsycINFO, PsycARTICLES and CINHAL databases were searched for primary studies, and hand searched reference lists of relevant papers for any other relevant studies.

Search results from each database were imported into Endnote and duplicate records were removed. RB and NA independently screened titles and abstracts to identify studies not eligible at this level. For the remaining records, full text

articles were sourced and reviewed independently by RB and NA, using the following criteria to assess eligibility for this review.

4.2.2 Inclusion criteria

- Randomised controlled trials (RCTs), quasi randomised or cluster randomised controlled trials, nested studies, case control studies, cohort (prospective) studies and cross-sectional studies.
- Study populations of older adults aged 65 and over. Where studies included mixed ages, studies were only included if the mean age of the study populations was 65 or over.
- Studies with older adults with differing levels of cognitive impairment or dementia.
- Studies that involved physical activity or exercise of any kind as an intervention.
- Studies with multifactorial interventions were included if there was a physical activity or exercise-based component in the intervention.
- Studies that used resting state or task-related fMRI to measure changes in brain connectivity or activity in response to physical activity or exercise.

4.2.3 Exclusion criteria

- Any studies using a cognitive training only comparator. Imaging studies have noted changes in fMRI outcomes in relation to cognitive training interventions in older adults with cognitive impairments [37].
- Abstracts, such as poster abstracts, review articles, commentaries, letters and editorials were also excluded.

4.2.4 Data extraction, quality assessment, data extraction and synthesis.

A data extraction table was created using Microsoft Excel and piloted on 3 studies to check that the tool was able to capture the data required. Data on participant characteristics such as age and gender, study characteristics such as study setting, intervention and comparator used were extracted. Brain regions or networks of interest that displayed significant change for both resting state and task-related fMRI outcomes and where available effects sizes and p-values were also extracted. Data were extracted by the first reviewer (RB) and quality checked by the second reviewer (NA).

RCTs included in the review were assessed for sources of bias using the Cochrane risk of bias tool (312). For non-randomised controlled trials, nested studies, case control studies, cohort studies and cross-sectional studies Newcastle Ottawa Scale was used to assess study quality (313).

The second reviewer and I independently appraised quality of the studies included, using the appropriate assessment tool based on study design. Where consensus on scoring was not achieved, this was resolved through discussions with another reviewer (RD, VvdW and RH).

Due to heterogeneity in study design, intervention characteristics (exercise/activity type, frequency, and duration), fMRI tasks and fMRI analysis methods used, it was not feasible to conduct a meta-analysis, therefore I completed a narrative synthesis of the results (314). Study, intervention, and participant characteristics were tabulated, study outcomes are presented based on fMRI outcome type – resting state or task-related brain activity. The summary of the main fMRI findings for each study with secondary outcomes such as

neuropsychological assessments and physical measures have also been tabulated.

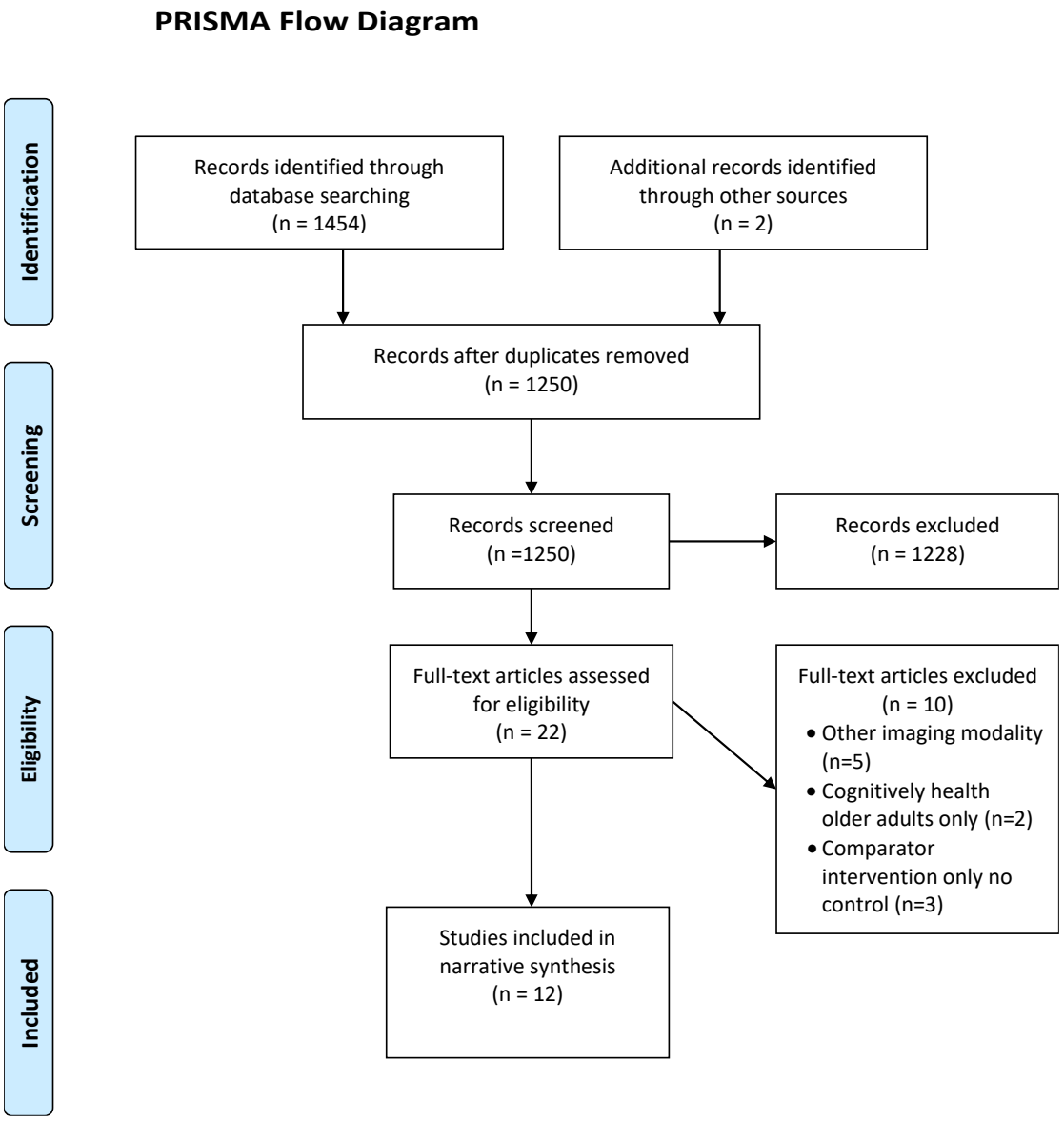

Figure 4. 1 PRISMA flow diagram of search and screening results.

4.3 Results

4.3.1 Search results

The searches were conducted in September 2020 (See Figure 4.1 for PRISMA diagram on study selection process) and then updated on 16th September 2021. Searches yielded 1454 studies and 2 further papers were identified through other sources. 22 full text articles were sourced and assessed for eligibility, of which 10 studies either failed to meet inclusion criteria (e.g. studies did not include fMRI, or participants were cognitively healthy) or were excluded because the comparator interventions included cognitive training and exercise. A total of 12 papers from 6 studies were included in the review (315–326).

4.3.2 Study Characteristics

Of the twelve papers included, three papers were from two RCTs (320,321,325), five papers were from two nested studies within RCTs (318,319,322,323,326), three papers were from separate case control studies (316,317,324) and one paper was from a cross sectional study (315) (see Table 4.1). Nested studies within RCTs refer to studies conducted within a larger RCT, whereby participants are recruited from the RCT post randomisation. Case control studies involve comparing cases or population of interest to a control group or healthy controls. A cross sectional study is an observational study which involves analysing data from a select population group at a specific time point (327).

Table 4. 1 Study details and participant characteristics for the studies included in the analysis.

Author/Year	Country of research	Design	Rs-fMRI or Ts-fMRI	N (at Baseline where applicable)	N (at follow up)	N dropout	Age – Mean (S.D.)	Male: Female	Diagnosis or method of determining cognitive status
Carson Smith et al. 2011 (315)	USA	Cross sectional	Ts-fMRI	18	N/A	N/A	Low PA = 73.6 (8.3); High PA = 75.0 (5.5)	Low PA = 2/7; High PA =2/7	Petersen criteria for amnestic MCI
Carson Smith et al. 2013 (316)	USA	Case control	Ts-fMRI	35			MCI = 78.7 (7.5); HC= 76.0(7.3)	MCI = 7/10; HC=3/15	MCI or healthy control status determined using NIH-Alzheimer's Association work group core clinical criteria for MCI.
Chirles et al. 2017 (317)	USA	Case control	Rs- fMRI	35			MCI = 79.6 (6.8); HC= 76.1 (7.2)	MCI = 6/10; HC= 3/13	Same as above
Hsu et al. 2017 (318)	Canada	Nested study within an RCT	Ts- fMRI	38	21	17	Aerobic Training = 72.0 (8.6); Control = 69.9 (9.2)	Control = 5/4, Aerobic training = 8/4	clinically diagnosed with mild SIVCI
Hsu et al. 2018 (319)	Canada	Nested study within an RCT	Ts – fMRI	38	21	17	Aerobic training = 71.7 (8.8); Controls = 72.3 (8.8)	Control = 4/7 and Aerobic training - 4/6	clinically diagnosed with mild SIVCI
Suo et al. 2016 (320)	Australia	RCT	Rs-fMRI	86	79	7	70.1 (6.7)	Not available	Petersen criteria for MCI

Qi et al. 2019 (321)	China	RCT	Rs-fMRI	38	32	6	Control =69.1 (8.1); Intervention = 69.1 (8.1)	Control = 4/12 Intervention = 5/11	Diagnosis of MCI
Tao et al. 2019 (322)	China	Nested study within an RCT	Rs-fMRI	69	57	12	Baduanjin = 66.17 (4.17); Walking = 64.32 (2.60); Control = 65.97 (5.66)	Baduanjin = 5/15; walking = 7/10; Control = 6/14	Diagnosis of MCI
Xia et al. 2019 (323)	China	Nested study within an RCT	Rs-fMRI	69	60	9	Baduanjin = 65.79 (4.35); Walking = 64.88 (3.30); Control = 65.86 (5.28)	Baduanjin = 6/17; Walking =11/12; Control = 6/17	Diagnosis of MCI
Broadhouse et al. 2020 (325)	Australia	RCT	Rs-fMRI	84	70	14	69.5 (SD = 6.6)	58/26	Petersen criteria for MCI
Won et al. 2021 (324)	USA	Case control design	Rs-fMRI	35	32	3	MCI = 78.8 (7.6); HC = 75.3 (7.4)	Female total = 23; MCI F = 10; F HC = 13	MCI or healthy control status determined using NIH-Alzheimer's Association work group core clinical criteria for MCI.
Liu et al. 2021 (326)	China	Nested study within an RCT	Rs-fMRI	69	57	12	Baduanjin = 66.17 (4.17); Walking = 64.32 (2.60); Control = 65.97 (5.66)	Baduanjin = 5/15; walking = 7/10; Control = 6/14	Diagnosis of MCI

Key: Rs-fMRI= resting state fMRI; Ts-fMRI= task-related fMRI.

4.3.3 Participant characteristics

Across the 6 studies (315–326) a total of 302 participants were recruited with mean age ranging from 64 years (S.D 2.6) to 79 years (S.D. 6.8). In total, 266 participants either had a clinical diagnosis of MCI or met the criteria for MCI through assessment as part of study screening criteria. Thirty-six healthy older adults were recruited as part of the case control studies. 42 participants did not complete follow up or were excluded from final analyses due to poor data quality. No studies with participants with dementia, which were eligible for inclusion, were identified in the search.

Eligibility criteria differed slightly across all studies. Participants were included if they had a clinical diagnosis of MCI (318,319,321–323,326), or met Petersen diagnostic criteria (315,320,325) or National Institute for Ageing-Alzheimer's Association criteria for MCI (315,317,324). Additionally participants were included if they scored <26 on the Montreal Cognitive Assessment, 24-30 on the Mini Mental State Exam, 0 or 0.5 Clinical Dementia Rating, had no impairments in activities of daily living, and engaged in less than 3 days of activity per week (315–323).

Participants were excluded if they failed to meet MRI specific inclusion criteria such as metal objects within the body or claustrophobia. Additionally, participants were excluded if they had any other neurological conditions such as epilepsy, brain tumour, Parkinson's disease, Multiple Sclerosis, Huntington's disease, or medical conditions such as hypertension, glaucoma, chronic obstructive pulmonary disease, untreated psychiatric conditions, taking medication that may affect cognition or were participating in other studies.

Table 4. 2 Intervention characteristics.

Author/Year	Intervention name / Assessment of PA	Description	Duration	Frequency	Setting (Community/Home)	Delivered by	N allocated / N dropout	Comparator/Control	Description	N allocated / N dropout
Carson Smith et al. 2011 (315)	Stanford Brief Activity Survey	Used to measure level of PA	N/A	N/A	N/A	N/A	9 participants with MCI reported High levels of PA	N/A	N/A	9 participants with MCI reported low levels of PA
Carson Smith et al. 2013; Chirles et al. 2017; Won et al. 2021 (316,317,324)	Treadmill walking	Treadmill walking exercise individually tailored.	12 weeks	30 minutes per session / 4 x per week	Community – local fitness centres	Qualified trainers, exercise psychologists	17 (participants with MCI) / 1	N/A	N/A	18 (healthy older adults) / 2
Hsu et al. 2017 and Hsu et al. 2018 (318,319)	Aerobic Training	Each session included a 10 min warm-up, 40 min of walking and a 10 min cool down.	6 months	60 minutes per session / 3 x per week	Community – outdoors	Qualified instructors	19 / 8	Educational materials about healthy diet	Monthly educational materials about cognitive impairment and a healthy diet.	19 / 10

Suo et al. 2016 and Broadhouse et al. 2020 (320,325)	PRT	Each session included 3 sets of 8 repetitions of 5–6 exercises (chest press, leg press, seated row, standing hip abduction, knee extension) using resistance machines.	6 months	75 minutes per session/ 2 x per week	Community	Research Assistants, Exercise Psychologists, Physiotherapists	19	PRT+CT/CT/SHAM	3 comparator interventions – (i) resistance training (PRT) + cognitive training/ (ii) cognitive training (CCT + sham resistance training (iii) sham resistance and cognitive training intervention (SHAM)	22 PRT+CCT = 22, CCT = 21, SHAM = 24 / PRT+CCT = 3; CCT + SHAM PRT= 2; SHAM = 2
Qi et al. 2019 (321)	Moderate Intensity Aerobic Dance	Each session involved warm-up, dance routine and cool down. Routine required memory, concentration, and dual-task function to complete the dance correctly.	3 months	25 minutes per session/ 3 x per week	Community	Physical therapist	19 / 3	Non exercise control group	No description provided	19 / 3

Tao et al. 2019, Xia et al. 2019 and Liu et al. 2021 (322,323,326)	Baduanjin	The Baduanjin exercise consisted of 10 postures Each session included a warm-up, 40-min Baduanjin training, and cool down (See Tao et al., 2019). And a health education program about cognitive disorders and healthy eating.	24 weeks	60 minutes per session /3 x per week	Community	Professional coach	23 / 3	Brisk walking /Control	Brisk walking group received walking training. Control group advised to maintain levels of activity. Both groups also received a health education program about cognitive disorders and healthy eating.	Brisk walking =23; Control = 23 / Walking = 6; Control = 3

4.3.4 Intervention characteristics

Five studies tested an exercise intervention (316–326) and one study used a survey to assess levels of physical activity (315). Intervention duration ranged from 3-6 months. Number of sessions per week ranged from 2 to 4, with each session lasting between 35 and 75 minutes. Interventions included aerobic exercise, treadmill walking, dance, resistance training as a standalone intervention or combined with cognitive training, brisk walking and baduanjin (low intensity mind-body based intervention like tai chi). Interventions were delivered by qualified professionals such as personal trainers, physical therapists, coaches, research assistants, physiotherapists and exercise psychologist in local fitness or community centres or outdoors. Comparator interventions were either usual care or usual activity control group, sham interventions, or educational materials about healthy diets (see Table 4.2 for more details on intervention characteristics).

4.3.5 Quality assessment

The two RCTs included in this review were assessed using the Cochrane risk of bias tool (312). One RCT was of high quality with a low risk of bias across all domains, the second RCT was of lower quality with some concerns around deviation from the intended intervention, selection of the reported results and measurement of the outcomes (see Table 4.3).

The Newcastle Ottawa Scale and adapted Newcastle Ottawa Scale for cross sectional studies (328) were used to assess quality of nested studies within RCTs, case control studies and cross sectional study. Nested studies within RCTs and the case control studies were of high quality. Differing non-response rates

between intervention and control groups was a potential source of bias for these studies. The cross-sectional study was also of good quality however lacked some detail around sampling strategy, sample size justification and description of response rate (see Table 4.4 and 4.5).

Table 4. 3 Quality assessment of RCTs using Cochrane Risk of Bias Tool.

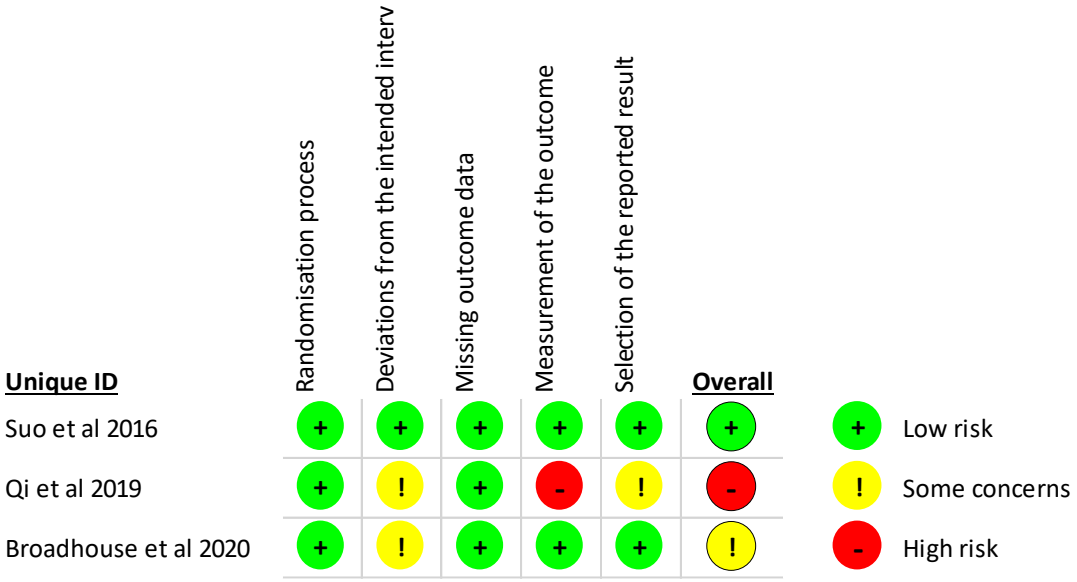

Table 4. 4 Quality assessment of nested studies, case control studies and cross sectional studies using the Newcastle Ottawa Scale.

Author/Year	**Selection**				**Comparability**	**Exposure (Nested studies and Case control studies only)**			**Total score /9**
	1. Is the case definition adequate?	2. Representativeness of the cases	3. Selection of controls	4. Definition of controls	Comparability of cases and controls based on the design or analysis	1. Ascertainment of exposure	2. same method of ascertainment for cases and controls	3. non-response rate	
Hsu et al. 2018 (319)	*	*	*	*	**	*	*		8
Hsu et al. 2017 (318)	*	*	*	*	**	*	*		8
Tao et al. 2019 (322)	*	*	*	*	**	*	*		8
Xia et al. 2019 (323)	*	*	*	*	**	*	*	*	9
Carson et al. Smith 2013 (316)	*	*	*	*	**		*		7

Chirles et al. 2017 (317)	*	*	*	*	**		*		7
Won et al. 2021 (324)	*	*	*	*	**		*		7
Liu et al. 2021 (326)	*	*	*	*	**	*	*		8

0-3 stars =high risk of bias, 4-6 stars = moderate risk of bias, 7-9 stars = low risk of bias.

Table 4. 5 Newcastle Ottawa Scale adapted for cross sectional studies.

Author/Year	**Selection**				**Comparability**	**Outcome (cross sectional studies only)**		**Total Score /10**
	1. Representativeness of the sample	2. Sample size	3. Non respondents	4. Ascertainment of exposure (risk factor)	Comparability of subjects in different outcome groups	1. Assessment of outcome	2. Statistical test	
Smith 2011 (315)				**	**	**	*	7

0-3 stars =high risk of bias, 4-6 stars = moderate risk of bias, 7-9 stars = low risk of bias.

Table 4. 6 Summary of fMRI methods, analyses, and outcomes.

Author/Year	**fMRI sequence type** (resting state or task)	**Name of task for ts-fMRI**	**Data processing and analysis software used**	**Type of analysis** (ROI, voxel wise)	**fMRI outcome measure**	**Brain area or brain networks of interest**
Carson Smith et al. 2011 (315)	Task-related	Famous face discrimination task	Analysis of Functional NeuroImages (AFNI)	Functional Region of Interest (ROI)	Changes in activation between famous and non-famous faces	Basal ganglia, frontal lobes, parietal, temporal, occipital lobes, cuneus and precuneus
Carson Smith et al. 2013 (316)	Task-related	Famous face discrimination task	Analysis of Functional NeuroImages (AFNI)	Spatial extent analysis and functional Region of Interest (fROI)	% signal change (famous minus non-famous faces) pre- and post-intervention	
Chirles et al. 2017 (329)	Resting state	Not applicable	Analysis of Functional NeuroImages (AFNI)	Seed based analysis and Region of Interest (ROI)	Connectivity results based on correlation maps of the mean BOLD time course from the PCC/precuneus seed ROI and the remaining voxels in the brain.	PCC/precuneus
Hsu et al. 2017 (318)	Task-related	Finger tapping motor task	FSL	Region of Interest (ROI)	mean network connectivity strength	FPN
Hsu et al. 2018 (319)	Task-related	Ericksen's Flanker task	FSL	Voxelwise threshold	Difference in % signal change (post intervention – baseline).	
Suo et al. 2016 (320)	Resting state	Not applicable	SPM8	Seed based functional connectivity	Correlation between mean signal time course in seed region and rest of the brain.	Hippocampus and posterior cingulate

Qi et al. 2019 (321)	Resting state	Not applicable	Data Processing Assistant for Resting-State fMRI	Whole brain	Changes in ALFF	Bilateral fronto-temporal, entorhinal, anterior cingulate and parahippocampal cortex
Tao et al. 2019 (322)	Resting state	Not applicable	Data processing and Analysis of Brain Imaging (DPABI) in MATLAB and SPM12	Seed to voxel correlational analysis and Region of Interest (ROI)	Changes in ALFF values	Medial Prefrontal Cortex, Right Hippocampus, Bilateral ACC
Xia et al. 2019 (323)	Resting state	Not applicable	Data Processing Assistant for Resting-State fMRI	Independent component analysis	DAN connectivity	DAN
Broadhouse et al. 2020 (325)	Resting state	Not applicable	SPM8	Region of interest functional connectivity analysis	Functional connectivity between hippocampus and posterior cingulate	Hippocampus and posterior cingulate
Won et al. 2021 (324)	Resting state	Not applicable	Analysis of Functional NeuroImages (AFNI)	Seed based correlation analysis	Functional connectivity of bilateral hippocampi and bilateral amygdala	Hippocampus and amygdala
Liu et al. 2021 (326)	Resting state	Not applicable	CONN toolbox and MATLAB	Seed based correlation analysis	Functional connectivity of locus coeruleus and ventral tegmental area	Locus coeruleus and ventral tegmental area

ACC=Anterior Cingulate Cortex; PCC=Posterior Cingulate Cortex; DAN=Dorsal Attention Network; FPN=Fronto-Parietal Network.

4.3.6 fMRI analysis approaches and outcome characteristics

Four articles used task fMRI and reported on task-related activation or deactivation and task-related functional connectivity outcomes (315,316,318,319). Eight articles used resting state fMRI and reported changes in low frequency fluctuation in the BOLD signal or changes in functional connectivity within and between brain regions (317,320–326). Analysis approaches used across the studies included functional region of interest analysis, seed-based functional connectivity, seed-based correlation analysis, whole brain analysis and spatial extent analysis (see Table 4.6). No study investigated the effects of exercise type, intervention duration and intervention intensity on functional connectivity and task-related activity.

4.3.7 Exercise induced changes measured by rs-fMRI

Two papers reported exercise induced changes in Amplitude of Low Frequency Fluctuations (321,322). ALFF are measurable low frequency fluctuations in the BOLD-signal that arise from spontaneous neural activity in brain (228). Six papers reported exercise induced changes in functional connectivity within and between brain regions (see table 4.6 for a summary of findings (317,320,323–326)).

4.3.7.1 Exercise induced changes in Amplitude of Low Frequency Fluctuations (ALFF)

Qi et al. (321), conducted a pilot RCT to test the effect of a dance intervention on ALFF in older adults with MCI. Post intervention significant increases in ALFF in the bilateral fronto-temporal, entorhinal, anterior cingulate and parahippocampal cortices were found in the exercise group (see Figure 4.2).

Tao and colleagues (322) investigated the effects of two different exercise interventions (Baduanjin and brisk walking) on ALFF. Compared to the brisk walking intervention and the control group, the baduanjin intervention was associated with a significant decrease in ALFF in the right hippocampus, bilateral lingual gyrus and right superior temporal gyrus and a significant increase in ALFF in the right medial prefrontal cortex, left dorsolateral prefrontal cortex and the bilateral anterior cingulate cortex (see Figure 4.2).

Based on the changes in ALFF noted in the right hippocampus and bilateral anterior cingulate cortex in response to the Baduanjin intervention, the authors conducted seed-based connectivity analysis to investigate functional connectivity changes. Baduanjin exercises were found to significantly increase resting state functional connectivity between the hippocampus and right angular gyrus (see Figure 4.3). No changes in functional connectivity were noted when using bilateral anterior cingulate cortex as the seed.

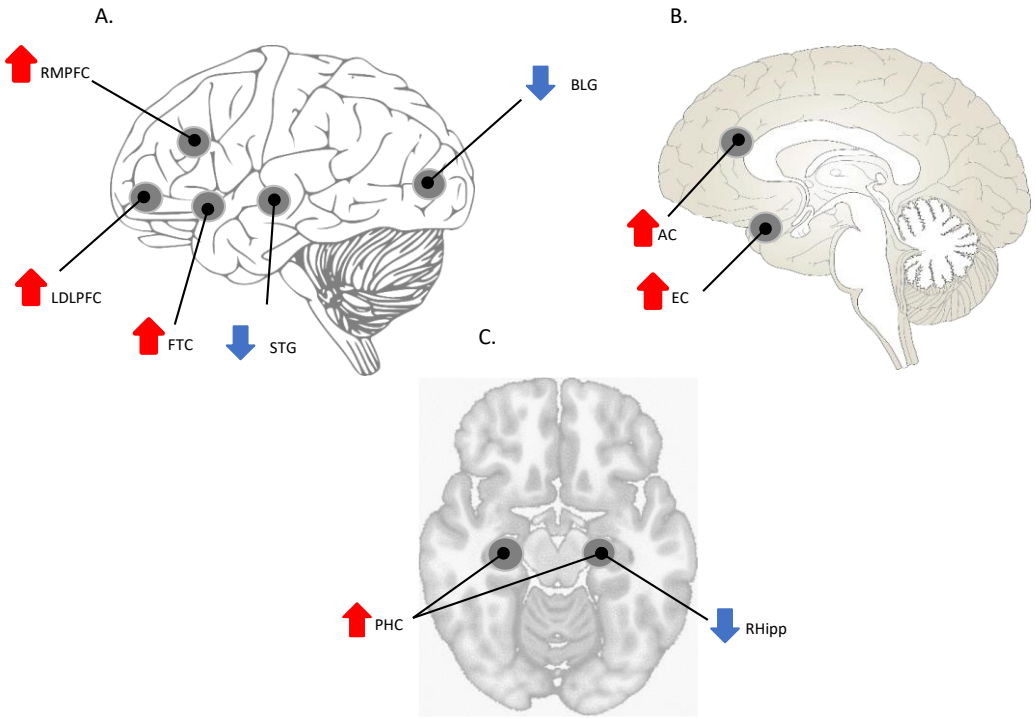

Figure 4. 2 Approximate spatial location of exercise related changes in Amplitude of Low Frequency Fluctuations during rest.

Key:

A = brain lobes and cerebellum; B = Sagittal view; C = Axial view.

Red arrow = post intervention increases in ALFF / Blue arrow = post intervention decreases in ALFF.

(Qi et al. 2019, Tao et al. 2019).

AC=Anterior Cingulate; EC=Entorhinal Cortex; BLG=Bilateral Lingual Gyrus; FTC=Fronto-Temporal Cortex; LDLPFC=Left Dorsolateral Prefrontal Cortex; PHC=Para-Hippocampal Cortex, RHipp=Right Hippocampus; RMPFC=Right Medial Prefrontal Cortex; STG= Superior temporal Gyrus.

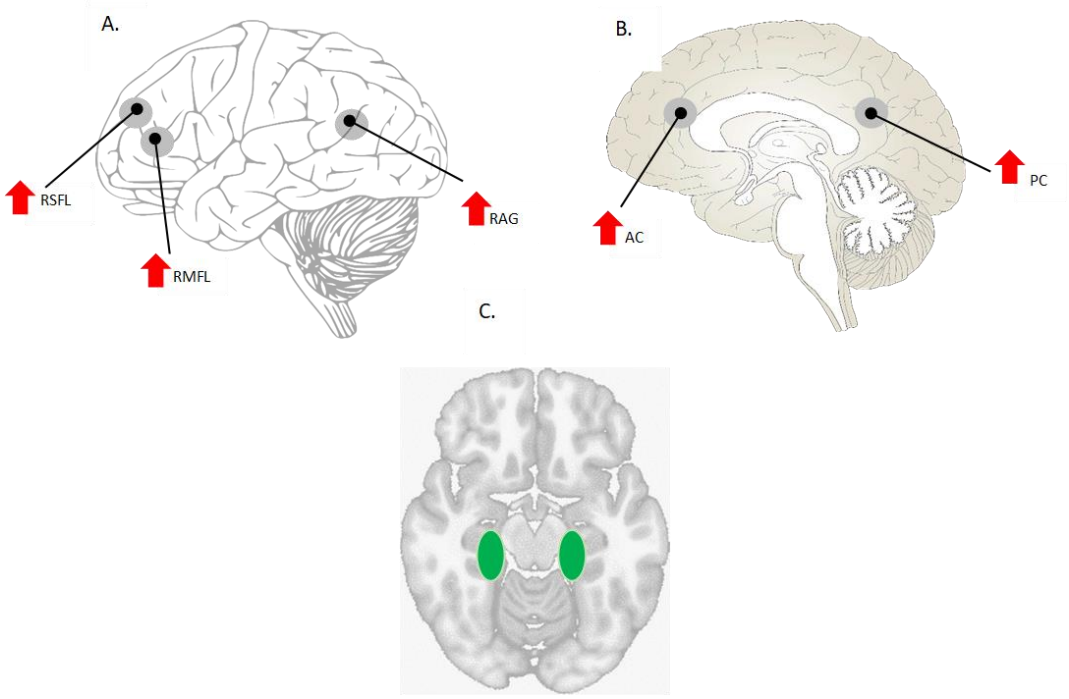

Figure 4. 3 Approximate spatial location of exercise related changes in functional connectivity during rest using hippocampus as the seed.

Key:

A = brain lobes and cerebellum; B = Sagittal view; C = Axial view.

Green circle = Approximate location of hippocampus (HIPP) / Red arrow = increase in functional connectivity with HIPP / Blue arrow = decrease in functional connectivity with HIPP.

(Tao et al. 2019; Suo et al. 2016; Broadhouse et al. 2020; Won et al. 2021).

AC= Anterior Cingulate; PC=Posterior Cingulate; RAG=Right Angular Gyrus; RMFL=Right Medial Frontal Lobe; RSFL=Right Superior Frontal Lobe.

4.3.7.2 Exercise induced changes in functional connectivity at rest

Three papers reported exercise induced changes in functional connectivity (317,320,323). A secondary analysis on the dataset presented by Tao et al. (2019) used Independent Component Analysis (ICA) to identify exercise induced changes in functional connectivity in the Dorsal Attention Network (DAN) in people with MCI (323). Brisk walking intervention increased DAN connectivity whereas the Baduanjin intervention decreased DAN connectivity (see Table 4.7).

Another secondary analysis by Liu et al. (2021), examined effects of baduanjin intervention on locus coeruleus and ventral tegmental area functional connectivity in this group. Baduanjin was associated with increased connectivity between locus coeruleus and right insula, bilateral temporal parietal junction, right supplementary motor area, right inferior frontal gyrus, right postcentral gyrus, right dorsolateral prefrontal cortex. For ventral tegmental area, the baduanjin intervention was associated with increased connectivity between bilateral anterior insula, right amygdala, bilateral putamen, bilateral caudate, right orbitofrontal gyrus, left nucleus accumbens, left superior parietal gyrus and right post central gyrus (326).

A case control study (317) examined the effects of aerobic exercise on posterior cingulate cortex / precuenus connectivity at rest in older adults with MCI and healthy older adults. Both MCI and healthy control groups displayed significant increases in connectivity between PCC and left post central gyrus. Additionally, the MCI group also demonstrated increased connectivity between PCC and inferior parietal lobe, right middle frontal gyrus, superior frontal gyrus, post central gyrus, parahippocampal gyrus, claustrum, bilateral precentral gyrus and

cerebellum post intervention (see Figure 4.4). A secondary analysis on this dataset by Won et al. (2021) investigated the effects of aerobic exercise on hippocampal connectivity. After exercise the MCI group displayed significant increases in functional connectivity between the anterior hippocampi and right posterior cingulate and between the posterior hippocampi and the right posterior cingulate. For the healthy controls, after exercise, significant increases in functional connectivity were noted between the posterior hippocampi, left cuneus and precuneus (324).

An RCT by Suo et al. (320) examined the effects of resistance training and combined resistance and cognitive training on bilateral hippocampi and posterior cingulate connectivity (see Figure 4.3 and 4.4). Resistance training significantly decreased posterior cingulate functional connectivity with the left inferior temporal lobe and the anterior cingulate cortex but significantly increased hippocampal functional connectivity with right middle frontal lobe. Resistance training was also found to significantly decrease hippocampal functional connectivity with the right inferior temporal lobe. The combination of resistance and cognitive training decreased posterior cingulate functional connectivity with the anterior cingulate cortex but increased hippocampal functional connectivity with anterior cingulate and right superior frontal lobe (43). Broadhouse et al. (2020) investigated the long terms effects of the resistance training intervention on hippocampal plasticity. This paper investigated resistance training related changes in hippocampal and posterior cingulate connectivity one year post intervention (325). Compared to control

groups, functional connectivity between posterior cingulate and hippocampus in the resistance training group was stronger at one year post intervention.

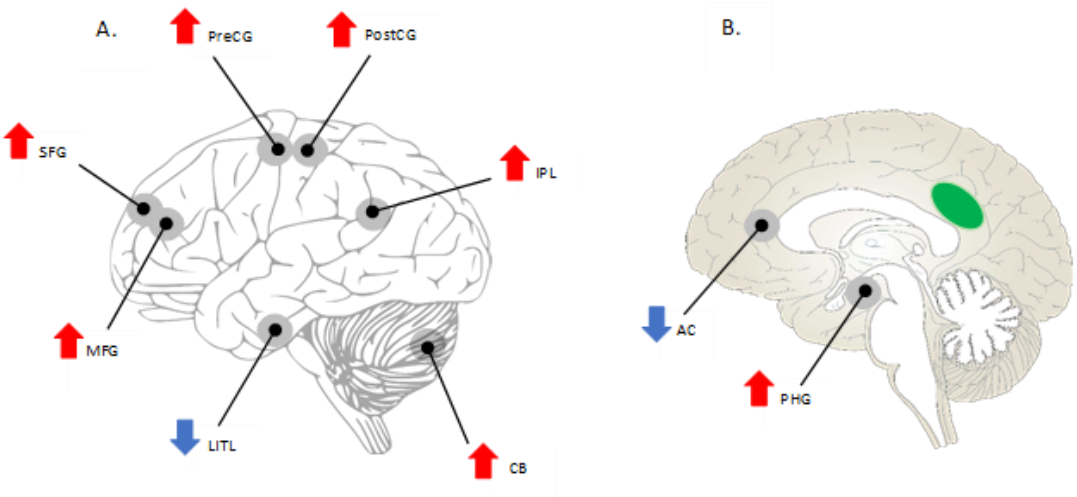

Figure 4. 4 Approximate spatial location of exercise related changes in functional connectivity during rest using Posterior cingulate as the seed.

Key:

Green circle = approximate location of Posterior Cingulate (PC) / Red arrow = increase in functional connectivity with PC / Blue arrow = decrease in functional connectivity with PC.

(Chirles et al. 2017 and Suo et al. 2016).

AC=Anterior Cingulate; CB=Cerebellum; IPL=Inferior Parietal Lobule; LITL= Left Inferior Temporal Lobe; MFG=Middle Frontal Gyrus; PHG=Para-Hippocampal Gyrus; PreCG=Pre-Central Gyrus; PostCG=Post Central Gyrus; SFG=Superior Frontal Gyrus.

Table 4. 7 Summary of findings.

Author/ Year	Study Design	fMRI	fMRI task performance	Secondary outcomes - Cognition / ADL's/ Balance/ Mobility / Cardiovascular Fitness/ Physical Activity
Carson Smith et al. 2011 (315)	Cross sectional	• 25% Greater volume of activation in high-PA group. • Significantly greater intensity of activation in the left caudate in High PA group compared to Low-PA (Mean (±S.D.): High-PA=0.358 (0.151%); Low-PA=0.149 (0.268%); F (1,16) =4.117, P=0.03; η2p=0.205)	No significant differences in task performance between high PA and low PA groups	• No significant difference in neuropsychological assessment scores between high PA and low PA • No significant differences in ADL, balance, mobility, cardiovascular fitness and physical activity outcomes between high and low PA groups
Carson Smith et al. 2013 (316)	Case control	• Significant decrease in volume of semantic processing related activity post intervention in both MCI and healthy controls in following regions L MTG (P=0.0230), L PHG (p=0.022), B PC/PCUN (p=0.0241), L Cerebellum (p=0.0001), R STG/MTG (p=0.0003), L PreCG (p=0.0091), R SPL/AG (p=0.0047), L LOG (p=0.0006)	• No significant differences between pre- and post-intervention and between groups for famous face recognition accuracy and reaction time.	• Significantly improvement on Trial 1 Learning AVLT from pre to post intervention in both groups (p=0.006). • No significant differences between groups ADL, balance and mobility scores pre and post intervention. • Intervention increased mean cardiorespiratory fitness in both groups post intervention (p=0.004). • MCI group displayed greater cardiorespiratory fitness compared to healthy controls, but this difference was not significant.
Chirles et al. 2017 (317)	Case control	• Post intervention increased correlation between the PCC/PCUN and R IPL in MCI group • Decreased correlation between PCC/PCUN and R IPL in healthy controls. • Increased correlation between PCC/PCUN and left post central gyrus across both groups. • Post intervention MCI group exhibited increased correlations between PCC/PCUN and R MFG, R PreCG, R SFG, R PostCG, L IPL, R PHG, R claustrum, L culmen. • No differences in PCC/PCUN connectivity post intervention in healthy control group.	N/A	• No significant differences in scores for ADLs, balance, and mobility between groups and between pre and post interventions. • For differences in cardiovascular fitness between groups and pre and post intervention see Carson Smith 2013

Hsu et al. 2017 (318)	Nested study within an RCT	• Post intervention AT<CG displayed significantly greater intra-network coupling of FPN during right finger tapping condition (p<0.02). • Significant correlation noted between change in FPN connectivity during right tapping condition and 6-minute walk test performance (*r*=-0.43, *p*=0.05). • Pre to post intervention reduction in FPN connectivity correlated with improved TUG performance (*r*=0.67, *p*=0.02).	Task performance appears to have not been measured or reported	• No significant differences between AT and CG on TUG, SPPB at follow up. • No significant differences between AT and CG on 6-minute walk test and PASE at follow up. • Noted trend of greater improvements in 6-minute walk test performance in AT compared to CG was noted but was not statistically significant.
Hsu et al. 2018 (319)	Nested study within an RCT	• Difference in % signal change (post minus pre intervention), AT showed reduced activity in L LOC (*p*<0.03) and R STG (*p*=0.03) compared to CG. • Significant correlation between reduction in % signal change of L LOC and STG and faster reaction times in flanker task (*r*=0.482, *p*=0.04) • Significant correlation between reduction in % signal change of R STG and improved incongruent condition performance post intervention (*r*=0.471, *p*=0.05).	• Faster reaction times on congruent trials of flanker task significantly associated with % signal change of L LOC (r=0.484, p=0.04) and R STG (r=0.482, p=0.04). • AT exhibited significantly improved reactions times for congruent (p<0.01) and incongruent trials (p=0.03) at follow up.	• Noted trend of greater improvements in 6-minute walk test performance in AT compared to CG but was not statistically significant.
Suo et al. 2016 (320)	RCT	• PC functional connectivity decreased with L ITL (F (67) =14.8, *p*<0.001) and ACC (F (67) =23.3, *p*<0.001) in PRT group. • Decreased functional connectivity between PC and ACC (F (65) =5.3, *p*=0.017) in PRT+CCT group. • Hippocampal functional connectivity increased with R MFL (F (67) =13.0, *p*=0.001) but decreased with (P<0.001) in PRT group. • Increased functional connectivity between hippocampus and ACC (F (66) = 4.6, *p*=0.005) and R SFL (F (65) = 7.0, *p*<0.001) in PRT+CCT group.	N/A	• PRT only and combination of PRT+CCT significantly improved on ADAS-Cog at follow up (p<0.05).
Qi et al. 2019 (321)	RCT	• Significant increase in ALFF in bilateral fronto-temporal, entorhinal, anterior cingulate and parohippocampal cortex (P<0.05) in EG post intervention. • No significant differences in these regions in the CG post intervention	N/A	• Post intervention scores on MMSE, MoCA, WMS-R LM and SDMT significantly increased in EG compared to baseline (P<0.05). • Change in WMS-R LM scores significantly higher in EG compared to CG (P<0.05). • No difference between groups on Berg balance scale pre- or post-intervention.

		• CG displayed activation in R right temporal and posterior cingulate cortex (P<0.05).		
Tao et al. 2019 (322)	Nested study within an RCT	• BAD>BWG Significant decrease in ALFF (low frequency band) in R Hipp (t=3.86; z=3.61) and increase in L mPFC (t=4.26; z=3.94) • BAD > BWG/CG significant increase in in ALFF (slow-4 band) in R mPFC (t=4.49; z=4.12) L DLPFC (t=3.95; z=3.68) and significant decrease in R LG (t=4.87; z=4.42) L LG (t=5.8; z=5.09) R STG (t=3.75; z=3.52). • BAD>CG Increased ALFF (Slow-5 band) in B ACC (t= 4.94; z= 4.46). • BAD>CG significantly increased resting state functional connectivity between Hipp and R AG (t=4.59; z=4.02).	N/A	• Significant negative correlation between changes in activity in right hippocampus and bilateral ACC and MoCA score changes across all groups at follow up (r=−0.291, p=.036).
Xia et al. 2019 (323)	Nested study within an RCT	• BAD>BWG/CG reduction in functional connectivity in R IPL, R ROL, R MTG, R PCUN and FFG (p<0.05). • BAD>CG Significant reduction in R ROL functional connectivity in (p=0.032). • Reduction in R PCUN functional connectivity differed significantly between BAD and BWG (p = 0.031). • Increase in R IPL functional connectivity significantly greater in BWG compared to BAD (p=0.001) and CG (p=0.029). • CG>BAD increase in functional connectivity of R MTG significantly greater in CG compared to BAD (p=0.032) and BWG (p=0.042). • Increase in R FFG functional connectivity significantly greater in BWG compared to BAD (p=0.032).	• Post intervention, average number of correct congruent trials on Stroop test significantly different between BAD, BWG and CG (p=0.038). • Significant increase in average number of correct congruent trials in BAD compared to CG (p=0.008).	• No significant differences between groups on divided attention, sustained attention and processing speed measures, post intervention.

Broadhouse et al. 2020 (325)	RCT	• Examined the change in functional connectivity between L PC and Hipp. • At 18 months follow up functional connectivity between PC and hippocampus was significantly stronger in PRT+CCT and PRT+SHAM compared to CCT+SHAM and SHAM+SHAM (p = 0.018)	N/A	• Non-significant relationship between change in left hippocampal and PC functional connectivity and change in ADASCog between baseline and 18-month follow up (p = 0.097).
Won et al. 2021 (324)	Case control design	• MCI group showed significant increase in connectivity between A-Hipp and RPC (p<0.0001) and between P-Hipp and RPC (p<0.0001) after exercise. • Control group showed significant increase in connectivity between P-Hipp and left CN (p=0.0005) and PCUN (p=0.0001) after exercise	N/A	• Cardiorespiratory fitness increased after the intervention across all participants (F(1,27) = 8.632, p = 0.007, η2p = 0.242) • Both MCI and control group displayed significant differences in RAVLT Trial 1 (p=0.023, η2p=0.242), LM immediate (p=0.004, η2p =0.249) and delayed recall (p=0.021, η2p=0.166)and recognition (p=0.006' η2p0.266) • MCI: Increased A-Hipp and RPC connectivity explained 38.3% of increased in LM recognition performance [R= 0.619,R2 = 0.383, p = 0.014, 95% CI 3.844, 28.330] • MCI: Increased P-Hipp and RPC connectivity explained 37.6% of increase in LM recognition performance [R= 0.613, R2 = 0.376, p = 0.015, 95% CI 3.344, 25.971] • MCI: Increased B-Hipp and BPC connectivity explained 27.4% of increase in LM recognition performance [R= 0.650,R2 = 0.422, p = 0.009, 95% CI 4.676, 26.597]

Liu et al. 2021 (326)	Nested study within an RCT	BAD>CG: • L LC increased connectivity with B TPJ, R INS, IFG, SMA, PostCG • R LC increased rsFC in the B ACC, B PreCG, R INS, AMG, TPJ, SMA, STG • L and R LC increased rsFC with R INS • Left VTA increased rsFC in B INS, PUT, CAD, R AMG, FG, PostCG, orbitofrontal gyrus, left nucleus accumbens and SPL. • Left VTA decreased rsFC L PCC • R LC and L VTA increased rsFC with R INS and R AMG BAD>BWG • R DLPFC and decreased rsFC in the bilateral cerebellum exterior • R LC increased rsFC in the right ACC • Right VTA increased rsFC R TPJ BWG>BAD • Right LC increased rsFC in R SMA, IOC, B PreCG and Post CG, L MOC and right cerebellum • Increased connectivity in right LC and right ACC in BAD BWG>CG • Decreased rsFC B PCUN	N/A	• Significant increase in MoCA scores BAD> CON (p = 0.05) and BAD>BWG (p = 0.037) • A significant positive correlation between rsFC R ACC and R INS (right ACC: r = 0.265, p = 0.046; right insula: r = 0.277, p = 0.037) and corresponding MoCA scores across all groups.

R=Right; L=Left; B=Bilateral; A= Anterior; P=Posterior ACC=Anterior Cingulate Cortex; AG=Angular gyrus; AMG=Amygdala; CN= Cuneus; CAD=Caudate; FFG=Fusiform gyrus; Hipp=Hippocampus; INS=Insula; IPL=Inferior parietal lobule; ITL=Inferior temporal lobe; IOC=Inferior Occipital Cortex; MOC; LOC=Lateral occipital cortex; Middle Occipital Cortex; LOG=Lateral occipital gyrus; LC=Locus Coeruleus; MFG=Middle frontal gyrus; MFL=Middle frontal lobe; MTG=Middle temporal gyrus; PHG= Parahippocampal gyrus; PreCG=Precentral gyrus; PostCG= Postcentral gyrus; PC=Posterior Cingulate; PCUN=Precuneus; PUT=Putamen; ROL= Rolandic Operculum; SFG=Superior frontal gyrus; SFL=Superior frontal lobe; SPL=Superior Parietal lobe; STG=Superior temporal gyrus; TPJ=Temporal parietal junction; VTA=Ventral Tegmental Area; AT=Aerobic training; BAD=Baduajin; BWG=Brisk walking group; CG=control group; EG=Exercise Group; PRT=Progressive resistance training; CCT=Cognitive training. RAVLT= Rey auditory verbal learning test; MoCA=Montreal Cognitive Assessment; MMSE=Mini Mental State Examination; WMS-R LM=Weschler memory scale-revised logical memory SDMT= Symbol digit modalities test; LM= Logical Memory Test.

4.3.8 Exercise induced changes measured by task-related fMRI

Four papers reported task-related fMRI outcomes. One paper reported task-related changes in brain activity in relation to self-reported levels of activity. Two papers reported changes in task-related brain activity post-exercise intervention. One paper reported changes in task-related functional connectivity in response to an exercise intervention (see Table 4.7 for summary of findings). fMRI tasks included famous face discrimination task, which tests semantic memory processing (315,316), finger tapping task which tests motor control (318) and the Ericksen Flanker task which tests attention and inhibition (319).

4.3.8.1 Exercise induced changes in task-related brain activity

The only cross-sectional study included in this review investigated the relationship between self-reported levels of activity and semantic memory processing related brain activity in people with MCI (315). Participants with self-reported high levels of physical activity displayed significantly greater activation in left caudate nucleus during famous face task conditions when compared with low activity group.

Aerobic exercise interventions appear to reduce task-related brain activity. A case control study found significant decreases, at follow up, in brain activation in response to famous face discrimination task in the medial and superior temporal gyrus, parahippocampal gyrus, posterior cingulate / precuneus, cerebellum, precentral gyrus, superior parietal lobe, angular gyrus, and lateral occipital gyrus, in both older adults with MCI and healthy older adults (316). Aerobic training was also associated with a significant reduction in activity in the left lateral occipital cortex and the right superior temporal gyrus during an attention

and inhibition task (see Figure 4.5). Reduction in activity in these brain regions was significantly associated with improved reaction times on the attention task (319).

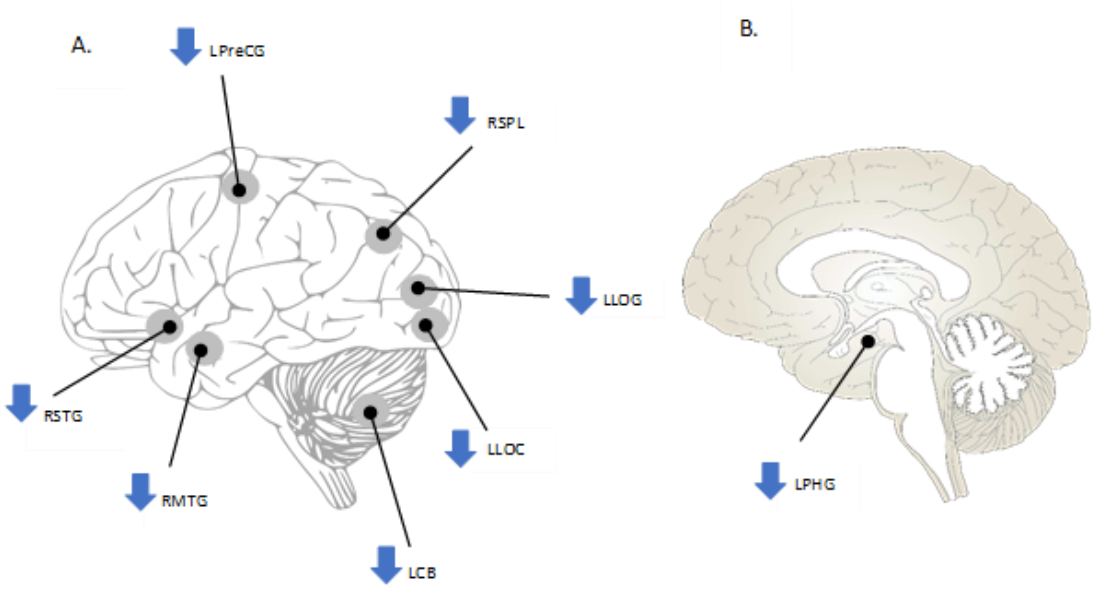

Figure 4. 5 Approximate spatial location of exercise-related changes in task-related activation during Semantic memory and attention inhibition tasks.

Key:

A = brain lobes and cerebellum; B = Sagittal view; C = Axial view.

Red arrow = Increase in activation / Blue arrow = decrease in activation.

(Hsu et al. 2018 and Carson Smith et al. 2013).

LCB= Left Cerebellum; LLOC=Left Lateral Occipital Cortex; LLOG=Left Lateral Occipital Gyrus; LPHG=Left Para-Hippocampal Gyrus; LPreCG=Left Pre-Central Gyrus; RMTG=Right Medial Temporal Gyrus; RSTG=Right Superior Temporal Gyrus.

4.3.8.2 Exercise induced changes in task-related functional connectivity

Only one study investigated exercise related changes in task-related functional connectivity. Hsu et al. (318), investigated the effect of a 6-month aerobic training intervention on FPN connectivity and mobility during a motor control task in older adults with MCI. At follow up compared to the intervention group, the control group displayed significantly greater within network connectivity during the right finger tapping condition only (318).

4.3.9 fMRI outcomes and relationship with cognition, mobility, balance, and cardiovascular fitness measures

Exercise related improvements in cognition were noted in nine papers (315,316,320–326) but were only significant in six of the papers (316,320–322,324,326). Three papers found no significant changes in cognition in response to exercise (315,323,325). Three papers did not include cognitive measures at follow up (317–319).

Three papers also investigated the effects of exercise on the relationship between functional connectivity and cognition. Tao et al. (322) found connectivity between right hippocampus and bilateral anterior cingulate cortex was associated with change in MoCA scores across all groups (baduanjin, brisk walking and control) at follow up. Liu et al. (326) found increased MoCA score at follow up, was positively correlated with increased connectivity between the right locus coeruleus and right insula/right anterior cingulate cortex across all groups (baduanjin, brisk walking and control). Won et al. (324) investigated the relationship between functional connectivity of the hippocampus and change in performance on memory tasks in healthy older adults and older adults with MCI.

In the MCI group, increased connectivity between the bilateral posterior hippocampi and the bilateral posterior cingulate were associated with increased LM recognition. For the healthy control group, no significant relationship between hippocampal connectivity and memory task performance were found (324).

Four papers reported improvements in cardiovascular fitness post intervention in both participants with MCI and healthy older adults (316–318,324). Differences in cardiovascular fitness between the MCI and healthy control groups were noted but not significant (316). One paper found reduction in FPN connectivity was significantly associated with improvements in balance and mobility (318).

4.4 Discussion

Previous research has highlighted that exercise can be beneficial for people with dementia, it can improve quality of life, cognition, executive dysfunction, balance, gait abnormalities and reduce falls risk (26,189). Reviews investigating the effects on exercise on brain activity have included a mixture of neuroimaging techniques such as MRI, PET, fMRI, fNIRS, EEG (180,306,307). Additionally, these reviews have included a variety of populations including healthy young adults, older adults without cognitive impairments, older adults at risk of cognitive decline and older adults with MCI (180,303,308).

This systematic review has focused specifically on the effects of exercise interventions on fMRI outcomes in older adults with MCI or dementia. Twelve papers from six studies were included in the review, five studies used study methodology which involved delivery of an exercise intervention and assessing

changes in neural activity/connectivity post-intervention (316–323). One study used a cross sectional design and self-reported measure to assess levels of physical activity in participants (315). All studies included older adults, with an average age of 65 and over with MCI. Additionally, case control studies also included healthy older adults aged 65 and over (316,317,324). No studies including people with dementia were identified.

Some of the studies included in this review took a more exploratory approach and conducted whole brain analysis, exploring exercise related changes in activation across the whole brain (315,316,319,321,322). The remaining studies explored exercise related changes in activation and connectivity in select brain regions and networks thought to be vulnerable to dementia pathologies including the hippocampus, posterior cingulate cortex within the default mode network, dorsal attention network, fronto-parietal network, locus coeruleus and ventral tegmental area (317,318,320,323–326).

All the studies included in the review reported exercise related changes in brain activity and connectivity at rest or in response to fMRI tasks in older adults with MCI. Studies reporting task-related fMRI outcomes highlighted an overall trend of reduction in task-related brain activity and functional connectivity post intervention (316,318,319) with the exception of one case control study which found an increase in task-related brain activity in participants with MCI who reported high levels of physical activity (316).

Previous task fMRI studies have highlighted people with MCI display increased task-related activation during memory tasks, indicating a compensatory mechanism through which the brain requires more input to complete the task

due to the presence of dementia related pathologies (250,330,331). As we get older and as neurodegenerative diseases become more prevalent in the brain, to circumvent the effects on performance, we engage in compensatory strategies. These strategies may include increased brain activation and recruitment of additional brain areas or networks to complete a task or maintain cognitive abilities (332). The studies included in this review identified a decrease in task-related brain activity post intervention in several areas including medial, superior, parahippcoampal and precentral gyrus, posterior cingulate, superior parietal lobe and left lateral occipital cortex (316,318,319). Decreased task-related activity post intervention in people with MCI suggests that exercise can increase the brains capacity to cope with dementia related pathologies, making the brain more efficient and reducing the need for the brain to employ compensatory strategies, indicating a partial return toward normal (333).

Exercise related changes were evident in resting state fMRI outcomes and suggest that different types of exercise of physical activity may impact spontaneous neural activity and functional connectivity in older adults with MCI in different ways. Aerobic exercise, dancing and brisk walking all increased spontaneous brain activity and functional connectivity in several brain regions including the hippocampus, anterior and posterior cingulate cortex and DAN. Progressive resistance training and baduanjin appeared to have a bidirectional effect on spontaneous brain activity and functional connectivity. Resistance training increased hippocampal connectivity whilst decreasing posterior cingulate cortex connectivity (320). Progressive resistance training induced changes in functional connectivity of the hippocampus and posterior cingulate

cortex were observable one year after intervention cessation (325). Baduanjin increased spontaneous activity in frontal lobes, increased functional connectivity of the locus coeruleus and ventral tegmental area and decreased hippocampal and DAN connectivity (322,323).

The medial prefrontal cortex, hippocampus, posterior cingulate cortex, anterior cingulate cortex, which are core regions of DMN, are often affected by AD related pathology in the early stages of the disease (284,334). fMRI studies have identified altered DMN, DAN and sensorimotor network connectivity in people with MCI and Alzheimer's disease (335). Findings from the included studies in this review indicate exercise may be able to influence neural networks that are affected by dementia related pathology in older adults with MCI (315–323). Additionally, some studies tested more than one type of exercise intervention and found differences in changes in neural activity and connectivity between interventions (320,322,323) which suggests that different types of interventions may benefit neural activity and network connectivity in people with MCI in different ways.

Balance and gait dysfunction are an early symptom of MCI and dementia and may be improved through exercise (189), though the neural mechanisms involved are still unclear. Lower connectivity between the dorsal attention network and the default mode network has been linked to decreased gait variability (336). Increased connectivity within the fronto-parietal network was associated with faster gait speed (337). The dorsal attention network plays a key role in top down processes and attention orientation, while the fronto-parietal network, known as the cognitive hub of control and plays a key role in executive

functions such as cognitive flexibility and motor planning. Studies included in this review have demonstrated that both networks exhibit changes in response to exercise interventions and changes in network connectivity were associated with better mobility (318,323). The fronto-parietal and dorsal attention networks may be key moderators through which exercise may be of benefit to postural control in older adults with MCI, though further work is needed to test this hypothesis.

The studies included in this review were of moderate to high quality, however there were a few notable limitations. None of the included studies reported justification for sample sizes and some studies did not report effect sizes for fMRI results (315–326). The studies included in this review had small sample sizes and may have been under powered. Study samples ranged from 18-86 participants (18-79 participants at follow up). Across the intervention groups, sample sizes ranged from 9-23 participants (316–326). Future work needs to look at replicating studies in large samples to ascertain if exercise related changes in neural activity and connectivity are still present. Across the studies participants were older adults diagnosed with MCI or older adults who met diagnostic criteria for MCI but had not been formally diagnosed. No study included people with dementia, highlighting a knowledge gap around effects of exercise on neural activity in this population.

There are a few limitations of the present review. Due to limited number of studies identified and the heterogeneity across study design, exercise interventions, fMRI analysis approaches, brain regions and networks of interest, it was not feasible to conduct a meta-analysis of the findings. Instead, a narrative

synthesis of the findings, based on fMRI outcome type was completed. The population of interest for this review was older adults with MCI or dementia, however no studies investigating effects of exercise on fMRI outcomes in people with dementia were identified, therefore findings should be treated with caution and are only relevant for people with MCI.

Further research is needed to study neural mechanisms through which exercises benefits older adults with cognitive impairments. Future work should confirm how different types of exercise affect connectivity of brain networks and regions involved in cognition, balance and gait which become impaired due to dementia related brain diseases. Identifying brain networks that exhibit changes in response to exercise could be useful for identification of potential biomarkers to provide additional objective outcome measures for future studies evaluating efficacy of interventions and for further personalisation of interventions for older adults with cognitive impairments (34,226,338).

4.5 Conclusion

Exercise can elicit changes in neural activity and connectivity of neural networks in people with MCI. However, studies investigating the effects of exercise interventions on fMRI outcomes in people with dementia are lacking, highlighting the need for more high-quality research using fMRI to understand exercise related changes in brain activity and connectivity in this population. Future work should also look to increase sample sizes and look to address issues around heterogeneity of study, intervention, fMRI task designs and fMRI analysis approaches.

5 Piloting a virtual reality-based balance task designed or older adults with cognitive impairments in healthy young adults

5.1 Background

Researchers have used task fMRI to study the networks and brain regions involved in cognitive functions such as memory, attention, emotion, motor control, language, and information processing (230). fMRI tasks are often highly controlled to retain experimental control and reduce the effects of confounding variables, meaning they are often not very realistic or representative of how we interact with the world around us (339). These tasks may not tell us much about the brain processes involved in complex actions such as whole-body movements (walking and balance). The movement limitation of fMRI means it is not possible to assess whole brain activity during whole-body movements such as walking, maintaining, or regaining balance.

In brief, motor imagery is a cognitive process in which an individual imagines they are performing a movement without actually performing the movement (82). Action observation involves observing an action, often performed by others. Neuroimaging studies have shown that motor imagery or action observation can elicit a similar neural response to executing the action in real life (36). Additionally, these techniques can be used alongside fMRI to investigate balance and gait related neural networks (340). A study by la Fougère et al. (36) used PET scanning and fMRI to compare neural activation in older adults during walking and imagined walking. The researchers reported that the

motor/premotor, multisensory cortices, para hippocampal gyrus and the cerebellum were active in both walking and imagined walking, providing evidence that motor imagery can recruit the similar brain networks as actual execution of the task.

Studies have also used motor imagery in combination with fMRI to investigate neural networks involved in walking, static and dynamic balance. A study by Ferraye et al. (95), found motor imagery of a dynamic balance task recruits both cortical and subcortical regions of the motor system including medial and lateral areas of the frontal cortex, basal ganglia and cerebellum. A combination of motor imagery and action observation alongside fMRI has been used to study neural correlates of static and dynamic balance in healthy young adults (341). For the motor imagery and action observation combined conditions and motor imagery only conditions, task related activity was noted in the putamen, cerebellum, supplementary motor area, premotor cortices, and primary motor cortex. Additionally, the dynamic balance task was associated with increased activity in the supplementary motor area and cerebellum compared to the static balance task (341). This indicates that the more demanding the balance task, the greater the neural response.

A comprehensive systematic review of the brain activity while walking compared brain activity of young and older adults during imagined standing and walking fMRI tasks. In younger adults, when compared to lying or standing, imagined walking was associated with increased activation in the prefrontal cortex, cingulate cortex, parietal areas, somatosensory cortex, temporal cortex, premotor cortex, putamen, insula, parahippocampal gyrus and cerebellum. In

addition to this, older adults also displayed increased activation in the right orbitofrontal cortex, dorsolateral prefrontal cortex and cortical visual areas (93).

The above studies have shown motor imagery tasks to be a useful way of investigating neural correlates of complex movements in healthy populations and age-related changes in balance and gait. Motor imagery has also been used alongside fMRI in certain clinical populations to study disease related changes in brain networks involved in balance and gait (342). Studies in patients with Parkinson's disease have used motor imagery to study gait related brain activity, comparing patients with symptoms of freezing gait to patients without symptoms of freezing gait and healthy controls (343,344). Patients with freezing gait were found to display altered activation in SMA, globus pallidus, ACC, frontal and posterior parietal regions in response to motor imagery tasks, when compared with patients without freezing gait (343,344).

Previous fMRI studies using motor imagery to study neural networks involved in balance and gait differed in task design and testing procedures, which may contribute to how accessible a task is to different populations. Some studies asked participants to recall movements from memory alone (35). Other studies physically trained participants in the movements of interest, such as a specific balance task or walking, running, then trained participants to imagine the movements they performed prior to undergoing an fMRI scan. During scanning session participants were then verbally instructed which condition to imagine (35,345,346). Some studies provided participants with still images or a video of the movement to imagine whilst in the scanner, using a screen and mirror system (341). Despite some of the limitations of motor imagery tasks and

heterogeneity in task design across studies, motor imagery paradigms combined with neuroimaging have enabled researchers to begin to uncover cortical involvement in postural control in healthy populations (347).

Using motor imagery and action observation with fMRI in people with MCI and dementia maybe useful in addressing the knowledge gap of how dementia related pathology may alter motor related brain activity and functional integrity of motor networks involved in balance and gait. The creation of knowledge of the functional brain changes relating to balance will be of use to researchers and clinicians in tracking progression of balance deficits in dementia as well as developing more targeted interventions to improve balance.

Previous imagined balance and gait tasks often relied on the individual imagining a task from memory, sometimes with a photo or video prompt (35,36,345,346). For people with MCI and dementia, imagining a task from memory whilst remembering complex task instructions may be difficult due to their cognitive impairments (348). To overcome the challenges of accessibility of motor imagery tasks for older adults with cognitive impairments a novel virtual reality-based walking and postural stability task was developed. The video clips for each condition (walking/obstacle navigation/balance), were recorded from the participant's point of view angle and designed to be delivered using goggles with LCD screens (like virtual reality goggles) to be more realistic and easier for older adults with cognitive impairments to imagine they are in the video.

The aim of this study was to pilot the novel virtual reality balance task in healthy younger adults prior to piloting the task with the target population of older adults with cognitive impairments. The objectives were to see (1) whether task

delivery was possible, (2) whether participants were able to view the task, (3) check the software and hardware used to administer the task was functioning and (4) assess whether the scanning experience with task was comfortable for participants. The secondary aim of the study was to run an exploratory whole brain analysis to explore whether brain activation increased in response to the more complex conditions in healthy young adults in response to the fMRI task. As well as this, in line with previous findings which showed deactivations in response to increasing task complexity in young adults (346), this study looked at whether brain activation was greater in the less challenging task conditions when compared with more complex task conditions.

5.2 Method

5.2.1 Setting

This study was conducted within the Sir Peter Mansfield Imaging Centre at the University of Nottingham Medical School, Queen's Medical Centre, Nottingham, UK.

5.2.2 Participants

Healthy volunteers were recruited to test the novel video based imagined walking, obstacle avoidance and balance fMRI task.

5.2.3 Inclusion and exclusion criteria

Healthy adults aged between 18 and 35 years old over, who were able to provide informed consent and physically undergo an MRI scan were eligible to take part.

Participants who were unable to complete the MRI safety questionnaire and/or complete the informed consent process were excluded from taking part in the

study. Participants with any known contraindication to MRI scanning (pacemaker, intracranial vascular clip, implanted medical device, and metallic fragment) were also excluded from the study. Participants who reported current or previous neurological, psychiatric, cognitive or mood disorders or any other significant medical condition were not eligible to take part. Participants who were claustrophobic, pregnant, or had a fixed dental brace or other craniofacial metalwork that was likely to cause significant image degradation or artefact were also excluded from the study.

5.2.4 Recruitment and data collection

The study was advertised across the University of Nottingham via posters and email. Those who expressed an interest in taking part were sent information about the study via email. After considering what study involvement entailed, those who were willing to take part and met the eligibility criteria outlined above were invited to the Sir Peter Mansfield Imaging Centre at QMC to undergo an MRI scan of the brain. On arrival to the imaging centre potential participants received further explanation about what the study involved and written informed consent was sought. Volunteers were also asked to complete the standard University of Nottingham MRI safety questionnaire, which was reviewed by a qualified radiographer prior to the scan.

Participants were shown three video clips corresponding to the three task conditions, walking, obstacle navigation and postural instability, on a TV prior to the scan and were instructed to imagine they are the individual in the video (see figure 5.1, 5.2 and 5.3). They then underwent a short 15-minute MRI scan during which they wore goggles (virtual reality goggles), with LCDs screens, through

which the fMRI task was presented. The CinemaVision goggle system produced by Resonance Technology: MRI Video Systems, Northridge CA was used to deliver the task. The goggle system was modified to be able to mount the goggles directly to the head coil. After the scan participants were asked to complete the MRI tolerability questionnaire (349) and were also asked for feedback on how they found the task using a free text box for participants to write their comments (see appendix A).

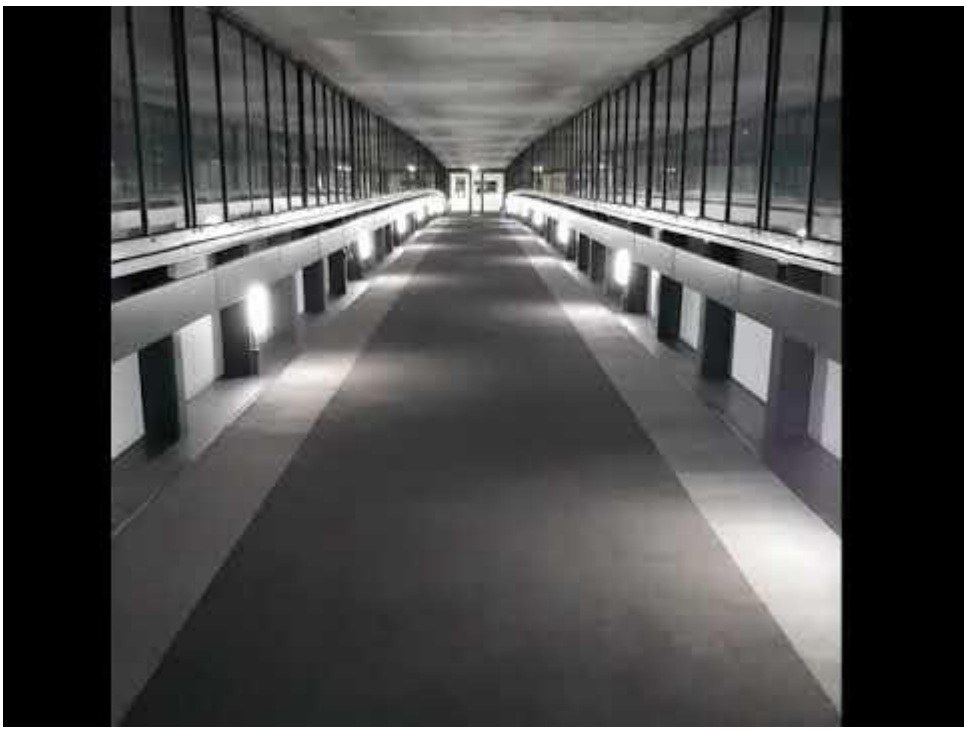

Figure 5. 1 Walking condition video.

Figure 5. 2 Obstacle navigation condition video.

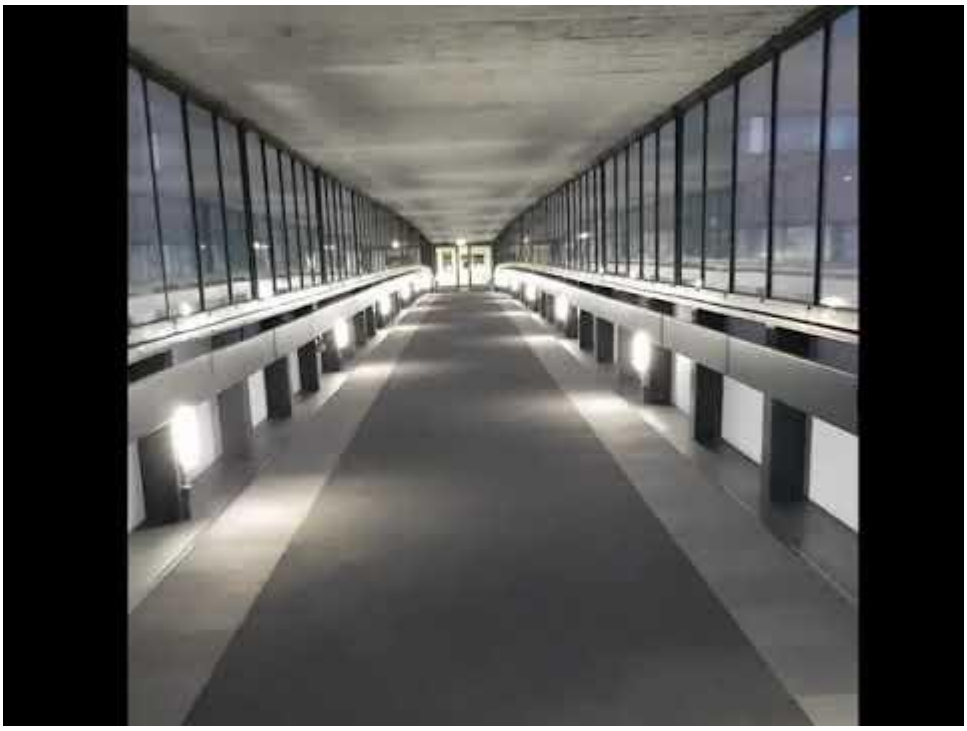

Figure 5. 3 Postural instability condition video.

5.2.5 fMRI task design and Image acquisition

The walking and balance fMRI task was a block design with 3 conditions: walking, obstacle avoidance and balance. The task involves watching videos relating to walking, obstacle navigation and simulated perturbations through virtual reality style goggles. The videos were shot from a first-person perspective to create an immersive experience. A video corresponding to each condition was presented for 22s followed by a 22s rest period where participants were presented with a fixation cross. Participants viewed each condition 3 times (except for the balance condition which was only presented twice due to timing issues between the task and scanner), with the task lasting 6 minutes. The task was designed in and delivered using PsychoPy2 (350).

Functional imaging was performed on a 3T MRI scanner (GE Healthcare discovery MR750), using a 32-channel head coil. T1, FSPGR BRAVO images were acquired using the following parameters: TR= 0.008144, TE= 0.003172, Flip Angle (FA) = 12, Inversion time = 0.45, Matrix= 256 x 256, Thickness= 1 and Voxel size = 1 x 1 x 1.

Functional images were acquired using echo planar imaging sequence using the following parameters: TR = 2000ms, TE = 30ms, Flip Angle (FA) = 77, Matrix = 64 x 64, Slices = 37, Thickness= 3, Voxel size = 3 x 3 x 3, Spacing between slices = 3.5, slices = 37 covering the whole brain and cerebellum.

5.2.6 Data analysis

Microsoft Excel was used for the analysis of the scanner tolerability questionnaire data and for task experience feedback. A Framework analysis approach (351) was applied to the feedback data on the task fMRI experience

data and involved the following steps: transcription, familiarisation, coding, developing an analytical framework and applying the framework was completed. The task experience feedback question and prompts informed the themes for the analysis framework; (1) “clarity of the videos”, (2) “task pace”, (3) “imagery ability” and (4) “ideas and recommendations for improvements” (see appendix B).

5.2.6.1 fMRI analysis

For this study exploratory whole-brain analyses were conducted using the general linear model (GLM) framework. The GLM framework is an extension of simple linear regression and is a powerful and widely used approach to analyse task-related fMRI data (352). The GLM uses a mass univariate approach, which involves constructing a separate model for each voxel. This approach assumes that voxels are independent of one another. The GLM is often expressed using the following equation, where Y is the time course for each voxel, X is the predictors or task regressors, Beta is the beta values and ε is the residuals:

$$\boldsymbol{Y = X\ \beta + \varepsilon}$$

Data processing and analysis was completed using Statistical Parametric Software (SPM) 12 (https://www.fil.ion.ucl.ac.uk/spm/software/). The first 5 volumes for each subject were discarded to allow for signal stabilisation. The remaining functional volumes for each subject underwent standard pre-processing steps including spatial realignment to correction for motion, slice timing correction, co-registration of fMRI images to the T1 structural image, registration to MNI space and smoothing using FWHM of 6mm to improve signal to noise ratio. The pre-processed and smoothed functional data were entered

into a 1st level analysis where the general linear model was applied to each voxel at the within-subject level (353,354). In the 1st level model, 3 regressors relating to each task condition (walking, obstacle avoidance, and slip perturbation) were included as predictor variables. In addition, six regressors relating to participants motion parameters, which were estimated during the motion correction stage of pre-processing, were included to control for head movement. At the first level, contrast volumes for each task condition against the implicit baseline were created. The contrast volumes from the 1st level analysis were then entered into a group level one-way between-subjects ANOVA. Simple effects Statistical Parametric Maps (SPMs) were computed to assess brain activation associated with each experimental task. Effects were reported at $p<.05$ corrected for multiple comparisons at the voxel level (FWE) with a cluster (k) threshold of 40 contiguous voxels.

To test the hypothesis that the more complex task conditions would elicit greater activation, one-tailed t-tests were conducted for the following contrasts: postural instability > obstacle navigation, postural instability > walking, obstacle navigation > walking (341). Based on previous findings that the healthy young adults displayed deactivations during more complex balance task (346), one-tailed t tests were conducted for the inverse to see if there was greater task related activation for the less demanding task conditions: walking > obstacle navigation, walking > postural instability and obstacle navigation > postural instability. Significant differences were recognized at a lower threshold of $p<.01$ uncorrected at the voxel level for multiple comparisons, with an extended cluster (k) threshold level of 40 contiguous voxels to reduce the risk of type 1 error. For

both simple effects and between condition contrasts, the AAL3 atlas tool (355) was used to assign anatomical labels to the results according to the nearest grey matter position.

5.2.7 Ethical approval

The study received ethical approval from University of Nottingham – ethics number B12012012a.

5.3 Results

Ten adults, 7 female and 3 male (mean age 24, SD 3.03), who were registered as students at the University of Nottingham met the study inclusion criteria, provided informed consent, and underwent the fMRI scan. Participation was voluntary and participants did not receive a reward for taking part in the study. Participants were in the scanner for approximately 15 minutes, with the task lasting for 6 minutes. Through these scanning sessions, an issue between task and scanner timing was noted, which meant the balance task condition was presented twice instead of three times. This issue was addressed prior to piloting the task with older adults with memory problems (see chapter 6). All participants completed their time in the scanner, indicating the scanning procedures were tolerable and all participants were able to view the task through the LCD goggles.

All 10 participants completed the MRI tolerability questionnaire (see table 5.1 for mean scores and range). Tolerability feedback was positive, mean rating for overall experience was 4.8/5, mean rating for length of time in the scanner was 4.5/5, and mean score for being able to see the video clearly was 4.6/5.

Seven participants provided written feedback about the video task and results of the framework analysis of the data is presented in table 5.2. For the visibility of videos theme, participants found the videos clear to see, however one participant reported seeing the cursor to be distracting. The issue around the distracting cursor was address for subsequent scanning sessions. Some participants found the task pace to be slow and it difficult to imagine being in the videos.

Table 5. 1 Mean ratings for MRI tolerability.

Questionnaire Item	**Min score**	**Mean score on a scale of 1-5**	**Max Score**
Overall experience	3	4.8	5
Lying flat on the MRI table	3	4.9	5
Having the technician position you in the MRI	5	5.0	5
Moving into the machine	3	5.0	5
Confinement inside the MRI	1	4.9	5
Not moving during the scan	1	4.4	5
Noise of the machine	2	4.4	5
Being alone in the scanner	2	4.6	5

Length of time in the scanner	3	4.6	5
Scanner temperature	3	4.6	5
Scanner smell	3	4.8	5
Post dizziness upon sitting	3	4.4	5
Ability to see clearly	3	4.7	5

Table 5. 2 Task experience feedback themes, subthemes and supporting quotes.

Themes	**Subthemes (occurrences)**	**Quotes from participants responses**
Visibility of videos	• Clear videos (2) • Distracting cursor (1)	• *Video was clear, would have been better without the cursor on the screen*
Task pace	• Walking pace (2) • Barrier height (1)	• *The slower speed made it feel a little unnatural but otherwise completely fine.* • *Make barrier higher.*
Imagery ability	• Difficulty/easy imagining (2) • Virtual reality (1)	• *At first, I found it difficult to imagine being the one in the video but after a short while I found it comfortable and easy.* • *Make it more real I tried to look into what people do in VR games because those really replicate real life phenomenon*.
Ideas or recommendations for improvement	• Screen width (2)	• *if video went to the edges of the screen, I would have been able to imagine it was me easier* • *It did take some reminding to imagine myself as the person walking, especially since it was a rectangle screen. Even if I was looking directly at the screen, I could notice the end of the screen and the black border around. Maybe a more curved extended screen covering the peripheral vision.*

5.3.1 Simple effects

Walking

In response to the walking condition, activity was detected bilaterally in the cerebellum, the left visual cortex, and the left middle frontal gyrus ($p<.05$ FWE corrected, see Table 5.3 and Fig. 5.4).

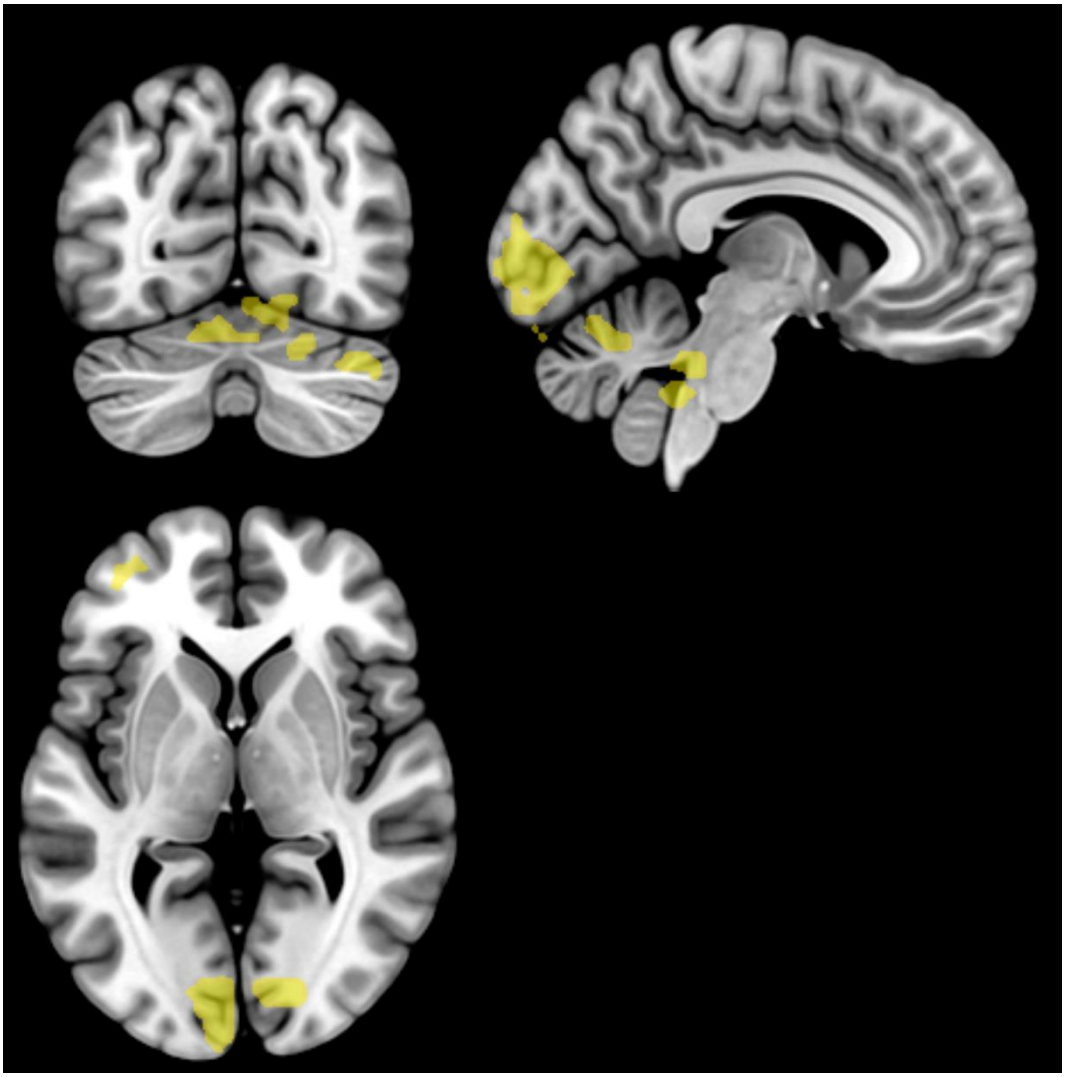

Figure 5. 4 Axial, Coronal and Sagittal view of brain activity associated with walking condition.

Obstacle navigation

In response to the obstacle navigation condition, significant activity was detected in bilateral precuneus, left middle frontal gyrus and the right visual cortex ($p<.05$ FWE corrected, see Table 5.3 and Fig. 5.5).

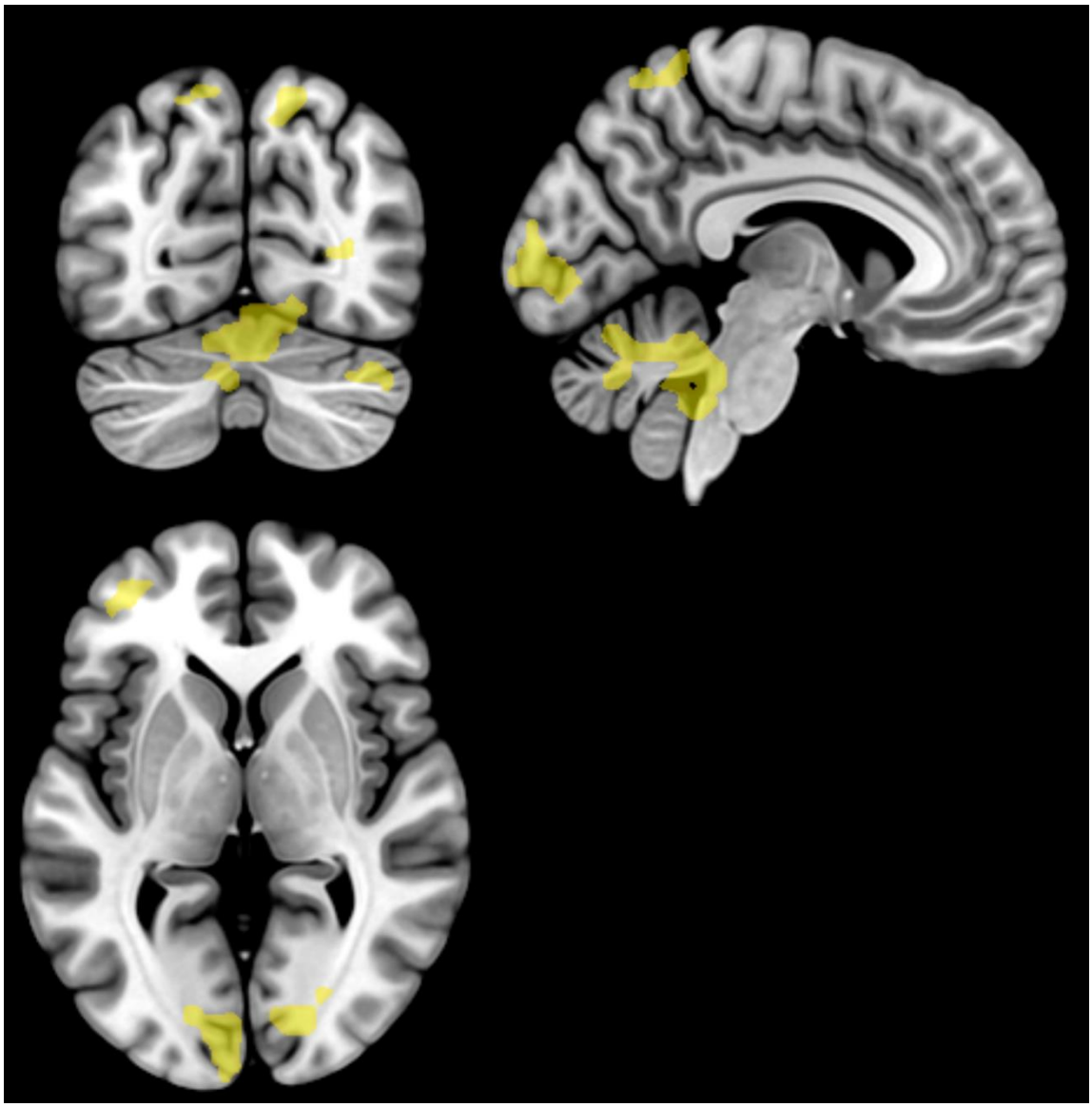

Figure 5. 5 Axial, Coronal and Sagittal view of brain activity associated with obstacle navigation condition.

Postural instability

In response to the postural instability condition, activity was detected bilaterally in the cerebellum, left precuneus and left middle occipital gyrus ($p<.05$ FWE corrected, see Table 5.3 and Fig. 5.6).

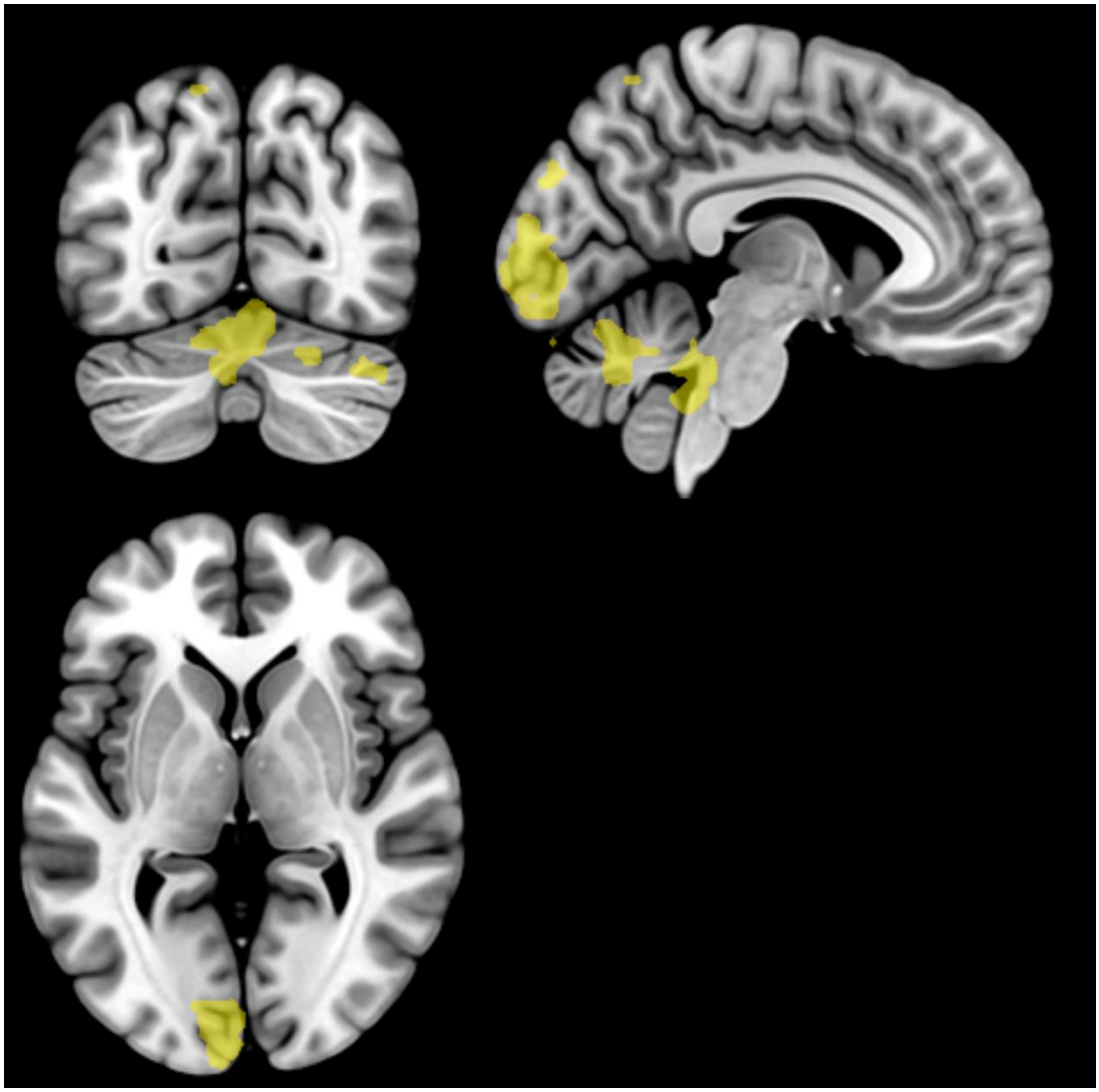

Figure 5. 6 Axial, Coronal and Sagittal view of activity related to postural instability condition.

5.3.2 Walking – Obstacle navigation/Postural instability

Compared to the walking condition significant increases in activity were noted in the left precuneus and right superior parietal lobule in the obstacle navigation condition (p<.01 uncorrected, see Tabl3 5.3 and Fig. 5.7). When exploring whether postural instability was associated with significantly greater activity compared with the walking condition, no voxels survived the lenient p threshold.

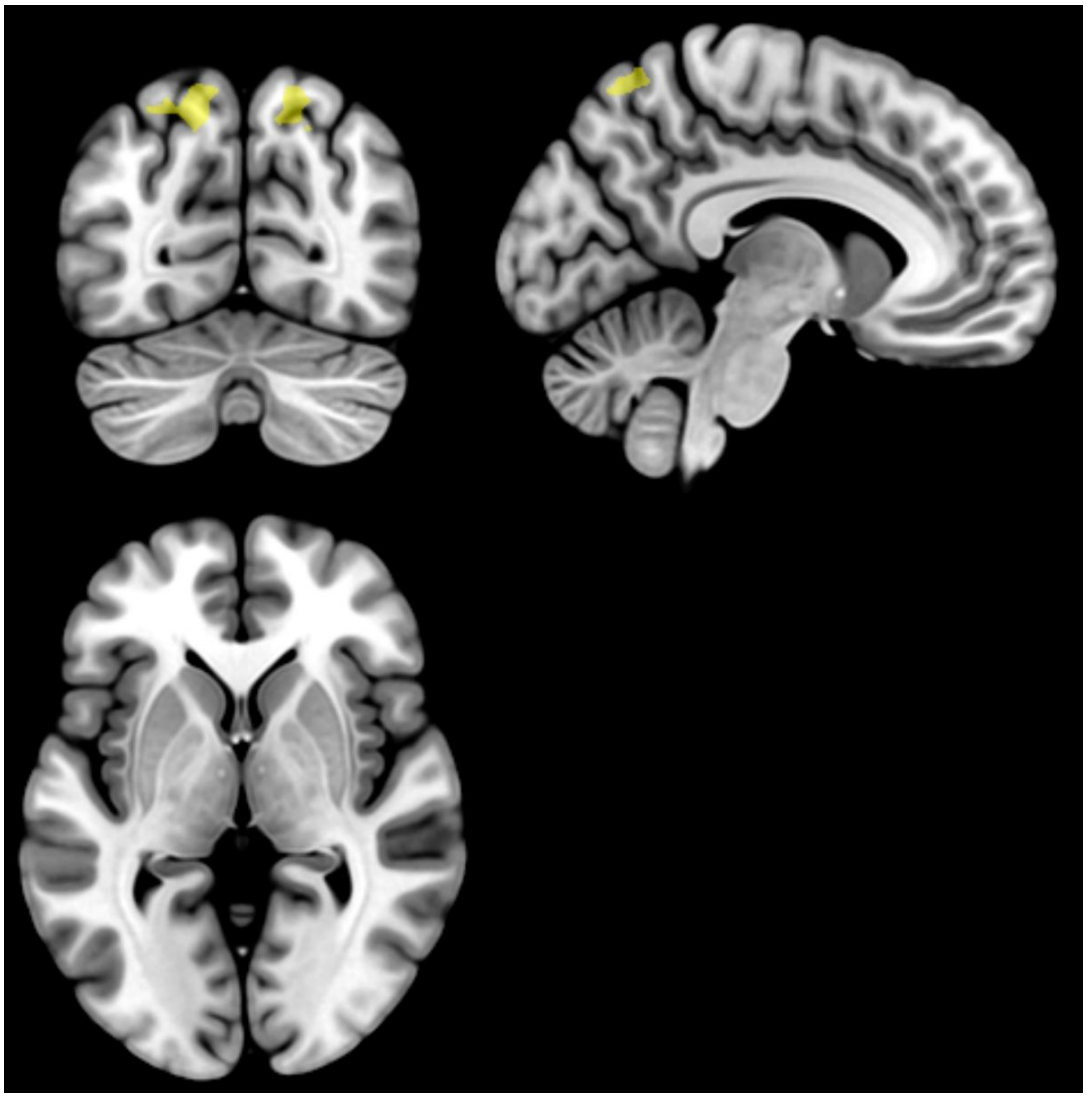

Figure 5. 7 Axial, Coronal and Sagittal view of walking<obstacle navigation.

Conversely, when compared to the postural instability condition, walking was associated with increased activation right postcentral and precentral gyrus, right putamen, right paracentral lobule, right inferior temporal gyrus, right insula and left middle temporal gyrus (p<.01 uncorrected, see Table 5.3 and Fig 5.8).

When compared with obstacle navigation condition, walking was associated with increased activation in the right superior parietal lobule and the left precuneus (p<.01 uncorrected, see Table 5.3 and Fig 5.9).

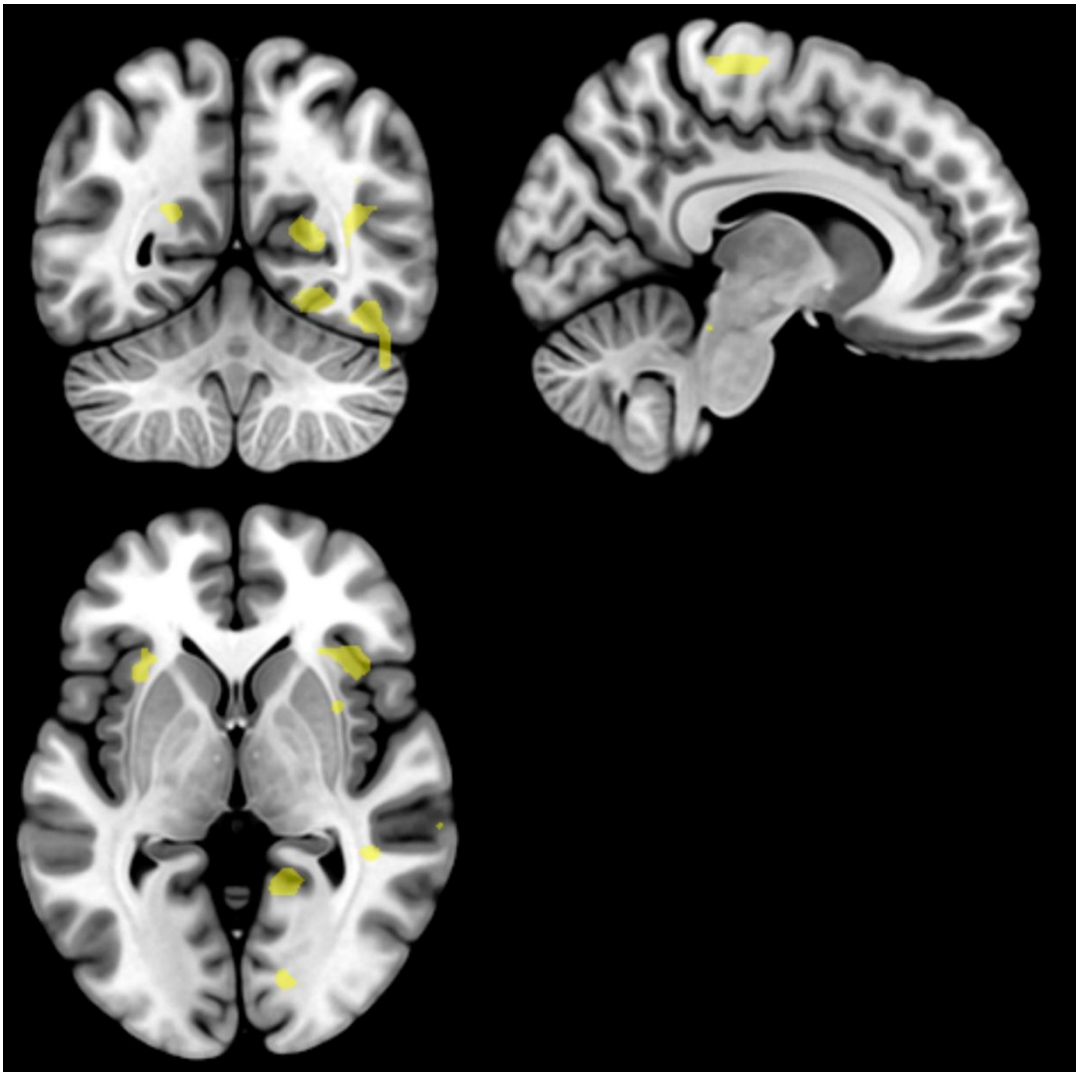

Figure 5. 8 Axial, Coronal and Sagittal view of walking>postural instability contrast.

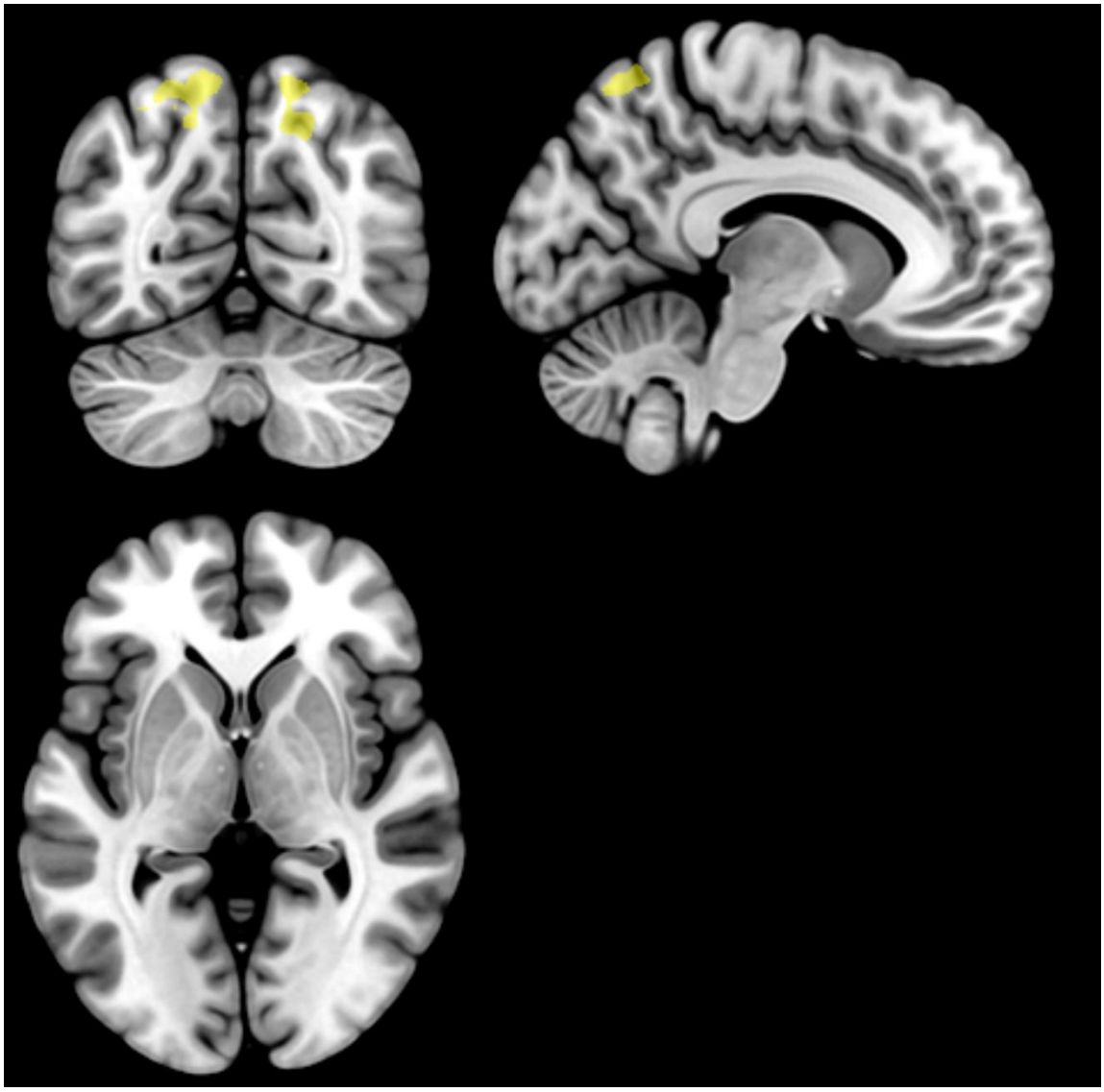

Figure 5. 9 Axial, Coronal and Sagittal view of walking>obstacle avoidance contrast.

5.3.3 Obstacle – Balance

There was no significant increase in activity in the postural stability condition when compared with the obstacle navigation condition. The obstacle navigation condition was associated with increased activation in the bilateral middle frontal gyrus, bilateral middle occipital gyrus, left precentral gyrus, right inferior and middle temporal gyri (P<.01 uncorrected) when compared with the postural instability condition (see Table 5.3 and Fig. 5.10).

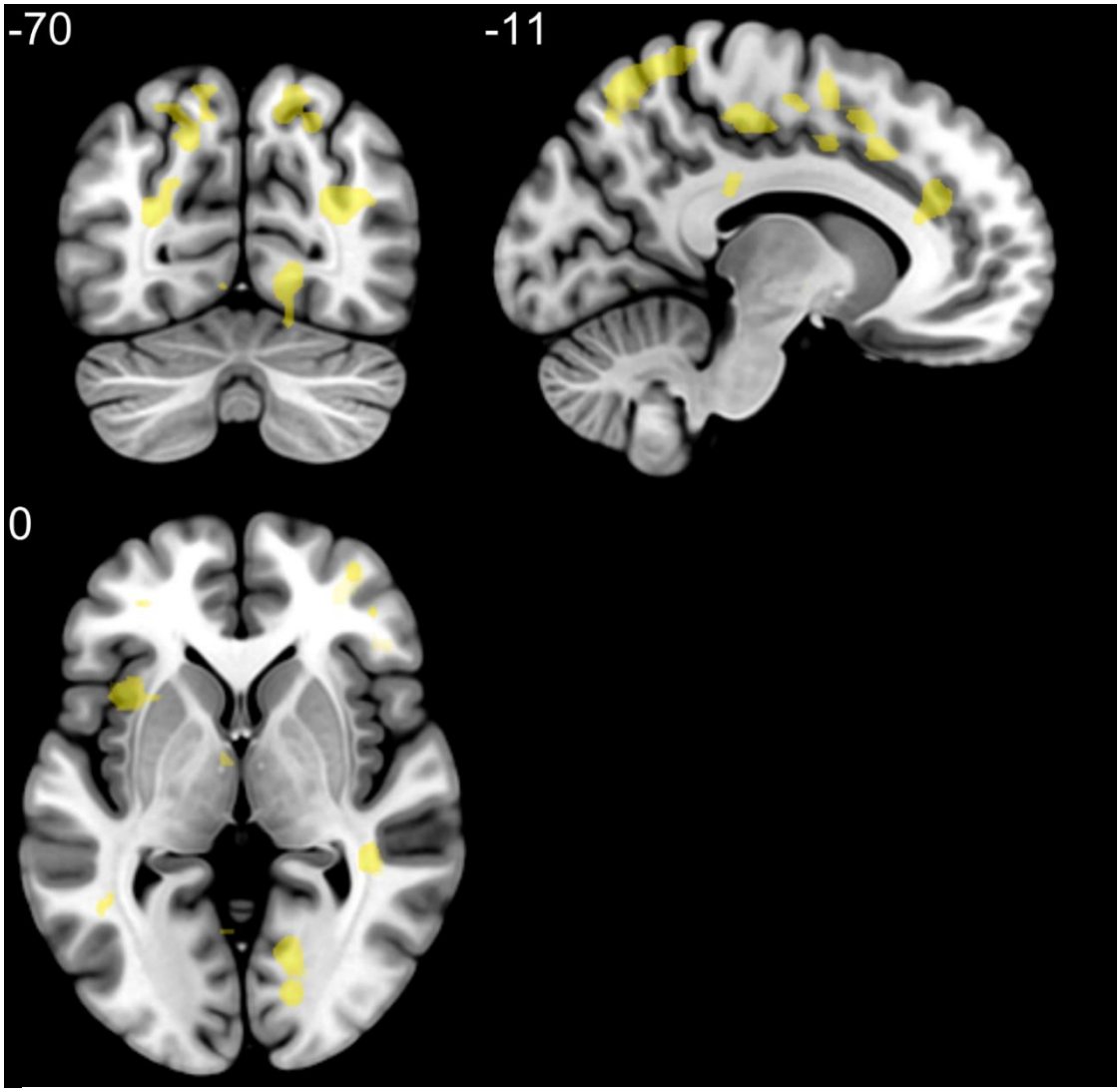

Figure 5. 10 Axial, Coronal and Sagittal view of brain activity for obstacle avoidance>balance contrast.

During each of the task conditions, walking, obstacle navigation and postural instability, activation was noted in the cerebellum, visual cortex, middle frontal gyrus and precuneus.

Task condition complexity associated increases in brain activation were noted in precuneus and superior parietal lobule during obstacle navigation condition compared to walking, however no regions of increased activation were found for

the postural instability condition when compared with the obstacle navigation and walking conditions.

When exploring task condition complexity related deactivations, increased activation was noted across motor cortex and somatosensory cortex, right putamen, right paracentral lobule, insula and temporal gyri during the less complex walking condition when compared with the more challenging postural instability condition. Additionally, increased activation in the right superior lobule and left precuneus were noted during the walking condition when compared with the obstacle navigation condition.

Table 5. 3 Spatial location (co-ordinates) of voxels with the highest z scores and t scores inside each cluster is displayed for each condition and for comparison of activation between conditions.

Task condition / contrast	**Anatomical location**	**x**	**y**	**z**	**cluster size**	**T score**	**Z score**
Walking*	Left calcarine	18	-88	5	484	14.86	6.75
	Right cerebellum	45	-70	-31	165	12.69	6.36
	Left cerebellum	-6	-46	-40	72	11.97	6.21
	Left middle frontal gyrus	-39	53	5	43	10.37	5.84
Obstacle navigation*	Left precuneus	-12	-64	65	179	17.47	7.13
	Left middle frontal gyrus	-42	26	41	71	16.70	7.03
	Right calcarine	18	-85	5	818	15.25	6.81
	Right precuneus	24	-43	23	66	12.46	6.31
Postural instability*	Left middle occipital gyrus	-21	-97	11	500	16.64	7.02

	Left precuneus	0	-55	62	58	14.75	6.73
	Left cerebellum	-6	-46	-40	107	13.64	6.54
	Vermis 9	33	-46	-43	47	12.53	6.33
	Right cerebellum	42	-73	-31	76	11.03	6.00
Walking < Postural instability**	No voxels survived p<0.01 threshold						
Walking < Obstacle navigation**	Left precuneus	-15	-70	59	115	5.56	4.19
	Right superior parietal lobule	15	-67	62	144	3.69	3.14
Obstacle navigation<Postural instability**	No voxels survived p<0.01 threshold						
Walking > Balance**	Right postcentral gyrus	36	-28	26	79	4.98	3.90
	Right putamen	30	8	5	42	4.96	3.89
	Right inferior temporal gyrus	42	-55	-13	237	4.51	3.64

	Right precentral gyrus	30	-13	44	56	4.29	3.52
	Left middle temporal gyrus	-51	-37	-13	40	4.20	3.46
	Right insula	39	23	-1	40	4.15	3.43
	Right paracentral lobule	9	-25	68	40	4.12	3.41
Walking > Obstacle navigation**	Right fusiform gyrus	30	-28	-22	106		
	Right inferior temporal gyrus	42	-52	-13	58	4.66	3.73
Obstacle navigation>Postural instability**	Bilateral middle occipital gyrus	24	-46	38	302	3.87	3.25
		-30	-73	20	42	4.30	3.52
	Bilateral middle frontal gyrus	-30	32	44	65		
		27	35	41	117	4.38	3.57
		30	47	5	126	4.06	3.38
	Right superior frontal gyrus	-24	2	41	622	6.21	4.48
	Left inferior parietal gyrus	-15	-58	65	507	5.69	4.25

	Right superior parietal gyrus	21	-58	59	255	5.47	4.15
	Right lingual gyrus	12	-64	-10	116	5.38	4.10
	Left Superior ACC	-12	35	23	44	4.53	3.65
	Left post central gyrus	-54	-4	38	85	4.04	3.36
	Right middle temporal gyrus	54	-25	-16	40	3.98	3.33

**p<.05 FWE corrected **p<.01 uncorrected.*

5.4 Discussion

The aims of this study were to (1) see if the video task was deliverable, (2) whether participants were able to view the task, (3) test software and hardware needed for task delivery and (4) assess tolerability of the scanning experience. A secondary aim of the study was to conduct exploratory whole brain analysis to look at task related activation in healthy young adults. Ten healthy young adults who were eligible and willing to undergo the MRI scan and complete the fMRI task were recruited. All participants were able to complete the task and their time in the scanner, there were no withdrawals from the study. Also, all participants completed MRI tolerability questionnaire and mean scores across the group for each item were high, which show MRI scanning procedures were well tolerated by participants. The task was deliverable, all participants reported being able to see the videos through the goggles.

The framework analysis approach to the task fMRI feedback explored four key themes, visibility of videos, task pace, imagery ability and ideas or recommendations for improvement. For the visibility of videos theme, participants found the videos clear to see. For task difficulty, participants reported the walking speed of the task was too slow and suggested increasing the height of the obstacle in the obstacle navigation condition to make the task more challenging. It is important to note that the task was designed for older adults with cognitive impairments, given that the healthy young volunteers found walking pace to be too slow and the obstacle not challenging enough, suggests that it may be well suited for the intended population. For the imagery ability theme, findings were mixed, with some participants finding it easy to

imagine themselves in the videos, whilst others found it more difficult. One participant suggested that replicating VR games more closely would make the task feel more real. This could improve participant's ability to imagine themselves completing the task. Some participants also provided suggestions on how to improve the task moving forward, which included adjusting the video so that the task was more immersive and easier to imagine oneself in the videos.

The fMRI data was successfully pre-processed, simple effects analysis revealed brain activation in brain regions associated with balance and gait including the cerebellum, visual areas and left middle frontal gyrus across all three task conditions. These findings are in line with observations in previous work (35,341,346). Jahn et al. (35) identified activity in cerebellar and visual areas in response to walking imagery. Additionally, Taube et al. (341) found motor imagery and action observation related activity in motor areas and cerebellum.

Previous work using motor imagery to investigate neural correlates of postural control and walking have reported that more challenging motor imagery-based balance and walking tasks elicit increased brain activity in healthy adults in the motor areas, putamen and cerebellum (341). In the present study, when comparing the effects of task complexity on brain activation, significant increases in activation were noted in obstacle avoidance condition, when compared to walking. However, there were no significant increases in activation in balance condition when compared with walking or obstacle avoidance conditions. The present findings did not confirm the effects of task complexity and related increased activation.

The present study found walking was associated with greater activation in pre and post central gyri, middle and inferior temporal gyri when compared with the more complex obstacle avoidance and postural instability conditions. Similar findings have been noted by Zwergal et al. (346), who noted that younger participants displayed deactivations of several brain regions as task demands increased.

Activation of several regions in response to the task conditions, may be representative of various functional networks involved in postural control. For instance the noted activation across the cerebellum, putamen, visual, somatosensory and motor cortices during the task conditions may correspond to sensorimotor network involvement (48,227,231). Task related activation in visual, parietal and temporal areas corresponding to the vestibular cortices provide further support for the need for multisensory integration to maintain balance (346). Additionally activation in the visual, parietal and temporal areas may represent the dorsal and ventral visual pathways which may play a key role in object navigation in gait and postural control tasks (48). The dorsal visual pathway projects forward and upwards from the visual cortex into the parietal lobe and is involved in scene processing, encoding object positioning, navigation and spatial working memory (356). The ventral visual pathway projects out to the temporal lobe from the visual cortex and is thought to be involved in processing of object features such as shape, colour, dimensions (356). Activation was also noted in the frontal regions which are involved in higher order cognitive processes such as executive function, attention and working memory (231,238). The exact role these regions and the related cognitive processes play

in postural control are still unclear, further work is needed to uncover their role which will be useful in understanding the mechanisms through which cognitive impairments impact balance and gait functioning.

There are several limitations to this study that are important to note. Firstly, the study sample size is small, so findings need to be treated with caution and may not be generalizable. Additionally, due to the small sample size, when comparing activation between conditions a more lenient *p* threshold was used and the analysis did not correct for multiple comparisons, increasing the risk of type 1 error of falsely rejecting the null hypothesis (357). A cluster threshold was applied to try to minimise the risk of type 1 error, nevertheless the findings must be treated with caution.

Timing issues between the task and scanner meant participants were not presented with the same number of trials in all conditions. The walking and obstacle conditions were presented three times each whereas the postural instability condition was presented twice. For the walking<postural instability and obstacle avoidance<postural instability contrasts, where no voxels survived the lenient uncorrected *p* threshold, it may be possible that the difference in task condition presentation may be contributing to the lack of effect seen in response to task complexity.

Previous work by Meulen et al. (358), investigated the effects on imagery ability and related brain activation. Participants with higher imagery ability scores, showed greater activation in motor areas, than participants with low imagery ability scores (358). The task used in this study was designed for older adults with cognitive impairments who often exhibit slower gait speed (359). Task

feedback showed the walking pace was too slow for participants in this study and may have impacted their ability to imagine themselves in the video. The task may not have been challenging enough for the healthy younger participants, which may be contributing the lack of increased activation in response to increasing task complexity.

5.5 Conclusion

This study shows that the novel video-based motor imagery task was deliverable, the software and hardware used to deliver the task work and participants were able to see the task clearly. Additionally, the scanning procedures were well tolerated by participants and overall experience was scored highly. Simple effects analysis showed activation in line with previous findings in the cerebellum, visual areas, precuneus and middle frontal gyrus. Task complexity was not associated with significant increases in activation, even at a lower threshold. This study found the opposite, the less demanding conditions, walking, and obstacle navigation were associated with greater activity than the more demanding obstacle navigation and postural instability conditions. Due to the small sample size and lenient uncorrected threshold for significance used findings need to be treated with caution. The next study chapter presents results from piloting this task with a subset of participants from the PrAISED RCT, who have MCI or dementia. Additionally, the pilot study also investigated the relationship between task related activity in motor areas, executive function, and balance.

5.6 COVID-19 impact

The original aims of this study were to pilot the fMRI task in healthy younger and healthy older volunteers. A second aim of the study was to quantify the neural response to the task in both groups and to identify between group differences in activation for each condition (walking/obstacle/balance). Based on previous work I hypothesised that older adults would exhibit greater task related activation in motor and vestibular areas across all conditions compared to healthy young adults (346).

Due to the ongoing COVID-19 pandemic, related lockdowns, and restrictions, which were ongoing between March 2020 and July 2021, it was not possible to recruit and scan 10 healthy older volunteers. Additionally, the scanner in the Medical School where the scans for the healthy young volunteers were conducted, was upgraded in early 2021. This also meant that scanning 10 healthy older volunteers was also not possible as it would be difficult to control for scanner differences during the between group analyses.

6. Using a virtual reality balance task to explore neural correlates of postural stability in older adults with dementia: A pilot study

6.1 Background

Older adults with MCI or dementia have an increased risk of falls and related consequences including fractures, reduced activity and loss of independence (26). Increased falls risk in this population has been attributed to dementia specific risk factors which include cognitive dysfunction, balance, gait and mobility dysfunction (26,147,359,360). Various studies and meta-analyses have highlighted that balance and gait dysfunction is often present at the early stages of dementia and may be an early precursor for cognitive decline (161,361–363). Unearthing the neural mechanisms involved in balance dysfunction in this population is important in being able to develop target interventions to improve balance and reduce risk of falls (364,365).

MRI studies have explored structural brain changes associated with balance and gait deficits in both healthy older adults and older adults with cognitive impairments. Healthy older adults with better mobility displayed increased grey matter in the cerebellum, basal ganglia, postcentral gyrus and superior parietal lobe (146). A comprehensive systematic review by Wilson et al. (366) found altered gait characteristics (slower gait speed and step length) were associated with reduced global grey matter and regional grey matter in frontal, parietal, supplementary motor areas, sensorimotor limbic areas, occipital cortex and basal ganglia in healthy older adults. In older adults with cognitive impairments

and dementia, postural instability was associated with reduced volume in the subcortical structures including the amygdala, thalamus, basal ganglia, caudate nucleus, putamen, nucleus accumbens, hippocampus, cerebellum and cortical structures including the inferior parietal cortex and frontal lobes (367,368). Systematic reviews exploring structural brain changes associated with postural stability and gait in older adults with cognitive impairments have found that gait dysfunction was associated with atrophy in the prefrontal and motor cortices, middle cingulate, insula, caudate, hippocampus and basal ganglia (364,369) .

Functional MRI has been increasingly used alongside motor imagery and action observation based postural control tasks to investigate brain regions and networks involved in postural control and how this affected by aging and neurodegenerative disorders (69,364,369). Zwergal et al. (346) investigated the effects of aging on neural activity associated with postural control during mental imagery of lying, standing, walking and running, comparing young and older adults. Older adults displayed increased activation in supplementary motor area, precentral gyrus, caudate nuclei, cuneus, precuneus, parahippocampal gyri and cerebellum during imagined walking and greater activation in middle and superior frontal gyrus, cuneus, precuneus, lingual gyrus, fusiform gyrus, postcentral gyrus, and superior temporal gyrus during imagined standing, when comparing with baseline. Increased activation in vestibular cortices and anterior cingulate cortices (ACC) during imagined running and imagined walking was noted in older adults whereas younger adults displayed a deactivation of multisensory vestibular cortices and ACC during imagined running, walking and standing conditions.

During both motor and visual imagery, older adults displayed stronger activation of left middle frontal gyrus, right supplementary motor area and right orbitofrontal cortex when compared with young adults (370). During motor imagery and action observation of static balance, older adults displayed increased activation in supplementary motor area and primary motor cortex compared to young adults. During motor imagery and action observation of dynamic balance, older adults displayed increased activity supplementary motor area, primary motor cortex, prefrontal cortex and the putamen when compared with younger adults (371). These findings of increased activation in older adults compared to younger adults could be a compensatory mechanism to mitigate the impact of age-related degeneration of brain regions associated with postural control.

Various systematic reviews and meta-analyses have also investigated static and dynamic postural control-related neural activity using a variety of neuroimaging modalities during actual movement, observed movement and imagined movement, across the lifespan (81,347). In healthy populations static postural control activated vermis in the cerebellum, vestibular nuclei, ponto mesencephalic junction, left midbrain, thalamus, caudate nucleus, putamen and basal ganglia, occipital gyrus, ACC and paracentral lobule (347). Dynamic postural control activated the brainstem, MLP, pons, thalamus, frontal lobe, SMA, parietal lobe, cingulate cortex, occipital lobe, insula. Reactive postural control recruited in the thalamus, SMA, superior temporal gyrus, occipital and cingulate cortex, putamen, cerebellum and PMC (347).A recent meta-analysis of neuroimaging studies measuring brain activity in response to motor imagery,

action observation and actual movement explored unique and overlapping networks across all three task types. Motor imagery involved bilateral dorsal and ventral premotor cortices, bilateral SMA, cingulate, putamen, inferior and superior parietal regions, right inferior parietal sulcus, left DLPFC, rostral inferior, middle superior parietal, basal ganglia and cerebellar regions (81).

A systematic review of studies using EEG and fNIRS alongside real and imagined balance and gait tasks to explore changes in brain activity in older adults with and without neurodegenerative disorders found older adults (with and without neurodegenerative disorders) displayed increased activation in the prefrontal cortex during balance and gait tasks when compared with young healthy adults (69). fMRI combined with motor imagery and action observation tasks is being used to explore how brain regions and networks involved in postural control are altered by neurodegenerative disease. In Parkinson's disease, a meta-analysis of fMRI studies exploring neural correlates of gait found decreased activation of the supplementary motor area when compared with healthy counterparts (372). In Amyotrophic Lateral Sclerosis, those with upper motor neuron degeneration, displayed altered activation of supplementary motor area, precentral gyrus, superior parietal lobule and dorsolateral prefrontal cortex during gait motor imagery task when compared with those with lower motor neuron degeneration and healthy controls (373).

Brain activity during balance and gait is under-researched in people with MCI and dementia (69). Using motor imagery in people with MCI and Dementia could help us to better understand how dementia changes neural activity involved in balance and gait. Motor imagery tasks require following complex instructions

and imagining movements from memory, which is likely to be challenging for older adults with MCI and dementia. For the current study, a novel VR based balance task was developed for older adults with MCI and dementia (see 5.2.5 for more details on the task design).

6.2 Study aims and research questions:

- Is the task deliverable?
- Can participants view the task?
- Are MRI scanning procedures well tolerated by participants?
- What are participants' experiences of the task?
- Do older adults with MCI/dementia show changes in activation/deactivation relating to different task conditions?
- Are there significant differences in BOLD signal parameter estimates in regions of interest (ROIs), corresponding to postural control between task conditions?
- Do we see a relationship between the difference in activity in ROIs corresponding to postural control, between conditions, and physical performance on BBS and TUG?

6.3 Methods

This study was a cross-sectional, pilot fMRI study within the multicentre PrAISED RCT.

6.3.1 Inclusion and exclusion criteria

Participants enrolled in this study met the following PrAISED inclusion criteria (2):

1) Aged 65 and over.

2) A diagnosis of MCI or dementia of any subtype (except dementia with Lewy bodies).

3) Has a family member, carer, or friend who knows the participant well and is willing to act as an informant.

4) Able to walk without human help.

5) Able to communicate in English.

6) Able to see, hear and have sufficient dexterity to complete neuropsychological tests.

7) Mental capacity to give consent and consent to taking part in the study.

8) Montreal Cognitive Assessment (MoCA) score 13-25.

In addition to the above inclusion criteria, participants were assessed for mental capacity and ability to consent to have additional MRI scans and be willing to participate in the study.

Participants meeting any of the following MRI specific exclusion criteria were excluded from taking part:

1) Known contraindication to MRI scanning (for example pacemaker/ implanted defibrillator, intracranial vascular clip, implanted programmable device, intra-ocular metallic fragment, etc).

2) Claustrophobia.

3) Cranioplasty, craniofacial reconstruction, fixed dental brace, or other craniofacial metalwork that is likely to cause significant image degradation or artefact.

6.3.2 Recruitment and study procedures

The consent form for the PrAISED2 RCT included an optional clause (Clause 7) asking if participants would be willing to be contacted to discuss related studies (see appendix C). Participants who indicated their agreement to this clause were introduced to the additional MRI study and provided with a participant information sheet by the researcher conducting the baseline assessment visit (see appendix F).

Participants who expressed interest in learning more about the MRI study at the PrAISED baseline visits, were followed up by telephone to discuss the study in more detail and ascertain if the participant was interested in taking part. Participants who expressed interest in undergoing an MRI scan were asked MRI safety screening questions to ensure that it was safe for them to undergo an MRI scan. At this point, any participants who declared any possible contraindications to having an MRI scan were advised it was not safe for them to undergo the MRI study. Participants who met MRI-specific eligibility criteria and were willing to take part in the study were visited in their homes by a researcher who assessed capacity and sought informed consent. After this, participants were booked in for the baseline MRI scan at the Sir Peter Mansfield Imaging Centre at Queen's Medical Centre.

All participants were required to complete their baseline MRI scan within 6 weeks of completing their PrAISED baseline visit. This was to ensure that all

participants completed baseline scanning before any intensive therapy from the PrAISED programme was delivered ensuring that the baseline measurements were true baselines. Due to the relatively short time frame in which consent and baseline scanning need to be completed, taking informed consent for the MRI study at the participant's home before them attending the imaging centre was not efficient. To improve the process and speed up the timeframe in which participants underwent their baseline scanning, an amendment to the study protocol was submitted to the NHS ethics committee, so that participants could be consented at the imaging centre before undergoing their baseline scan (see appendix E).

For the new process, if the participant was eligible to have an MRI scan and were interested in taking part, I arranged an appointment to attend the Sir Peter Mansfield Imaging Centre at the Queen's Medical Centre, Nottingham. At the appointment, I discussed the study with the participant in more detail and asked the participant to complete the standard University of Nottingham MRI safety questionnaire which was subsequently checked by a qualified radiographer. Participants with a history of possible intraocular metallic foreign body (e.g. metalworkers, welders, exposure to shrapnel blast, etc.) were not able to undergo an MRI scan unless it could be confirmed that there was no risk of retained metal fragments e.g. by checking records of previous x-ray or CT scans.

Participants who met the criteria and were happy to take part in the study were asked to sign a consent form before proceeding with the MRI scan (see appendix G). Before going into the scanner, all participants were presented with three videos clips to watch on video screen corresponding to each task condition and

instructed to try to imagine themselves in the video. As in the healthy volunteer pilot study, all participants were given goggles with LCD screens to wear so that they were able to see the task. The radiographer ensured participants were positioned correctly on the scanner bed and used padding around the head to limit movement. Once in the scanner, all participants could communicate with the radiographer and researcher through the intercom system and be advised when the task was about to begin. After completing the scan, participants were asked to complete an MRI tolerability questionnaire and provide feedback on their experiences of the fMRI task.

Participants were to undergo a second follow-up multimodal MRI scan, 12 months later, after completing their PrAISED follow-up assessments. Due to COVID-19 lockdowns, closure of the imaging centre, restrictions, and shielding guidance, follow-up scans were not possible, and the planned longitudinal study could not be completed (see chapter 8 for more details on the impact of COVID-19 on the proposed research for this thesis).

6.3.3 PrAISED baseline assessments

As part of the PrAISED RCT, all participants underwent a comprehensive baseline assessment. A detailed list of the assessments is available in the protocol which has been published (223). The work presented in this thesis was interested in the following measures completed by PrAISED participants at baseline:

- Demographics:
    - Age.
    - Sex.

- Ethnicity.
- Diagnosis (MCI or dementia).
- Dementia type (if known).

- Activities of daily living:
  - Nottingham Extended Activities of Daily Living Scale (NEADL) – completed by the participant (374).
  - Disability Assessment in Dementia (DAD) - completed by the informant (375).
- global cognition and executive function:
  - Montreal Cognitive Assessment (MoCA) was used to screen participants, assess eligibility for the PrAISED RCT and to measure global cognition (376).
  - Verbal fluency (animal naming) – testing cognitive flexibility.
  - CANTAB assessments (377):
    - Spatial Span test (SSP) to assess visuospatial working memory capacity.
      - Outcome = longest sequence correctly recalled.
    - Multi-Tasking Test (MTT) to assess executive function and attentional set-shifting:
      - Median reaction time for switching.
      - Median reaction time for congruent blocks.
      - Median reaction time for incongruent blocks.
- Berg Balance Scale (BBS) – widely used assessment in clinical practice, involving 14 tasks of increasing difficulty to assess both sitting and standing, static and dynamic balance (378,379).

- Timed up and go (TUG) – measures mobility, balance, walking ability, and falls risk in older adults (380).
- In addition to these assessments, after scanning participants also completed an MRI tolerability questionnaire and provided written feedback about the fMRI task experience.

6.3.4 Task fMRI design and delivery

MRI compatible glasses with adjustable lenses to allow correction of vision were provided to those who normally wear glasses. Whilst in the scanner the participant was also provided with protective earplugs as MRI scanners can be very noisy. Most people undergo MRI scanning without any difficulty, but if needed the participant was able to contact the MRI technician during the scan via an intercom or with an emergency buzzer.

Participants underwent a multimodal MRI scan, which lasted for approximately 45 minutes. Participants completed the same VR based balance task as the healthy volunteer group. Details of the task design are provided in the previous chapter (see section 5.2.5). Based on findings from task delivery in the healthy volunteer pilot study, the scanning time for the fMRI task was adjusted so that each condition was presented 3 times to the participant. When the participant was not engaged in the fMRI task, they were given a wildlife television programme (David Attenborough's 'Planet Earth') to watch through the goggles whilst in the scanner. This was to help participants to stay awake prior to the fMRI task and to make the scanning experience more comfortable.

6.3.5 MRI data acquisition

Functional imaging was performed on a 3T MRI scanner (GE Healthcare discovery MR750), using a 32-channel head coil. T1, FSPGR BRAVO images were acquired using the following parameters: TR= 0.008144, TE= 0.003172, Flip Angle (FA) = 12, Inversion time = 0.45, Matrix= 256 x 256, Thickness= 1 and Voxel size = 1 x 1 x 1.

Functional images were acquired using echo planar imaging sequence using the following parameters: TR = 2000ms, TE = 30ms, Flip Angle (FA) = 77, Matrix = 64 x 64, Slices = 37, Thickness= 3, Voxel size = 3 x 3 x 3, Spacing between slices = 3.5, slices = 37 covering the whole brain and cerebellum.

The task fMRI sequence lasted for 6 minutes 50 seconds and a total of 200 volumes were collected.

6.3.6 MRI data processing

The task fMRI data was pre-processed using MRIcron, FSL, SPM12 and MATLAB, via the University of Nottingham high performance computing system (for more details see 5.2.6).

In brief, the first 5 volumes were discarded to allow for signal stabilisation. After this, I performed the following pre-processing steps:

- Distortion correction to correct for the displacement of the signal due to inhomogeneities in the magnetic field around the sinuses and ear canals.
- Images were then realigned to correct for head motion using 6 degrees of freedom (3 translations and 3 rotations).
- Slice timing correction.

- Co-registration to T1 image.
- Registration to standard space (Montreal Neurological Institute template space) using 3 x 3 x 3 voxel size.
- Smoothing using a full width half maximum of 6mm (twice the voxel size) to improve signal to noise ratio.

6.3.7 MRI data analysis

I performed subject-level analysis, including task condition timing and movement parameters to compute contrast images for each condition per subject. The contrasts images from the subject-level analysis were entered into a group one way within-subjects ANOVA. Simple effects for each condition and t tests for the following contrasts were calculated at the group level: walking > postural instability, walking > obstacle navigation, obstacle navigation > postural instability, postural instability > obstacle navigation, postural instability > walking and obstacle navigation > walking.

For simple effects, results are reported using $p<.05$ Family Wise Error (FWE) corrected threshold and a voxel (k) threshold of 40 contiguous voxels. For differences between the conditions, results are reported using a more lenient threshold of $p<.001$ uncorrected and a voxel (k) threshold of 40 contiguous voxels. A voxel threshold was included for between condition contrasts to account for and reduce the impact of type 1 error that is likely when correction for multiple comparisons is not applied to the data (381,382).

The whole-brain analysis involves fitting a general linear model to BOLD signal at each voxel and comparing computed test statistics to a threshold to assess activation. This method is widely used in task fMRI studies; however, it is not

without its limitations. Statistical tests are performed at each voxel with thousands of voxels being tested simultaneously, leading to issues of multiple testing and increased risk of false positives, or type 1 error (357). One method to mitigate the problems around multiple comparisons and type 1 error, is to use conservative thresholds, which improves specificity but can affect sensitivity reducing the power to detect activation when it is present (383).

An alternative approach to whole-brain analysis, ROI analysis can be used for exploration or to improve statistical control (384). ROI analysis involves focusing on specific brain regions, rather than the whole brain, which reduces the number of statistical tests conducted. This can reduce the impact of the multiple testing problem, improve the sensitivity and power of statistical analysis and reduce the risk of type 1 error (384,385). ROI analysis in fMRI research does have some limitations in that it is prone to double-dipping or circular analysis. This is where the same dataset is used for the selection of ROIs and analysis (386,387). To overcome this bias, a common practice is to predefine ROIs before performing the analysis (388).

ROIs can be defined based on anatomical and functional characteristics (384). Functional ROIs are brain regions that are assumed to be involved in a particular function (e.g., the visual cortex likely to be involved in a task of visual processing). Functional ROIs can be defined in two ways. The first is the functional localiser approach, which involves using a separate dataset to identify voxels within a specific region that show a particular response (352,384). The second approach is to use previous studies and meta-analyses to identify ROIs involved in the task or function being investigated (389).

Anatomical ROIs use anatomical landmarks such as gyri and sulci to define brain regions. There are two widely used approaches to defining anatomical ROIs; the first is based on individual subjects anatomy and the second is based on using anatomical atlases. There is a range of atlases that can be used to define anatomical ROIs, the AAL atlas (355) and the Talairach atlas (390) are based on single-subject MRI scans. These atlases must be used with caution to define ROIs as it is difficult to match up brain images across a group of participants to an atlas based on a single individual (384). The best practice when using an atlas-based approach to defining ROIs is to use probabilistic atlases based on macro-cytoarchitecture. The probabilistic cytoarchitecture atlas was first introduced by Korbinian Brodmann in 1909 (391). Brodmann mapped the cerebral cortex dividing it into several areas, today known as Brodmann's areas, based on differences in spatial distribution, shape and density of neuronal cell bodies (391). This work has informed the development of probabilistic cytoarchitectonic maps (392–394).

In addition to the exploratory whole-brain analysis described above a region of interested analysis was also conducted. Previous studies and meta-analyses investigating motor imagery and action observation related neural activity in healthy populations, older adults and clinical populations including stroke, brain injury and Parkinson's disease were consulted to select regions of interest (81,346,347,371,395–397). In line with previous findings, the left and right premotor area (4a), bilateral supplementary motor area (6mc), bilateral anterior cingulate cortex, bilateral prefrontal cortex and bilateral parieto-insular vestibular cortex were selected as regions of interest (see figure 1).

To create anatomical-based ROIs corresponding to these regions the SPM anatomy toolbox version 3 was used (392–394). This toolbox is based on Brodmann's cytoarchitecture maps of the brain and has more precision in defining brain regions compared to other single subject-based atlases such as the AAL atlas (355) and the Talairach atlas (390). Though it is important to note that these atlases are based on data from healthy adults and not representative of clinical populations. For the clinical population of interest in this study, older adults with MCI and dementia, there are currently no anatomical templates available for dementia subtypes,

After creating the ROIs in the SPM anatomy toolbox, the ROIs were converted to NIFTI format, the ROIs were then co-registered to the fMRI dataset to ensure ROI mask resolution matched that of the fMRI data. The co-registered ROIs were then imported into MARSBAR and converted to a compatible format. For each ROI, I then extracted mean parameter estimates for each condition (walking, obstacle navigation, and slip perturbation). The parameter estimates were then entered into SPSS for further analysis (see section 6.3.8).

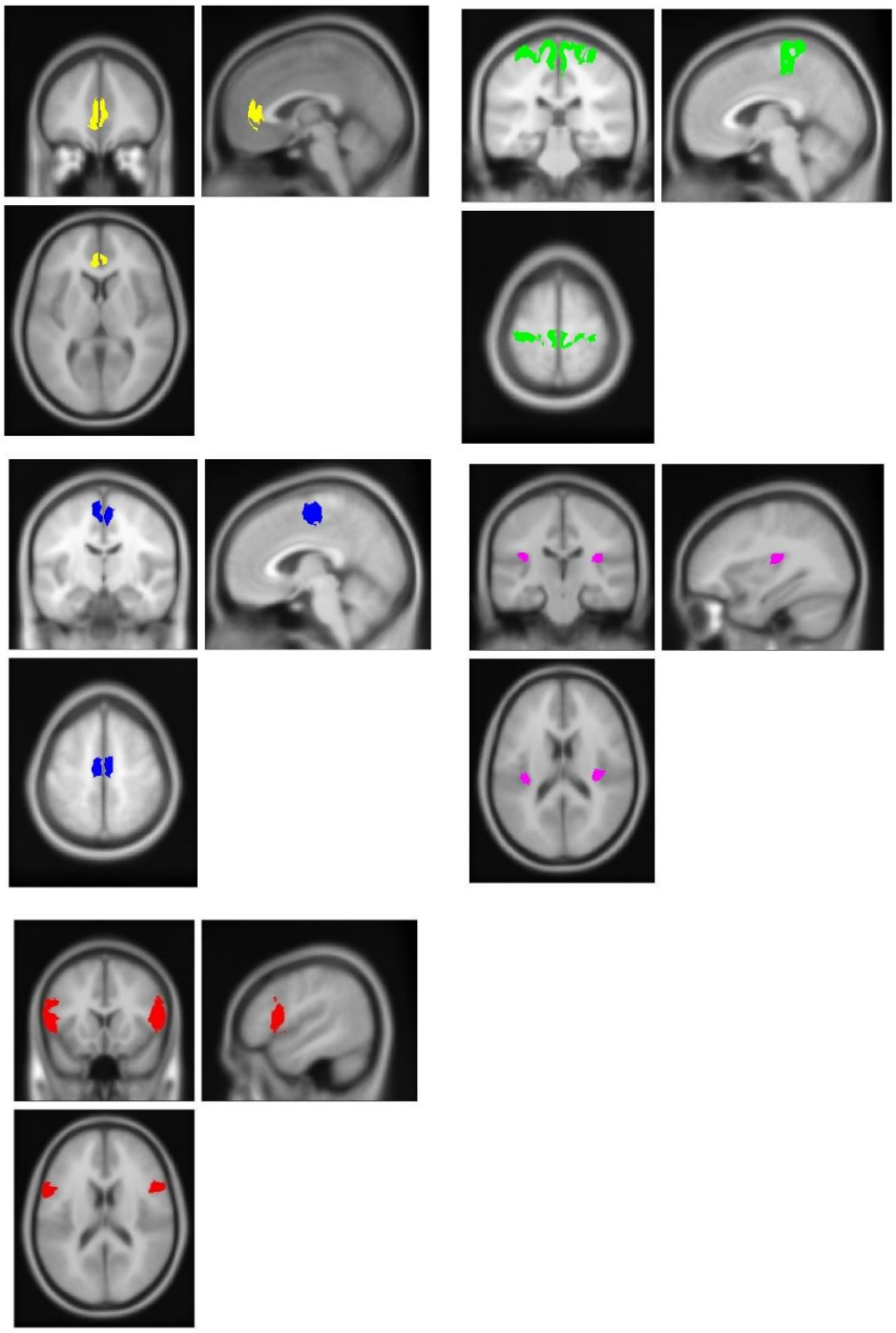

Figure 6. 1 Axial, Coronal and Sagittal view of regions of interest.

Key: Green = Bilateral premotor cortex (area 4a); Blue = Bilateral supplementary motor area (area 6mc); Magenta = Bilateral secondary somatosensory cortex (area OP2); Yellow = Bilateral anterior cingulate cortex (area P24ab); Red = Bilateral inferior frontal gyrus (area Br44).

6.3.8 Statistical analysis

The parameters estimates for each of the ROIs per condition were imported into SPSS along with the behavioural data for further analyses. The demographic and clinical characteristics of the sample were summarised using descriptive statistics. The tolerability questionnaire and task feedback data were analysed using the same procedures as in the healthy volunteer pilot study (see section 5.2.6). A framework analysis approach (351) was used to analyse participants responses about their task experience feedback for the following themes: 1) video clarity and 2) task difficulty. For responses not fitting these a priori themes, I used an inductive approach to identify codes and then looked for links between the codes to find additional key themes. During the analysis of participants' responses an additional theme of interest of 3) generalised feedback emerged.

To investigate the differences in activation in the ROIs between the conditions and differences in activation between the ROIs, a 3 (condition: walking, obstacle navigation, and balance) x 10 (ROI: Bilateral premotor cortex, bilateral supplementary motor area, bilateral anterior cingulate cortex, bilateral inferior frontal gyrus, and bilateral parietal-insula vestibular cortex) two-way within-subjects ANOVA was conducted. Parametric assumptions of the data were assessed through visual inspection of histograms and Shapiro-Wilk test of normality and Mauchly's test of sphericity to assess whether data were normally distributed and whether the relationship between pairs of experimental conditions is equal (398). Normality assumptions for ROI, balance and cognition variables were tested using the Kolmogorov-Smirnov test and thorough visual

inspection of histograms. Mauchly's test was used to assess sphericity, when this assumption was violated, Greenhouse-Geiser corrected values were reported.

Multiple linear regression was used to explore the relationship between core processes of executive function (working memory, cognitive flexibility, and cognitive control), static and dynamic balance performance. Regression analysis was also used to investigate the relationship between ROI activity in response to each condition and performance on measures of static and dynamic balance. A hierarchical approach was used, entering age and MoCA score covariates in the first step, and then including ROI parameter estimates in the second step for each condition. As this was an exploratory analysis, no prior assumptions of the relative importance of the independent variables were made and therefore the 'enter' method was used.

Prior to conducting regression analysis, data were assessed to ensure they met the necessary assumptions. Linear relationship between explanatory variables (ROIs for each condition and differences between conditions i.e. postural instability minus walking) and outcome variables (BBS and TUG) were assessed through visual inspection of scatter plots. Multicollinearity between explanatory variables were assessed through Pearson's correlations and Durbin Watson statistic. Scatter plots of residual values were visually inspected to assess whether the variance of residuals was constant and indicated assumptions of homoscedasticity were met. Additionally, Cook's distance was also calculated to ascertain whether there were any outliers influencing the model.

Finally, to explore whether executive function mediated the relationship between ROI activation for each condition and balance performance, an

exploratory mediation analysis was conducted. For the PROCESS package in SPSS was used (399). Mediation analysis is often used to explore whether mediators (m) explain how or why an independent variable (x) may influence a particular outcome (y) (see figure 6.2, (399)).

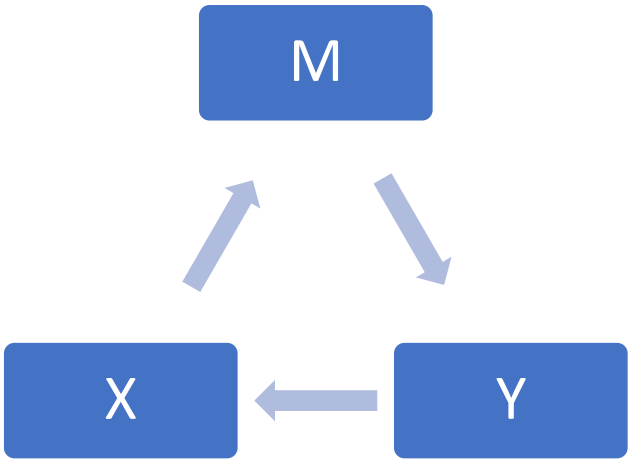

Figure 6. 2 Diagram of a mediation model.

6.3.9 Ethical approval

This study has received NHS and HRA approval – ethics number 18/YH/0059 (appendix D).

6.4 Results

6.4.1 PrAISED participant recruitment and participant characteristics

A total of 120 participants recruited to PrAISED between February 2019 and March 2020 signed clause 7 of the PrAISED RCT consent form, agreeing to be contact about other related studies. Seventy-two participants were excluded due to not being able to contact them within the given timeframe for baseline scanning, not being available, not interested in taking part or not eligible due to MRI specific contraindications. A total of 49 participants were recruited and

consented to the PrAISED MRI sub study (see table 6.1 for more information on participant characteristics including scores on measures of cognition, activities of daily living and balance). Four participants were withdrawn prior to scanning, 45 participants underwent a baseline MRI scan, and 5 participants withdrew during scanning (see figure 6.3 for recruitment flow diagram). Mean age of participants was 81.8 years, 34 were male, 10 participants reported a diagnosis of mild cognitive impairment, and 35 participants reported a diagnosis of dementia. The original sample size target was 80 participants. At the point of COVID-19 pandemic and start of the first lockdown in March 2020 56% of the recruitment target had been reached. Unfortunately, due to COVID-19 related restrictions and lockdowns it was not possible to resume recruitment or conduct follow up scans for participants recruited.

Table 6. 1 Demographics and descriptive statistics for participants recruited from PrAISED RCT.

Measure type	**Measure name**	**Mean / n**	**S.D.**	**Min**	**Max**
Demographics	Age/y	81.8	6.68	68	96
	Gender (M:F)	34:10	-	-	-
	Diagnosis (MCI: Dementia)	10:35	-	-	-
Dementia subtype	Alzheimer's disease	15	-	-	-
	Vascular disease	9	-	-	-
	Frontotemporal dementia/Pick's disease	1	-	-	-
	Mixed dementia	12	-	-	-

Global cognition	MoCA/30	20.11	3.28	14	26
Executive dysfunction	Verbal fluency	12	5	4	25
	CANTAB Spatial Span test Length forward	4	1.15	2	8
	CANTAB Multitasking test – Switch response latency	1036.75	299.35	440.50	1676.00
	CANTAB Multitasking – Congruent response latency	873.27	157.74	564.50	1362.50
	CANTAB Multitasking test – Incongruent response latency	991.26	162.41	690.50	1317.00
Balance	Berg balance scale /56	47.36	10.85	6	56
	Timed Up and Go/seconds	17	13	8	87
Activities of daily living	Nottingham extended activities of daily living (Self-reported)/22	15.48	4.60	3	22
	Disability Assessment in Dementia (informant completed)/100	74.54	24.66	15	100

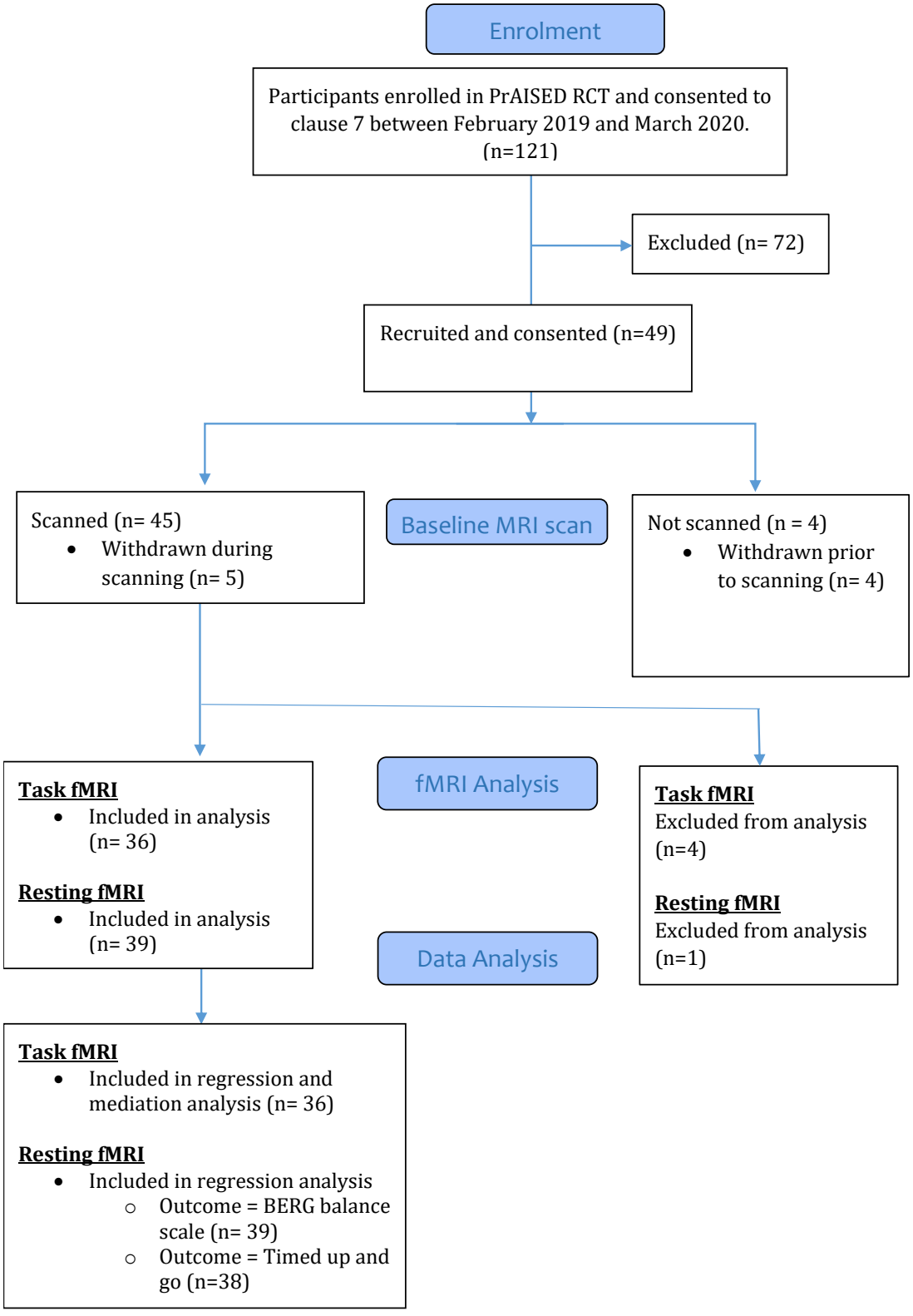

Figure 6. 3 Participant recruitment flow chart.

For task-related whole-brain analysis and ROI analysis (ANOVA), 36 datasets were included in the analysis. Nine sets were excluded due to issues with data quality including excess movement, significant degradation of T1 structural image, withdrawing during scanning, before completing or during fMRI task. Participant characteristics for 36 participants included in the task fMRI analysis are reported in table 6.2.

Table 6. 2 Participant characteristics for resting state fMRI analysis.

Measure type	Measure name	Mean	S.D.	Min	Max
Demographics	Age	79.6	6.88	65.5	93.7
	Gender (M:F)	26 : 10	-	-	-
	Diagnosis (MCI : Dementia)	9 : 27	-	-	-
Global cognition	MoCA/30	20.28	3.16	14	26
Executive dysfunction	Verbal fluency	12.57	5.29	4	25
	CANTAB Spatial Span test Length forward	3.82	.950	2	5
	CANTAB Multitasking test – Switch response latency	1038.27	306.48	440.50	1676.00
	CANTAB Multitasking – Congruent response latency	875.81	160.18	564.50	1362.50
	CANTAB Multitasking test – Incongruent response latency	997.74	160.80	739.50	1317.00
Balance	Berg balance scale/52	47.14	11.32	6	56
	Timed Up and Go/seconds	17.08	14.30	8	87
Activities of daily living	Nottingham extended activities of daily living (Self-reported)/22	15.62	4.80	3.00	22.00
	Disability Assessment in Dementia (informant completed)/100	77.50	23.74	15.00	100.00

6.4.2 MRI tolerability and task experience feedback

Thirty-two participants completed MRI tolerability questionnaire. Responses indicate scanning experience was well tolerated with mean score for overall experience being 4/5, mean rating for length of time in the scanner was also 4/5 as was mean score for being able to see the video clearly (see table 6.3).

Table 6. 3 Mean ratings for MRI tolerability.

Questionnaire Item	Min score	Mean score on a scale of 1-5	Max Score
Overall experience	1	4	5
Lying flat on the MRI table	3	4	5
Having the technician position you in the MRI	3	5	5
Moving into the machine	3	5	5
Confinement inside the MRI	2	4	5
Not moving during the scan	1	4	5
Noise of the machine	1	4	5
Being alone in the scanner	2	4	5
Length of time in the scanner	2	4	5
Scanner temperature	1	4	5
Scanner smell	2	5	5
Post dizziness upon sitting	1	4	5
Ability to see clearly	1	4	5

In total, 25 participants provided written feedback about the video task. Feedback on video clarity was generally positive, most participants reported being able to see the task. Feedback on task difficulty was mixed, some participants found the task more challenging than others. A few participants also provided more general feedback regarding the scanning experience overall (see table 6.4 for framework analysis results of participant feedback on the task).

Table 6. 4 Participant task experience feedback themes, subthemes, and participant quotes.

Themes	**Subthemes (x n)**	**Quotes from participant responses**
Video clarity	a. Clear videos (13) b. Video positioning (3) c. Videos not clear (2)	*a. "Videos were very clear and well adjusted for me."* *b. "Walking across the footbridge, video not clear, not central."* *c. "Screen not clear as was wearing glasses."*
Task difficulty	a. Easy/difficult imagining (11) b. Innovative (1) c. Extreme postural instability condition (2)	*a. "I could easily imagine I was in the situations."* *a. "Very hard to imagine but clear to see videos."* *b. "The videos were innovative, relaxing and thought provoking at times. Unusual experience but very good. Videos were very clear and well adjusted for me."* *c. "Video quite clear, I could easily imagine I was in the situations, but the tilting floor parts felt quite extreme at times. Thankfully they were over quickly."*

General feedback	a. Videos reduced claustrophobia (1) b. Scanner noise (1) c. Feedback about the research team (2) d. Inclusion of foot position in videos (1)	*a. "Clear to see, difficult to imagine, with videos don't feel as claustrophobic."* *b. "After 2 days of having the scan, I still have ringing in my ears. I thought I was going to get headphones but only had ear plugs which dropped out before I was put in the machine. Video clear, just noise."* *c. "Clear to see, image of feet in the video would have made it easier to see. If you can see the footing, it might have been easier to imagine."*

6.4.3 Exploratory whole-brain analysis

6.4.3.1 Simple effects

For simple effects analysis, voxel-wise t-tests for each condition against the implicit baseline were conducted. For the walking condition, activation was noted in the left calcarine cortex, right middle frontal, and precentral gyri ($p<0.05$ FWE corrected, see Table 6.5 and Fig. 6.4).

For the obstacle navigation condition, activation was noted in the left calcarine cortex and right middle frontal gyrus. ($p<0.05$ FWE corrected, see Table 6.5 and Fig. 6.5).

For the postural instability condition, activation was noted in the left calcarine cortex and right superior parietal lobule ($p<0.05$ FWE corrected, see Table 6.5 and Fig. 6.6).

6.4.3.2 Contrasts

The differences in activation and deactivation between the conditions for walking - postural instability, walking - obstacle and obstacle - postural instability were explored. No voxels survived $p<.05$ FWE threshold or more lenient $p<.001$ threshold (see Table 6.5).

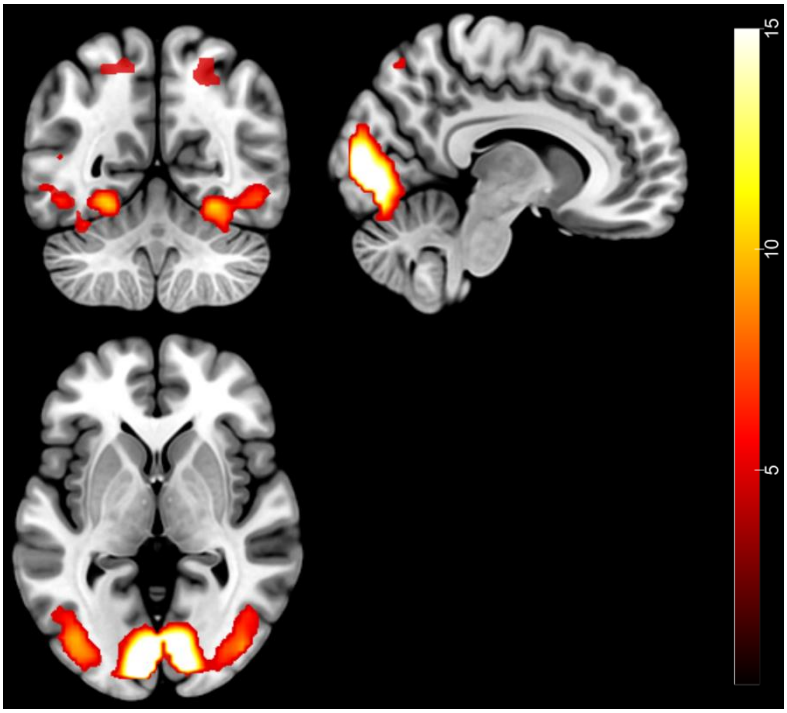

Figure 6. 4 Axial, Coronal and Sagittal view of activation during the walking condition.

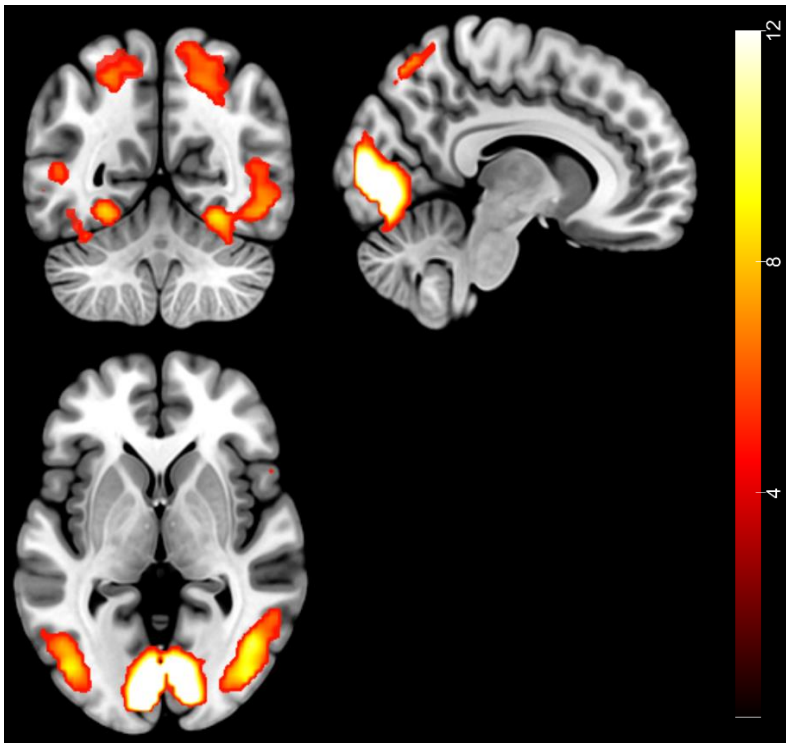

Figure 6. 5 Axial, Coronal and Sagittal view of activation during obstacle navigation condition.

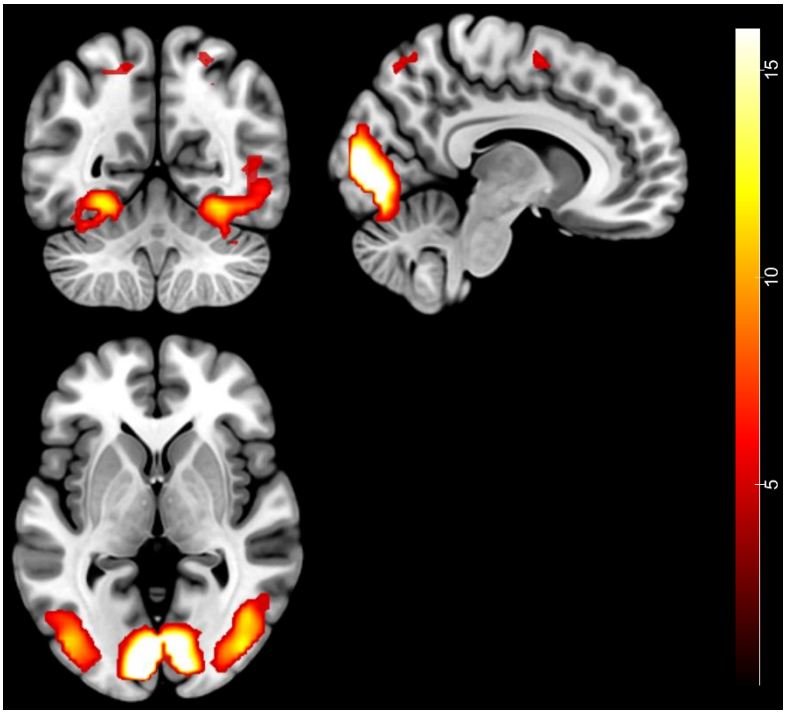

Figure 6. 6 Axial, Coronal and Sagittal view of activation during postural instability condition.

Table 6. 5 Spatial location (coordinates) of voxels with the highest z scores and t scores inside each cluster is displayed for each condition and for comparison of activation between conditions.

Task condition	Anatomical location	x	y	z	cluster size	T score	Z score
Walking*	Left calcarine cortex	-6	-94	-1	3508	30.11	> 8
		12	-91	8		25.66	> 8
		9	-79	-4		22.03	> 8
	Right middle frontal gyrus	30	-1	50	18	6.28	5.57
	Right precentral gyrus	48	11	32	10	5.88	5.28
Obstacle navigation*	Left calcarine cortex	-6	-94	-1	3879	23.7	> 8
		-9	-82	-7		22.8	> 8
		9	-79	-4		22.17	> 8
	Right middle frontal gyrus	27	-1	53	66	8.24	6.87
Postural instability*	Left calcarine cortex	-6	-94	-1	3624	32.7	> 8
		12	-91	11		25.3	> 8
		9	-79	-4		24.5	> 8
	Right superior parietal lobule	15	-70	59	94	9.85	7.77
		27	-64	53		6.07	5.42
		6	-61	59		5.22	4.78

**p<.05 FWE corrected.*

6.4.4 ROI analysis

ROI data was generally normally distributed (see Appendix A for histograms and p values for the Shapiro-Wilks test for each ROI). Data generally met parametric assumptions therefore I proceeded with a 3 (condition: walking, obstacle navigation, postural instability) x 10 (ROI: L+R SMA, L+R PMC, L+R PIVC, L+R ACC, L+R PFC) within-subjects ANOVA.

6.4.5 ANOVA results

Mauchly's test indicated the assumption of sphericity had been met for the condition variable, $\chi 2(2) = 3.24$, $p = .19$ (see Appendix A). However, for the region of interest variable, the assumption of sphericity was violated $\chi 2(44) = 194.74$, $p < .001$. As sphericity assumptions were violated for the region of interest variables, degrees of freedom were corrected using Green-House Geisser estimates of sphericity ($\varepsilon = .46$). The ANOVA revealed no significant effect of condition $F(2,70) = 1.14$, $p = .32$. A significant effect of ROI was noted $F(9,315) = 2.92$, $p = .02$. There was no significant interaction between condition and ROI $F(18,630) = .51$, $p = .80$.

6.4.6 Relationship between task condition ROI activity, executive function, and balance

Two hierarchical multiple linear regression models were constructed to explore the relationship between core processes of executive function (working memory, cognitive flexibility, and cognitive control, measured by CANTAB tests) and balance (static and dynamic, measured using BBS and TUG).

Six hierarchical multiple linear regression models were constructed to explore the relationship between activation in ROIs (SMA, PMC, PFC, PIVC, ACC) for each condition (walking, obstacle avoidance and postural instability) and performance on BBS and TUG, while controlling for age and cognition.

6.4.6.1 Assumption testing results

Generally, Pearson's correlations between independent variables were below <0.9 (398) and Durbin Watson statistics values were close to 2 (range 1.95 – 2.36), which showed that generally independent variables were not highly correlated with one another. P-Plots for the models indicated that the assumption of normality of the residuals were met. Additionally, Cook's distance values were generally less than 1 indicating that no outliers significantly influenced the models.

6.4.6.2 Executive function and balance

Berg balance score

In step 1, age or MoCA scores did not significantly contribute to the regression model (p>.05) explaining 10% of the variance in BBS. In step 2, introducing verbal fluency scores, spatial span test score, multitasking rest reaction times for switching, congruent and incongruent conditions explained a further 6 % of

variance in the BBS. However, the changes in R^2 were not significant ($p>.05$, see table 6.6). The individual explanatory variables were examined further, and none was significantly associated with BBS.

Timed Up and Go

In step 1, age or MoCA scores did not significantly contribute to the regression model ($p>.05$) accounting for 10% of the variance in TUG performance. In step 2, introducing verbal fluency scores, spatial span test score, multitasking rest reaction times for switching, congruent and incongruent conditions explained a further 24% of variance in the TUG performance. However, the change in R^2 was not significant ($p>.05$, See table 6.7). The individual explanatory variables were examined further and the reaction times for the switch condition of the multitasking test was significantly associated with TUG performance ($\beta = 0.75$, $p<.05$).

Table 6. 6 Executive function and BBS.

Variable	Unstandardised coefficients		Standardised coefficients		95% CI	
	B	Std Error	*β*	*p*	*Lower*	*Upper*
Step 1						
Age	-0.16	0.33	-0.09	0.63	-0.83	0.51
MoCA	1.06	0.65	0.29	0.11	-0.27	2.39
Step 2						
Age	-0.03	0.40	-0.02	0.95	-0.85	0.79
MoCA	1.27	0.88	0.35	0.17	-0.56	3.09
Verbal Fluency	-0.04	0.56	-0.02	0.94	-1.21	1.12
SSP_Length forward	0.63	2.47	0.05	0.80	-4.47	5.73
MTT_Switch_RL	0.00	0.01	0.07	0.82	-0.02	0.03
MTT_Congruent_RL	-0.02	0.03	-0.32	0.46	-0.09	0.04
MTT_Incongruent_RL	0.00	0.03	0.02	0.96	-0.06	0.06

Note:
Step 1: F = 1.53, p = 0.24, R^2=0.10, R^2(Adjusted) = 0.03
Step 2: F = 0.63, p = 0.72, R^2=0.16, ▲R^2 = 0.06, R^2(Adjusted) = -0.09 ▲R^2 (Adjusted) = -0.13

Key: MTT = CANTAB Multitasking Test; SSP = CANTAB Spatial Span Test, RL = Reaction Latency.

Table 6. 7 Executive function and TUG.

Variable	Unstandardised coefficients		Standardised coefficients		95% CI	
	B	Std Error	*β*	*p*	*Lower*	*Upper*
Step 1						
Age	0.56	0.41	0.25	0.18	-0.28	1.40
MoCA	-0.74	0.81	-0.17	0.37	-2.41	0.93
Step 2						
Age	0.46	0.44	0.21	0.31	-0.45	1.38
MoCA	-1.44	0.98	-0.32	0.16	-3.47	0.59
Verbal Fluency	0.28	0.62	0.10	0.66	-1.01	1.57
SSP_Length forward	-1.67	2.79	-0.11	0.56	-7.46	4.13
MTT_Switch_RL	***0.04***	***0.02***	***0.75***	***0.03***	0.00	0.07
MTT_Congruent_RL	0.01	0.03	0.12	0.76	-0.06	0.08
MTT_Incongruent_RL	-0.06	0.03	-0.67	0.08	-0.13	0.01

Note:
Step 1: F = 1.49, p = 0.25, R^2=0.10, R^2(Adjusted) = 0.03
Step 2: F = 1.64, p = 0.18, R^2 = 0.34, ▲R^2 = 0.24, R^2(Adjusted) = 0.13 ▲R^2 (Adjusted) = 0.10

Key: MTT = CANTAB Multitasking Test; SSP = CANTAB Spatial Span Test, RL = Reaction Latency.

6.4.6.3 Walking condition

Berg Balance score

In step 1 age and MoCA scores accounted for 16% of the variance in BBS (p>.05). Only MoCA scores were significantly associated with BBS in this step (β = 0.334, p<.05). In step 2, introducing the parameter estimates for regions of interest during walking condition explained a further 51% of variance in the BBS and this change in R^2 was significant (p<.01).

The individual explanatory variables in step 2 were further examined, and ROI parameter estimates during the walking condition that were significantly

associated with BBS included left premotor cortex (β = 1.86, p<.01), left supplementary motor area (β = -1.17, p<.01) and the right premotor cortex (β = -1.86, p<.01, see table 6.8).

Timed Up and Go

In step 1, MoCA scores and age accounted for 18% of the variation in TUG performance (p<.05). In step 2 introducing the parameter estimates for regions of interest during walking condition explained a further 46% of the variance in TUG performance and this change in R^2 was significant (p<.01).

The individual explanatory variables were further examined, and ROI parameter estimates during the walking condition that were significantly associated with TUG performance included the left premotor cortex (β = -1.54, p<.001), left supplementary motor area (β = 0.99, p<.05), right premotor cortex (β = 1.64, p<.05, see table 6.9).

Table 6. 8 Walking condition AND BBS.

Variable	Unstandardised coefficients		Standardised coefficients		95% CI	
	B	Std Error	*β*	*p*	*Lower*	*Upper*
Step 1						
Age	-0.29	0.27	-0.18	0.28	-0.83	0.25
MoCA	***1.20***	***0.58***	***0.33***	***0.05***	***0.02***	***2.37***
Step 2						
Age	***-0.51***	***0.24***	***-0.31***	***0.05***	***-1.01***	***-0.01***
MoCA	***1.55***	***0.61***	***0.43***	***0.02***	***0.28***	***2.82***
Left PMC	***42.78***	***9.27***	***1.86***	***0.00***	***23.60***	***61.96***
Left SMA	***-29.79***	***8.63***	***-1.17***	***0.00***	***-47.65***	***-11.93***
Left PIVC	8.33	5.29	0.24	0.13	-2.61	19.28
Left ACC	3.47	4.31	0.22	0.43	-5.45	12.38
Left PFC	-6.79	5.33	-0.28	0.21	-17.81	4.23
Right PMC	***-33.11***	***7.67***	***-1.86***	***0.00***	***-48.98***	***-17.24***
Right SMA	13.32	7.48	0.66	0.09	-2.16	28.81
Right PIVC	1.13	3.62	0.05	0.76	-6.36	8.62
Right ACC	-4.97	5.81	-0.23	0.40	-16.99	7.06
Right PFC	7.03	3.88	0.39	0.08	-1.00	15.06

Note:
Step 1: F = 3.13, p = 0.06, R^2=0.16, R^2(Adjusted) = 0.11
Step 2: F = 3.95, p<.001, R^2 = 0.67, ▲R^2 = 0.51, R^2(Adjusted) = 0.50 ▲R^2 (Adjusted) = 0.40

Table 6. 9 Walking condition AND TUG.

	Unstandardised coefficients		Standardised coefficients		95% CI	
Variable	B	Std Error	*β*	*p*	*Lower*	*Upper*
Step 1						
Age	***0.66***	***0.33***	***0.32***	***0.05***	***-0.012***	***1.345***
MoCA	-1.01	0.73	-0.23	0.17	-2.5	0.472
Step 2						
Age	***1.02***	***0.32***	***0.50***	***0.01***	***0.35***	***1.69***
MoCA	-1.16	0.84	-0.26	0.18	-2.90	0.58
Left PMC	***-44.48***	***13.30***	***-1.54***	***0.00***	-72.06	-16.89
Left SMA	***31.27***	***12.13***	***0.99***	***0.01***	6.13	56.42
Left PIVC	-14.67	7.18	-0.34	0.05	-29.57	0.23
Left ACC	3.53	5.86	0.18	0.55	-8.62	15.68
Left PFC	5.68	7.19	0.19	0.43	-9.24	20.60
Right PMC	***36.37***	***10.49***	***1.64***	***0.00***	14.61	58.12
Right SMA	-12.04	10.12	-0.48	0.24	-33.04	8.95
Right PIVC	-4.61	4.95	-0.17	0.36	-14.88	5.66
Right ACC	-5.18	7.94	-0.19	0.52	-21.64	11.28
Right PFC	-6.46	5.36	-0.29	0.24	-17.56	4.65

Note:
Step 1: F = 1.49, p = 0.25, R^2=0.098, R^2(Adjusted) = 0.032
Step 2: F = 1.637, p = 0.177, R^2 = 0.243, ▲R^2 = 0.243, R^2(Adjusted) = 0.133 ▲R^2 (Adjusted) = 0.101

6.4.6.4 *Obstacle navigation condition*

Berg Balance score

In step 1 age and MoCA scores accounted for 16% of the variance in BBS (p>.05). Only MoCA scores were significantly associated with BBS in this step (β = 0.334, p<.05). In step 2 introducing the parameter estimates for regions of interest during obstacle navigation condition explained a further 41% of variance in the BBS, however the change in R^2 was not significant (p>.05).

The individual explanatory variables were further examined, and ROI parameter estimates during the obstacle navigation that were significantly associated with BBS included the right premotor cortex (β = -0.74, p=<.05) and the right anterior cingulate cortex (β = 0.75, p<.05, see table 6.10).

Timed Up and Go

In step 1, MoCA scores and age accounted for 18% of the variance in TUG performance (p<.05). In step 2 introducing the parameter estimates for regions of interest during obstacle navigation condition explained a further 47% of variance in the TUG performance and this change in R^2 was significant (p<.05).

The individual explanatory variables were further examined, and ROI parameter estimates during the obstacle navigation condition that were significantly associated with TUG performance included the left supplementary area (β = 0.95, p<.01) and the right anterior cingulate cortex (β = -0.77, p<.05, see table 6.11).

Table 6. 10 Obstacle navigation condition and BBS.

	Unstandardised coefficients		Standardised coefficients		*95% CI*	
Variable	B	Std Error	*β*	*p*	*Lower*	*Upper*
Step 1						
Age	-0.29	0.27	-0.18	0.28	-0.83	0.25
MoCA	1.20	0.58	0.33	0.05	0.02	2.37
Step 2						
Age	-0.06	0.25	-0.04	0.81	-0.59	0.47
MoCA	0.70	0.64	0.20	0.28	-0.62	2.02
Left PMC	3.22	9.98	0.11	0.75	-17.43	23.87
Left SMA	-15.43	9.31	-0.49	0.11	-34.68	3.82
Left PIVC	1.71	3.69	0.08	0.65	-5.93	9.35
Left ACC	-11.16	5.66	-0.67	0.06	-22.87	0.55
Left PFC	8.09	6.44	0.33	0.22	-5.24	21.41
Right PMC	***-18.83***	***9.04***	***-0.74***	***0.05***	-37.53	-0.13
Right SMA	15.97	9.74	0.57	0.11	-4.18	36.12
Right PIVC	4.21	5.98	0.12	0.49	-8.17	16.59
Right ACC	***15.47***	***7.06***	***0.75***	***0.04***	0.86	30.09
Right PFC	2.71	4.62	0.16	0.56	-6.84	12.27

Step 1: F = 3.13, p = 0.06, R^2=0.16, R^2(Adjusted) = 0.11
Step 2: F = 2.58, p = 0.03, R^2 = 0.57, ▲R^2 = 0.41, R^2(Adjusted) = 0.35 ▲R^2 (Adjusted) = 0.24

Table 6. 11 Obstacle navigation condition and timed up and go.

	Unstandardised coefficients		Standardised coefficients		*95% CI*	
Variable	B	Std Error	*β*	*p*	*Lower*	*Upper*
Step 1						
Age	0.67	0.33	0.32	0.05	-0.01	1.35
MoCA	-1.01	0.73	-0.23	0.17	-2.50	0.47
Step 2						
Age	0.53	0.31	0.26	0.10	-0.11	1.17
MoCA	-0.52	0.74	-0.12	0.49	-2.05	1.01
Left PMC	4.39	11.54	0.12	0.71	-19.54	28.32
Left SMA	***38.42***	***11.55***	***0.95***	***0.00***	14.46	62.38
Left PIVC	-6.43	4.35	-0.25	0.15	-15.45	2.60
Left ACC	13.59	6.62	0.65	0.05	-0.14	27.33
Left PFC	-11.70	7.48	-0.36	0.13	-27.21	3.80
Right PMC	2.29	11.28	0.07	0.84	-21.11	25.69
Right SMA	-20.77	11.28	-0.58	0.08	-44.17	2.63
Right PIVC	10.60	8.16	0.23	0.21	-6.33	27.53
Right ACC	***-19.75***	***8.29***	***-0.77***	***0.03***	-36.93	-2.56
Right PFC	-0.93	5.40	-0.04	0.87	-12.13	10.27

Step 1: F = 3.47, p = 0.04, R^2=0.18, R^2(Adjusted) = 0.13
Step 2: F = 3.39, p = 0.01, R^2 = 0.65, ▲R^2 = 0.47, R^2(Adjusted) = 0.46 ▲R^2 (Adjusted) = 0.33

6.4.6.5 *Postural instability condition*

Berg Balance scale

In step 1 age and MoCA scores accounted for 16% of the variance in BBS ($p>.05$). Only MoCA scores were significantly associated with BBS in this step ($\beta = 0.334$, $p<.05$). In step 2 introducing the parameter estimates for regions of interest during the postural instability condition explained a further 56% of variance in the Timed Up and Go performance and this change in R^2 was significant ($p<.01$).

The individual explanatory variables were further examined, and ROI parameter estimates during the postural instability condition that were significantly associated with TUG performance included the left supplementary area ($\beta = -0.89$, $p<.05$) and the right premotor cortex ($\beta = -0.92$, $p<.05$) and the right supplementary motor area ($\beta = 0.64$, $p<.01$, see table 6.12).

Timed Up and Go

In step 1, MoCA scores and age accounted for 18% of the variance in TUG performance ($p<.05$). In step 2 introducing the parameter estimates for regions of interest during the postural instability condition explained a further 39% of variance in the TUG performance and this change in R^2 was non-significant ($p>.05$).

The individual explanatory variables were further examined, and ROI parameter estimates during the postural instability condition that were significantly associated with TUG performance included the left supplementary area ($\beta = 0.68$, $p<.05$, see table 6.13).

Table 6. 12 Postural instability condition and BBS.

	Unstandardised coefficients		Standardised coefficients		*95% CI*	
Variable	B	Std Error	*β*	*p*	*Lower*	*Upper*
Step 1						
Age	-0.29	0.27	-0.18	0.28	-0.83	0.25
MoCA	***1.20***	***0.58***	***0.33***	***0.05***	***0.02***	***2.37***
Step 2						
Age	-0.08	0.30	-0.05	0.79	-0.70	0.54
MoCA	***1.13***	***0.47***	***0.32***	***0.03***	***0.16***	***2.11***
Left PMC	14.60	9.16	0.49	0.12	-4.34	33.54
Left SMA	***-25.10***	***7.28***	***-0.89***	***0.00***	-40.15	-10.05
Left PIVC	-1.06	4.90	-0.03	0.83	-11.21	9.08
Left ACC	5.20	3.20	0.39	0.12	-1.42	11.82
Left PFC	-3.43	4.64	-0.17	0.47	-13.03	6.17
Right PMC	***-23.58***	***9.68***	***-0.92***	***0.02***	-43.61	-3.54
Right SMA	***14.98***	***6.06***	***0.64***	***0.02***	2.45	27.52
Right PIVC	-1.69	3.12	-0.08	0.59	-8.13	4.76
Right ACC	-8.91	4.98	-0.43	*0.09*	-19.21	1.39
Right PFC	5.37	3.82	0.30	0.17	-2.54	13.27

Note:
Step 1: F = 3.13, p = 0.06, R^2=0.16, R^2(Adjusted) = 0.11
Step 2: F = 4.42, p<.001, R^2 = 0.70, ▲R^2 = 0.54, R^2(Adjusted) = 0.54 ▲R^2 (Adjusted) = 0.43

Table 6. 13 Postural instability and TUG.

	Unstandardised coefficients		Standardised coefficients		*95% CI*	
Variable	B	Std Error	*β*	*p*	*Lower*	*Upper*
Step 1						
Age	0.67	0.33	0.32	0.05	-0.01	1.35
MoCA	-1.01	0.73	-0.23	0.17	-2.50	0.47
Step 2						
Age	0.26	0.47	0.13	0.59	-0.71	1.23
MoCA	-1.14	0.73	-0.25	0.13	-2.65	0.36
Left PMC	-18.81	14.02	-0.46	0.19	-47.89	10.27
Left SMA	**25.25**	**12.10**	**0.68**	**0.05**	0.15	50.34
Left PIVC	-3.51	7.61	-0.08	0.65	-19.29	12.27
Left ACC	-3.01	5.23	-0.18	0.57	-13.87	7.84
Left PFC	3.68	7.20	0.14	0.61	-11.24	18.60
Right PMC	31.25	15.25	0.95	0.05	-0.38	62.87
Right SMA	-14.35	10.49	-0.49	0.19	-36.10	7.39
Right PIVC	0.56	4.80	0.02	0.91	-9.38	10.50
Right ACC	7.12	7.79	0.28	0.37	-9.02	23.27
Right PFC	-8.57	5.93	-0.39	0.16	-20.86	3.73

Note:
Step 1: F = 3.47, p = 0.04, R^2=0.18, R^2(Adjusted) = 0.13
Step 2: F = 12.36, p = 0.04, R^2 = 0.56, ▲R^2 = 0.39, R^2(Adjusted) = 0.33 ▲R^2 (Adjusted) = 0.20

6.4.7 Mediation analyses

To investigate whether executive function mediated task related ROI activation and balance performance, a series of exploratory mediation analyses were conducted using PROCESS macro in SPSS (399). Based on the results above, only task switching reaction time (a measure of cognitive flexibility) was significantly associated with timed up and go performance (however the regression model was non-significant), therefore exploratory mediation analyses were conducted for the TUG outcome only. For each condition, ROIs that were significantly associated with TUG performance from the regression models, were included as independent variables. The multitasking switch condition reaction time was included as a moderator variable and timed up and go performance was included as the outcome variable. A total of six mediation models were constructed, three for the walking condition, two for obstacle navigation condition and one for the postural instability condition.

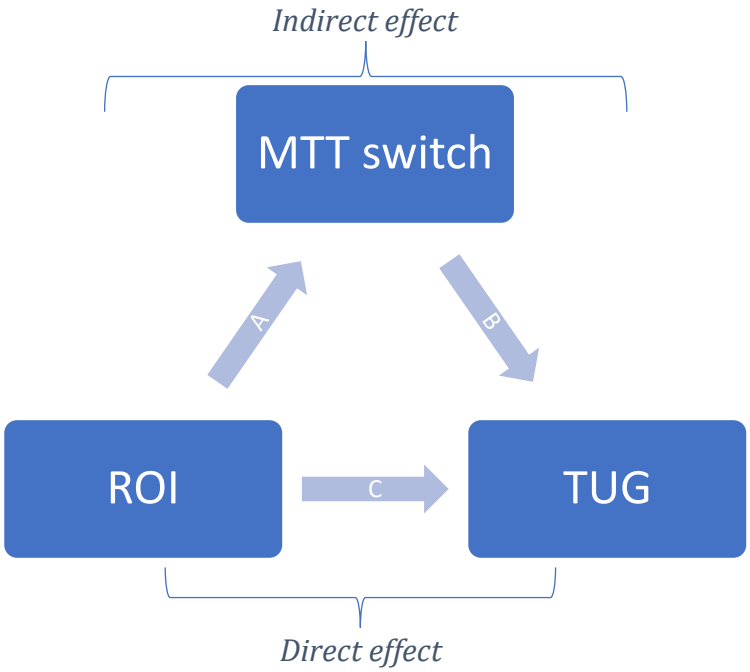

Figure 6. 7 Diagram for mediation model.

For each condition, ROI parameter estimates were not significantly associated with multitasking switch condition reaction times (figure 6.7, path A, table 19). The association between multitasking switch condition reaction times and TUG performance were also not significant (figure 6.7, path B, table 6.14). The direct association for ROI and TUG performance was significant Figure 5, path C, table 19), however the indirect effect (figure 6.7 path A and B, table 6.14) was non-significant.

Table 6. 14 Mediation analysis between task activation in regions of interest, MTT switch reaction time and Timed Up and Go performance.

		Path A						Path B					
		Association between condition ROI and MTT switch reaction time						Association between MTT switch reaction time and TUG					
						95% CI						95% CI	
Condition	ROI	β	Std Beta	SE	*p*	Lower	Upper	β	Std Beta	SE	*p*	Lower	Upper
Walking	Left PMC	-3.95	-0.01	114.41	0.97	-237.60	229.71	0.01	0.26	0.01	0.14	0.00	0.03
	Left SMA	31.39	0.05	127.32	0.81	-228.64	291.42	0.01	0.23	0.01	0.16	0.00	0.03
	Right PMC	120.70	0.26	83.08	0.16	-48.97	290.38	0.01	0.15	0.01	0.38	-0.01	0.02
Obstacle	Left SMA	150.28	0.17	156.54	0.35	-169.43	469.99	0.01	0.21	0.01	0.24	-0.01	0.03
	Right ACC	-23.06	-0.04	96.02	0.81	-219.16	173.04	0.01	0.25	0.01	0.18	-0.01	0.03
Balance	Left SMA	57.18	0.07	142.15	0.69	-233.13	347.49	0.01	0.23	0.01	0.19	-0.01	0.03

		Path C									
		Direct effect Association condition ROI and TUG						Indirect effect			
						95% CI				95% CI	
Condition	ROI	β	Std Beta	SE	*p*	Lower	Upper	β	SE	Lower	Upper
Walking	Left PMC	10.10	0.35	4.88	0.05	0.12	20.08	-0.05	1.60	-3.55	3.37
	Left SMA	13.74	0.42	5.24	0.01	3.02	24.45	0.34	1.29	-2.24	3.20
	Right PMC	8.71	0.40	3.73	0.03	1.09	16.33	0.85	0.99	-1.10	2.90
Obstacle	Left SMA	10.15	0.25	7.13	0.17	-4.42	24.73	1.47	2.06	-2.30	6.16
	Right ACC	-3.80	-0.16	4.34	0.39	-12.67	5.07	-0.26	1.76	-3.87	3.58
Balance	Left SMA	10.70	0.30	6.22	0.96	-2.02	23.42	0.62	1.73	-2.88	4.37

6.5 Discussion

In this chapter, a novel virtual reality video balance task was piloted in older adults with MCI and dementia. The feasibility of task delivery, tolerability of scanning procedures were tolerated and participants' views on the task experience were explored. Additional aims of this chapter were to explore whole-brain activation in response to the task conditions and investigate differences in activation between the conditions. Furthermore, relationships between activation in cortical ROIs thought to be involved in postural control, in response to each task condition and performance on balance measures were explored. Finally, this study investigated whether the relationship between ROI activation in each condition and performance on balance measures was mediated by executive function.

The findings show that the fMRI task was deliverable, and fMRI data could be collected from all participants who completed their time in the scanner. Overall, scanner experiences were rated highly by participants, indicating, scanning procedures were generally well tolerated. The following themes were explored in the task experience feedback data using a framework approach; 1) video clarity, 2) task difficulty, 3) general feedback. Generally, videos were clear to see, two participants reported difficulties with the clarity of videos, this was partly due to positioning in the scanner and issues around vision and being able to adequately match participants' glasses lenses with MRI compatible lenses and frames. Perceived task difficulty was mixed across participants, some found the task easy and were able to imagine themselves in the videos whilst others reported finding it difficult to imagine themselves in the videos. In the general

feedback theme, two participants reported that the postural instability task felt quite extreme at times and another participant found the watching the videos helped them to feel less claustrophobic during the scanner. Feelings of claustrophobia is a common phenomenon in both clinical and research MRI scanning, making it difficult to recruit and retain participation in imaging studies (400). The use of videos has been explored in paediatric populations as a way of enabling children to feel less claustrophobic in the scanner and reduce motion (401–403). The use of videos within populations of older adults with cognitive impairments to improve scanner experiences has not yet been explored and could be an easily implemented solution to improve both scanner experience, recruitment, and retention of participants with dementia.

Whole-brain analysis of task-related activation for each condition showed activation of primary visual cortex, right middle frontal gyrus and right precentral gyrus during walking, primary visual cortex and right middle frontal gyrus during obstacle navigation and primary visual cortex and right superior parietal lobule during postural instability. The primary visual cortex plays a key role in receiving and integrating visual stimuli (404). The middle frontal gyrus is thought to be involved in reorienting attention, attentional control, and more recently evidence suggests a role in planning movement (405). The precentral gyrus or premotor cortex is involved in voluntary movement execution (406). The superior parietal lobule is involved in visuospatial perception, attention, planned movement and sensory integration (407). Activation in the visual cortex during all three conditions, is in line with previous work in healthy young and older adults (341,346). Frontal and parietal activation noted in this study in

response to walking, obstacle navigation and postural instability has also been noted in healthy populations, systematic reviews and meta-analyses (81,93,98,347).

There were no significant differences in activation between the task conditions, even when applying a lenient threshold. The lack of significant differences in activation could be attributed to the number of trials per condition. Task based fMRI studies usually have large numbers of trials for each condition, which in turn lengthens the time in the scanner. Given the population of interest, tasks with larger numbers of trials may not be feasible as older adults with cognitive impairments struggle to be able to sustain long periods of concentration. Based on this, each condition was presented three times. In task fMRI study design, there is a trade-off between number of trials presented and the sample size, increasing the number of trials presented can mean fewer participants are needed and vice versa (408). The sample size of this study was relatively small. This may also be contributing to the lack of significant difference in activation between the task conditions.

An alternative explanation for the lack of significant differences in activation between task conditions could be the effect of imagery ability. Analysis of task experience feedback highlighted some participants found imaging themselves in the videos quite difficult. This may have affected how well participants were able to engage with the task and could be contributing the lack of differences noted between the conditions. Previous work by van der Meulen et al. (117) found imagery ability influenced activation patterns in response to motor imagery gait task.

The cerebral cortex plays an important role in both postural control and is also affected by dementia in the early stages of the disease. For the ROI analysis, the focus was the cerebral cortex and previous motor imagery studies and meta-analyses were consulted to select ROIs (81,346,347,371,396,397). No differences in activation in supplementary motor areas, parieto-insula vestibular, anterior cingulate and prefrontal cortices between the task conditions were found. As well as the factors mentioned above that may have contributed to non-significant findings (task design, sample size, imagery ability, participant ability and task difficulty), the method of defining ROIs to extract regional activity may have also had an impact. The present study used cytoarchitecture maps of the brain to define the ROIs (392). These maps are more reliable than anatomical maps in distinguishing between brain regions. However variability in brain sizes and degree of pathology means precise location of ROIs can differ between individuals which could lead to the true activation of ROI being missed for some participants (384).

Another set of interesting findings were the relationships between executive function, ROI activation and balance. Based on previous work (145,167,409,410) The relationship between core processes of executive function, namely working memory, cognitive flexibility and inhibition control and static and dynamic balance was examined. There was no relationship of significance between executive function and static balance, however cognitive flexibility appeared to be associated with dynamic balance. The relationship between ROI activation during each task condition and static and dynamic balance was explored. During the walking condition, bilateral premotor area and left supplementary motor

area were associated with static and dynamic balance. In the obstacle condition, the right premotor cortex and right anterior cingulate cortex were associated with static balance, while left supplementary motor area and right anterior cingulate cortex were associated with dynamic balance. For the postural instability condition, right premotor cortex and bilateral supplementary motor area were associated with static balance and only the left supplementary motor area was associated with dynamic balance. During walking and postural instability condition, activity in motor regions was associated with balance performance, whilst, interestingly in the obstacle condition, both motor areas and anterior cingulate cortex were involved.

The anterior cingulate cortex plays a key role in executive function, specifically in decision making, planning, and error detection (411). Given navigating an obstacle requires elements of planning and decision making, the relationship between anterior cingulate cortex activity during this condition and both static and dynamic balance is noteworthy. Additionally, the anterior cingulate cortex is involved in error detection, however during the postural instability condition only motor regions were associated with static and dynamic balance. Given participants were mildly impaired and generally had good balance, perhaps response to external perturbations is still automatic or reactionary, not yet impacted by dementia related pathology.

In this study three core cognitive abilities that underpin cognitive function: cognitive flexibility, attentional set shifting, and visuospatial working memory were explored. Executive function is comprised of lots of different cognitive

abilities, there may be cognitive abilities that are more relevant to postural stability that still need to be explored.

Previous work has shown that balance and executive function may have shared neural substrates as executive dysfunction is associated with postural control deficits (412). Based on this, it was hypothesised that executive function would mediate the relationship between ROI activation in each task condition and balance. Contrary to previous work and the current hypothesis, there was no significant relationship between ROIs significantly associated with dynamic balance and executive function for any of the task conditions. Also, I did not find that executive function mediated the relationship between theses ROIs and dynamic balance. Findings from regression and mediation analyses need to be treated with caution due to the small sample size. It is recommended for each variable, there should be between ten observations per variable (413). Given the large number of variables of interest in this study and the small sample there is a risk of overfitting and overestimating the model.

6.6 Conclusions

- This study has shown that scanning was well tolerated by participants, the task was deliverable, task experience feedback indicated participants were able to view and engage with the task, though some found this easier than others.
- Filler videos and video tasks may reduce feelings of claustrophobia, which could be useful tool to improve scanning experience for older adults with cognitive impairments.

- Whole brain activation during walking was noted in visual cortex, middle frontal gyrus, and precentral gyrus. During obstacle navigation, activation was noted in visual cortex and middle frontal gyrus. During postural instability activation was noted in visual areas and superior parietal lobule.
- The relationship between ROI activation during each condition and balance appears to be complex. During the walking condition, premotor and supplementary motor regions were associated with dynamic and static balance. During the obstacle navigation condition, the anterior cingulate cortex was also associated with static and dynamic balance, which plays a key role in planning. Perhaps during more complex postural control tasks such as navigating an object require more input from brain regions involved in higher order processing and executive function.
- Brain networks involved in postural stability during walking and responding to external perturbations may still be automatic and require less involvement of brain regions involved in higher order cognitive functions during early stages of cognitive impairment and dementia.

7. Functional connectivity and balance in dementia: A resting state fMRI study

7.1 Background

Resting-state fMRI is a task-free alternative approach and enables researchers to map the functional organisation of the brain and explore how it is linked to human functions and behaviours. Resting-state fMRI has led to the identification of large scale, highly replicable resting-state cortical networks, which correspond to networks involved in core cognitive processes. This type of fMRI also enables the quantification of intra and internetwork connectivity strength (228).

Neural correlates of balance and gait in older adults with dementia have received little attention to date. Given the effects of balance and gait dysfunctions, and consequently falls, it is important to understand how neural correlates of balance and gait are altered in people with dementia. Much of functional MRI research in dementia has used resting-state fMRI to quantify altered functional connectivity because of underlying pathology (see chapter 3 for an overview of resting-state fMRI research in dementia). The default mode network has been most consistently identified to be impacted by Alzheimer's disease-related pathology (232,252). Additionally, changes in dorsal attention network, central executive network and salience network have been observed in people with MCI and AD as well as those at risk of cognitive decline (290,294,414). Studies using resting-state fMRI to explore the impact of dementia-related pathology on functional connectivity have been discussed in more detail in chapter 3.

Resting-state fMRI has been applied in healthy young and older adults, alongside balance and gait assessments to explore relationships between functional connectivity of brain regions, large scale networks, and balance or gait performance. A study comparing functional connectivity of sensorimotor network between young and older adults found, older adults displayed decreased local efficiency of sensorimotor network and increased global efficiency of the network when compared with younger adults (415). Decreased local efficiency of sensorimotor in older adults was associated with increased gait variability (415). Yuan et al. (416) exploring the relationship between functional connectivity and gait speed during single and dual task conditions, in healthy older adults, found task performance was correlated with connectivity within sensorimotor network, visual network, vestibular network and left fronto-parietal network (416). Dual task performance specifically was associated with increased functional connectivity in sensorimotor network and left fronto-parietal network when compared with single task condition (416). Zhou et al. (417) explored the relationship between complexity of resting state functional networks and gait speed during single and dual task conditions in older adults. The researchers found those with lower complexity within sensorimotor, dorsal attention and ventral attention networks displayed slower walking speeds during both single and dual task conditions (417). A longitudinal study exploring age-related changes in inter and intra network functional connectivity and the relationship between falls status found that older adults with a history of falls displayed greater connectivity between DMN and FPN and lower connectivity between SMN and FPN (418). This study also found that older adults who had

fallen exhibited lower connectivity between SMN and FPN and this was associated with greater decline in mobility (418).

Recent studies have begun to explore the relationship between functional connectivity, balance, and executive function in older adults with functional limitations, early-stage Parkinson's disease and MCI. Lo et al. (337) explored the relationship between gait characteristics and network connectivity in healthy older adults and older adults with functional limitations. Faster gait speed was associated with greater functional connectivity within the FPN, specifically the bilateral frontal gyri. Steadier gait was associated with lower functional connectivity with DAN and DMN. Also, within the DAN and DMN, gait velocity was linked to right superior parietal sulcus. This work was recently extended to include older adults with mild Parkinson's disease (336). Across all participants, increased connectivity between DAN and DMN was associated with greater gait variability. In healthy controls, decreased gait variability was associated with negative relationship between DMN-SMN, DMN-VAN, and DMN-FPN connectivity. In the group with Parkinson's disease, decreased gait variability was associated with negative relationship between DMN and limbic network connectivity (336).

A limited number of studies have begun to explore the relationship between functional connectivity, balance, and gait in older adults with MCI. Hsu et al. (419) explored patterns of functional connectivity, specifically within SMN and FPN, that were associated with slower gait speed in older adults with MCI. Slower gait was associated with greater connectivity between SMA-bilateral ventral visual area, lower connectivity between SMA-bilateral superior left

occipital area, and SMA-bilateral frontal eye field area. Increased DMN-SMN functional connectivity has been linked to slower gait speed and increased postural sway in older adults with MCI (420). Additionally, increased functional connectivity within the DMN was associated with poorer dual task performance (420). This work has been extended to explore the effects of falls history on the relationship between functional connectivity and postural sway in older adults with and without a history of falls and with or without a diagnosis MCI (421). Older adults with MCI who had fallen, displayed stronger connectivity between DMN-SMN when compared with those without MCI. Additionally, a linear increase in DMN-SMN connectivity was noted from healthy older adult fallers, older adults non-fallers with MCI to older adult fallers with MCI (421). This increase in DMN-SMN connectivity was associated with increased postural sway and slower gait.

To date, the relationship between functional connectivity and balance in people with dementia has not been investigated and research in people with MCI is limited. This population is likely to display balance and gait dysfunction in the early stages of the disease and have an increased risk of falls and related adverse consequences. Developing our understanding of how intra and interconnectivity of large-scale resting-state networks are related to balance performance, will enable the development of knowledge of the neural correlates involved and inform future work to improve detection of those at risk of falls and development of interventions to improve balance.

For this chapter, I conducted an exploratory resting-state fMRI study with older adults with MCI and dementia. In this study, I used a data-driven approach to

identify large scale networks and explore the relationship between the strength of intra and internetwork connectivity and performance on measures of balance.

7.2 Methods

This study was a cross-sectional resting-state fMRI study within the multicentre PrAISED RCT.

7.2.1 Inclusion and exclusion criteria

In brief, participants were aged 65 or over, with a diagnosis of MCI or dementia, with a MoCA score in the range of 13-25. Participants who met specific MRI exclusion criteria (e.g., pacemaker, intra ocular metallic fragment, claustrophobia), were excluded from taking part in the study. More detail has been provided in the previous chapter (see section 6.3.1).

7.2.2 Recruitment

Participant recruitment procedures have been provided in detail in the previous chapter (see section 6.3.2). In brief, participants were recruited from the PrAISED RCT Nottinghamshire and Derbyshire sites who signed clause 7 on the consent form (willing to be contacted about additional related studies, see appendix C) were introduced to the MRI study by the researcher conducting their baseline visit. I contacted participants who expressed interest in the study at the PrAISED baseline visit by telephone to discuss the study in more detail and check participants met the inclusion and exclusion criteria for the study.

For participants who were eligible and willing to take part, I arranged an appointment for the participants (and their carer if they wished to accompany the participant) to attend the Sir Peter Mansfield Imaging Centre at the Queen's

Medical Centre, Nottingham. At the appointment, I discussed the study with the participant in more detail and rechecked eligibility using the MRI safety questionnaire, which was also checked by a qualified radiographer. For eligible participants, I sought written informed consent before proceeding with the MRI scan.

7.2.3 PrAISED assessments

As part of the PrAISED RCT, participants completed a comprehensive battery of assessments at baseline including cognition (MoCA, verbal fluency, CANTAB visuospatial working memory test, CANTAB multitasking test), activities of daily living (NEADL and DAD) and balance (TUG and BBS). See the previous chapter for more details on the measures completed by participants (section 6.3.3).

7.2.4 Resting-state fMRI scanning procedures

Participants were presented with a fixation that was visible through the MRI-compatible goggles. Participants were instructed to stay awake and focus on the cross on the screen.

7.2.5 MRI data acquisition

Functional imaging was performed on a 3T MRI scanner (GE Healthcare discovery MR750), using a 32-channel head coil. T1, FSPGR BRAVO images were acquired using the following parameters: TR= 0.008144, TE= 0.003172, Flip Angle (FA) = 12, Inversion time = 0.45, Matrix= 256 x 256, Thickness= 1 and Voxel size = 1 x 1 x 1.

Functional images were acquired using echo planar imaging sequence using the following parameters: TR = 2000ms, TE = 30ms, Flip Angle (FA) = 77, Matrix = 64

x 64, Slices = 37, Thickness= 3, Voxel size = 3 x 3 x 3, Spacing between slices = 3.5, slices = 37 covering the whole brain and cerebellum. The resting-state fMRI sequence lasted for 6 minutes and a total of 180 volumes were collected.

7.2.6 fMRI data processing

The SPMIC-UoN/BRC pipeline (422) on the Linux server was used to pre-process and analyse the resting-state fMRI data. The pipeline uses various MRI image processing software including FSL, Free Surfer, and ANTS. The pipeline required pre-processing of structural T1 data to be completed before pre-processing epi-based fMRI data as the functional pre-processing pipeline was dependent upon outputs generated by the processing of structural data. Structural T1 data underwent bias-field correction, skull stripping, tissue segmentation, and subcortical segmentation, linear and non-linear registration to standard space, multimodal tissue segmentation, and free surfer analysis.

Once structural data pre-processing was completed, functional data underwent went the following pre-processing steps; Removal of non-brain tissue, Distortion correction, motion correction, intensity normalization, slice timing correction, physiological noise removal (using FSL's ICA-AROMA tool), registration to structural T1 image, and registration to standard space. Like the task-related fMRI, individuals with more than 3mm movement (greater than the voxel size) were excluded from the analyses.

7.2.7 fMRI data analysis

Independent component analysis (ICA) was used to identify large scale resting-state networks. ICA is a data-driven approach that separates multivariate data into statistically independent spatial components and their associated time

series. When applied to resting-state fMRI data, ICA decomposes the BOLD dataset into components representing neural signals of interest, structured noise, and random noise (423,424). This technique does not require a priori modelling, providing flexibility for the exploratory analyses presented in this chapter.

The functional connectivity analysis pipeline within the suite of the SPMIC-UoN/BRC image processing pipelines (422) and FSLnets, on the university's Linux server was used to analyse the resting-state fMRI dataset. I fed the pre-processed resting-state fMRI data into the pipeline which included the following steps; Group independent component analysis (ICA) was conducted by concatenating the 4D datasets from all subjects and were decomposed using the multivariate exploratory linear optimized decomposition into independent components (MELODIC) tool in FSL (423). Given the exploratory nature of the analysis and the use of the data driven a dimensionality estimate was not prespecified. The independent components (IC) identified at the group ICA stage were then entered into a dual regression analysis to generate subject-specific spatial maps and time courses for each component (425). Dual regression analysis is based on multiple regression and involves two stages. In the first stage, the independent components from the group ICA were used as template maps and regressed against each participant's 4D dataset. The second stage involved variance normalising the time courses and regressing them against each participant's data set to create participant-specific spatial maps corresponding to each IC.

To identify components of interest, using the 'fslcc' command independent components maps were cross correlated with Yeo et al.'s (426), 7 resting state network masks. Independent components which correlated with network masks were marked as networks of interest.

Intra network connectivity

From the dual regression outputs, the mean z scores for each independent component of interest were extracted as a measure of the strength of functional connectivity within the networks of interest. The z scores were then imported into SPSS (version 26) for further analyses to investigate the relationship between intra network connectivity and balance. More detail on these analyses is provided later in this chapter (see section 7.2.8).

Internetwork connectivity

For each subject, the time courses for each network of interest identified in the dual regression analysis were entered into the FSLnets package implemented in MATLAB v2019b. Partial correlation matrices between the networks were calculated for each participant. The correlation coefficients were transformed to z values using Fisher's r to z transformation. The z values for internetwork connectivity were imported into SPSS for further analysis to investigate relationships between functional connectivity and balance.

7.2.8 Statistical analysis

SPSS was used to conduct regression analyses to explore the relationship between inter or intra network connectivity and performance on BBS and TUG measures. Prior to conducting regression analyses the same process used to assess normality, linear relationships between explanatory and outcome

variables, multicollinearity and homoscedasticity for the task-related dataset was used for this dataset (see section 6.3.8). Normality and linear relationships between explanatory variables (intra and inter network connectivity of components of interest) and outcome variables (BBS and TUG) were assessed through visual inspection of scatter plots. Pearson's correlation and Durbin Watson statistic were used to test for multicollinearity between explanatory variables. Scatter plots of residual values were visually inspected to assess whether the variance of residuals was constant and indicated assumptions of homoscedasticity were met (see appendix B). Additionally, Cook's distance was also calculated to ascertain whether there were any outliers influencing the model.

For the regression models a hierarchical approach was used, entering age and MoCA score covariates in the first step, and then including intra and internetwork functional connectivity metrics in the second step. As this was an exploratory analysis, I made no prior assumptions of the relative importance of the independent variables and therefore used the 'enter' method. Separate multiple linear regression analyses were conducted for internetwork functional connectivity and intra network connectivity, with BBS and TUG as the dependent variables.

7.2.9 Ethical approval

This study has received NHS and HRA approval – ethics number 18/YH/0059 (appendix D).

7.3 Results

Of 45 participants recruited from the PrAISED trial, resting-state fMRI datasets for 39 participants were included in the analysis (see section 6.4.1 for more detail on participant recruitment). Reasons for exclusion included withdrawal during scanning (n=5) and poor data quality of either the resting-state fMRI data or structural imaging data which would affect registration between fMRI and MRI images (n=1). Participant characteristics for the participants included in the analyses in this chapter are presented in table 7.1.

Table 7. 1 Demographics and descriptive statistics for participants included in resting state fMRI analysis (n=39).

Measure type	Measure name	Mean	S.D.	Min	Max
Demographics	Age	81.8	6.71	68	96
	Gender (M: F)	28:11			
	Diagnosis (MCI: Dementia)	9:30			
Global cognition	MoCA	20.05	3.24	14	26
Executive dysfunction	Verbal fluency	12.66	5.31	4	25
	CANTAB Spatial Span test Length forward	4.03	1.16	2	8
	CANTAB Multitasking test – Switch response latency	1002.35	304.67	440.50	1676.00
	CANTAB Multitasking – Congruent response latency	846.74	141.21	564.50	1167.00
	CANTAB Multitasking test	966.56	156.59	690.50	1317.00

	– Incongruent response latency				
Balance	Berg balance scale	47.15	11.22	6	56
	Timed Up and Go	16.89	14.20	8	87

7.3.1 ICA analysis / resting-state network identification

The group ICA estimated 128 components. To identify components that represented functional resting-state networks, all components were correlated with Yeo et al.'s (426) 7 networks masks. Of the 128 components identified, 7 components correlated with visual, limbic, dorsal attention, sensorimotor and default mode networks (see table 7.2 and figure 7.1).

Table 7. 2 ICA independent components and corresponding resting-state networks.

Independent component number	**Corresponding RSN Network (Yeo et al. 2011)**	**R**
01	Limbic (Lim)	0.307
11	SensoriMotor Network (SMN)	0.244
57	Visual (Vis)	0.418
63	Limbic (Lim)	0.238
75	Default Mode Network (DMN)	0.429
88	SensoriMotor Network (SMN)	0.231
100	Dorsal Attention Network (DAN)	0.212

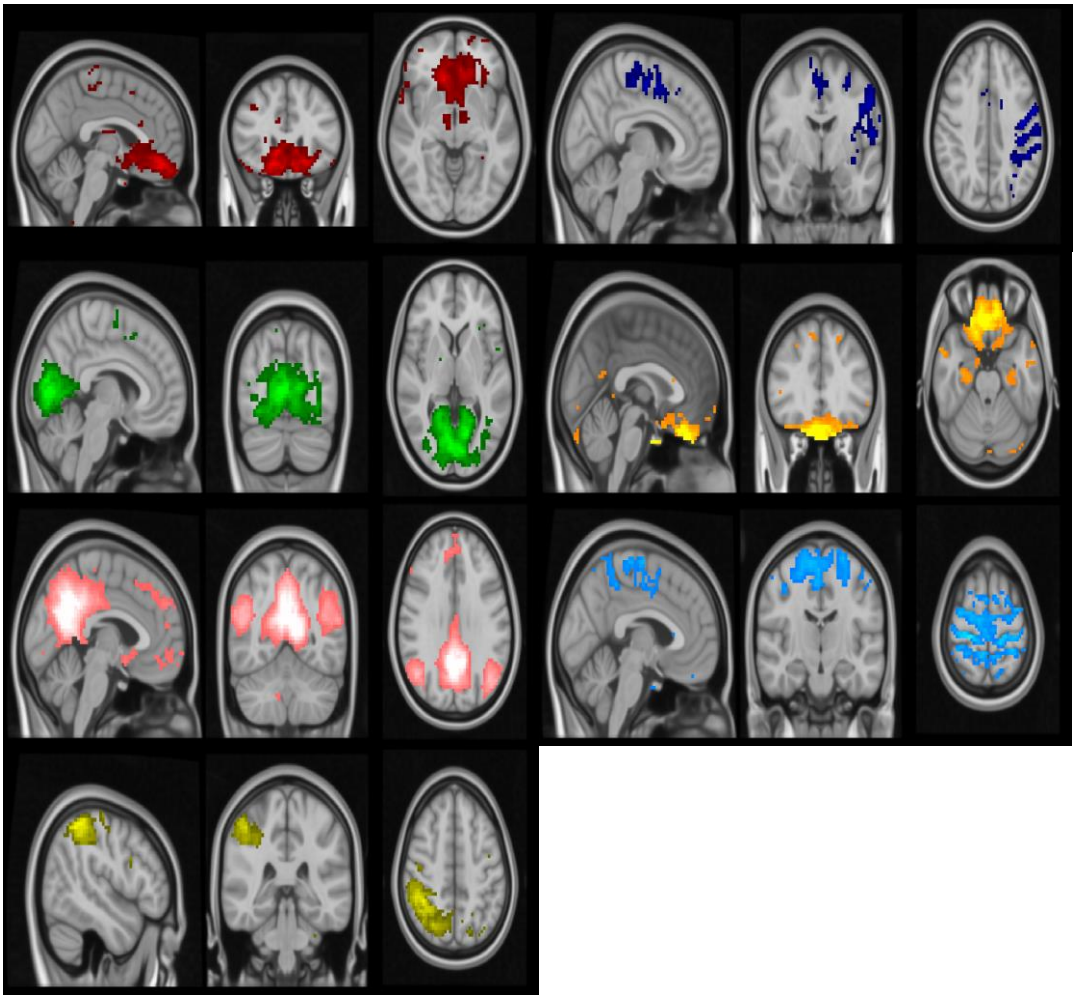

Figure 7. 1 Group functional connectivity maps for each Resting State Network.

Key: Red = Limbic IC_1; Indigo = Sensorimotor IC_11; Green = Visual IC_57; Orange = Limbic IC_63; Pink = Default mode IC_75; Blue = Sensorimotor IC_88; Yellow = Dorsal Attention IC_100.

7.3.2 Relationship between functional connectivity and balance

To explore the relationship between functional connectivity of independent components of interest and balance performance, I constructed 4 hierarchical regression models. In step 1 of the models, age and MoCA scores were included as covariates. In step 2, the independent variables included were either intra network connectivity or internetwork connectivity metrics. The outcome variables of interest were performance on the BBS and TUG.

7.3.2.1 Assumption testing

Data were assessed to check whether any assumptions of linear regression were violated. Linear relationship between independent variables (intra or inter network functional connectivity) and outcome variable (BBS or TUG) were assessed through visually inspect of scatter plots. Pearson's correlations and Durbin Watson statistics were checked to assess for multicollinearity. Scatter plots of residuals were checked to assess assumptions of homoscedasticity. P-Plots were checked to assess normality of residuals and Cook's distance was calculated to check whether there were outliers (>1) that significantly influenced the regression models.

7.3.2.2 Berg Balance score

Intra network functional connectivity

In step 1, MoCA and age scores accounted for 16% of the variance in BBS (p=.05). In step 2, introducing z scores for intra network connectivity for each of the seven components of interest explained a further 10% of the variance in BBS however the change in R^2 was non-significant (p>.05). The independent variables

entered in step 2 were examined further, none were significantly associated with BBS (see table 7.3).

Inter network functional connectivity

In step 1, MoCA and age scores accounted for 16% of the variance in BBS (p=.05). In step 2, introducing z scores for inter network connectivity between 7 networks of interest (excluding connectivity between two components corresponding to limbic network and two components corresponding to sensorimotor network) explained a further 35% of the variance in BBS however the change in R^2 was non-significant (p>.05). The individual independent variables were examined further, none were significantly associated with BBS at p<.05 (see table 7.4).

7.3.2.3 Timed up and go

Intra network functional connectivity

In step 1, MoCA and age scores accounted for 15% of the variance in TUG performance (p>.05). In step 2, introducing z scores for intra network connectivity for each of the seven components of interest explained a further 22% of the variance in TUG performance however the change in R^2 was non-significant (p>.05). The individual independent variables were examined further, and none were significantly associated with TUG performance (see table 7.5).

Inter network functional connectivity

In step 1, MoCA and age scores accounted for 15% of the variance in TUG performance (p>.05). In step 2, introducing z scores for inter network connectivity between 7 networks of interest (excluding connectivity between two components corresponding to limbic network and two components

corresponding to sensorimotor network) explained a further 38% of the variance in TUG performance however the change in R^2 was non-significant ($p>.05$). The individual independent variables were examined further, and none were significantly associated with TUG performance (see table 7.6).

Table 7. 3 Intra network connectivity and BBS.

	Unstandardised coefficients		Standardised coefficients		95 % CI	
Variable	β	Std Error	B	p	Lower	Upper
Step 1						
Age	-0.32	0.25	-0.20	0.21	-0.83	0.19
MoCA	1.10	0.54	0.32	0.05	0.02	2.19
Step 2						
Age	-0.24	0.31	-0.15	0.44	-0.87	0.39
MoCA	1.24	0.63	0.36	0.06	-0.06	2.54
Visual	0.02	10.40	0.00	1.00	-21.24	21.28
SMN_1	7.72	16.21	0.09	0.64	-25.44	40.87
SMN_2	-7.40	13.96	-0.09	0.60	-35.96	21.15
DAN	-8.15	10.63	-0.14	0.45	-29.89	13.58
Limbic_1	-4.78	13.97	-0.07	0.73	-33.34	23.78
Limbic_2	13.07	15.40	0.15	0.40	-18.42	44.56
DMN	-9.13	11.14	-0.17	0.42	-31.92	13.66

Note
Step 1: $F = 3.32$, $p = 0.05$, $R^2 = 0.16$, R^2 (adjusted) = 0.11
Step 2: $F = 1.11$, $p = 0.39$, $R^2 = 0.26$, $\blacktriangle R^2 = 0.10$, R^2 (adjusted) = 0.03, $\blacktriangle R^2$ (Adjusted) = -0.08

Table 7. 4 Inter network connectivity and BBS.

Variable	Unstandardised coefficients		Standardised coefficients		95 % CI	
	β	Std Error	B	*p*	Lower	Upper
Step 1						
Age	-0.32	0.25	-0.20	0.21	-0.83	0.19
MoCA	1.10	0.54	0.32	***0.05***	0.02	2.19
Step 2						
Age	-0.25	0.43	-0.15	0.58	-1.16	0.67
MoCA	2.13	0.93	0.62	***0.03***	0.18	4.08
Lim1-SMN1	-0.20	1.36	-0.05	0.89	-3.07	2.67
Lim1-Vis	0.17	0.75	0.05	0.82	-1.41	1.76
Lim1_DMN	-0.02	1.43	0.00	0.99	-3.04	3.00
Lim1_SMN2	-0.94	1.21	-0.20	0.45	-3.50	1.62
Lim1_DAN	0.60	1.76	0.12	0.74	-3.12	4.32
SMN1_Vis	1.68	1.21	0.35	0.18	-0.88	4.24
SMN1_Lim2	-0.30	0.79	-0.08	0.71	-1.96	1.36
SMN1_DMN	0.35	1.28	0.07	0.79	-2.36	3.06
SMN1_DAN	0.33	0.95	0.08	0.73	-1.68	2.35
Vis_Lim2	-0.30	1.06	-0.07	0.78	-2.54	1.95
Vis_DMN	2.08	1.18	0.49	0.10	-0.42	4.58
Vis_SMN2	0.65	1.12	0.16	0.57	-1.71	3.01
Vis_DAN	-0.63	1.75	-0.13	0.72	-4.31	3.06
Lim2_DMN	2.63	1.50	0.61	0.10	-0.53	5.79
Lim2_SMN2	1.29	1.39	0.26	0.37	-1.63	4.22
Lim2_DAN	-1.93	1.13	-0.47	0.11	-4.31	0.46
DMN_SMN2	-0.72	1.13	-0.20	0.54	-3.10	1.67
DMN_DAN	-1.18	1.16	-0.28	0.32	-3.62	1.26
SMN2_DAN	-0.39	1.00	-0.11	0.70	-2.50	1.71

Note
Step 1: F = 3.32, p = 0.05, R^2 = 0.16, R^2 (adjusted) = 0.11
Step 2: F = 0.82, p = 0.67, R^2 = 0.50, ▲R^2 = 0.35, R^2 (adjusted) = -0.11, ▲R^2 (Adjusted) = -0.22

Table 7. 5 Intra network connectivity and TUG.

	Unstandardised coefficients		Standardised coefficients		95 % CI	
Variable	β	Std Error	B	p	Lower	Upper
Step 1						
Age	0.60	0.32	0.29	0.07	-0.06	1.25
MoCA	-0.94	0.69	-0.22	0.18	-2.34	0.45
Step 2						
Age	0.45	0.36	0.22	0.22	-0.29	1.18
MoCA	-1.17	0.75	-0.27	0.13	-2.71	0.37
Visual	12.93	12.53	0.18	0.31	-12.74	38.59
SMN_1	1.35	19.12	0.01	0.94	-37.81	40.52
SMN_2	-4.63	16.60	-0.05	0.78	-38.63	29.38
DAN	-5.15	13.93	-0.07	0.72	-33.69	23.39
Limbic_1	**32.68**	**16.51**	**0.38**	**0.06**	**-1.14**	**66.50**
Limbic_2	2.42	19.16	0.02	0.90	-36.83	41.67
DMN	3.87	13.08	0.06	0.77	-22.92	30.66

Note
Step 1: F = 3.08, p = 0.06, R^2 = 0.15, R^2 (adjusted) = 0.10,
Step 2: F = 1.81, p = 0.11, R^2 = 0.37, ▲R^2 = 0.22, R^2 (adjusted) = 0.16, ▲R^2 (Adjusted) = 0.06

Table 7. 6 Inter network connectivity AND TUG.

	Unstandardised coefficients		Standardised coefficients		95 % CI	
Variable	β	Std Error	B	*p*	Lower	Upper
Step 1						
Age	0.596	0.321	0.292	0.07	-0.06	1.25
MoCA	-0.944	0.685	-0.217	0.18	-2.34	0.45
Step 2						
Age	0.13	0.54	0.06	0.81	-1.02	1.28
MoCA	-2.17	1.17	-0.50	0.08	-4.66	0.31
Lim1-SMN1	0.12	1.71	0.03	0.95	-3.50	3.74
Lim1-Vis	0.68	0.97	0.14	0.49	-1.37	2.72
Lim1_DMN	-0.84	1.79	-0.16	0.65	-4.62	2.95
Lim1_SMN2	0.58	1.51	0.10	0.71	-2.62	3.78
Lim1_DAN	0.48	2.20	0.08	0.83	-4.19	5.15
SMN1_Vis	-2.40	1.52	-0.39	0.13	-5.61	0.82
SMN1_Lim2	-0.24	0.98	-0.05	0.81	-2.32	1.84
SMN1_DMN	1.13	1.73	0.17	0.52	-2.53	4.79
SMN1_DAN	-0.05	1.19	-0.01	0.97	-2.58	2.47
Vis_Lim2	-0.63	1.33	-0.11	0.64	-3.44	2.18
Vis_DMN	-1.95	1.48	-0.37	0.21	-5.09	1.18
Vis_SMN2	***-2.75***	***1.42***	***-0.53***	***0.07***	***-5.76***	***0.26***
Vis_DAN	-0.51	2.20	-0.08	0.82	-5.18	4.15
Lim2_DMN	-0.40	2.14	-0.07	0.86	-4.94	4.15
Lim2_SMN2	-0.69	1.81	-0.11	0.71	-4.52	3.15
Lim2_DAN	0.78	1.49	0.15	0.61	-2.38	3.94
DMN_SMN2	0.04	1.41	0.01	0.98	-2.95	3.02
DMN_DAN	0.87	1.51	0.16	0.57	-2.34	4.07
SMN2_DAN	0.42	1.25	0.09	0.74	-2.23	3.07

Note
Step 1: F = 3.08, p = 0.06, R^2 = 0.15, R^2 (adjusted) = 0.10
Step 2: F = 0.87, p = 0.62, R^2 = 0.53, ▲R^2 = 0.38, R^2 (adjusted) = -0.08, ▲R^2 (Adjusted) = -0.18

7.4 Discussion

In this chapter the relationship between functional connectivity within and between large scale resting state networks and balance in older adults with MCI and dementia was explored. This study adds to the limited body of work available exploring functional connectivity and balance in MCI and dementia. Previous work has highlighted changes in functional connectivity within various resting state networks such as DMN, SMN and FPN were related to poorer mobility and balance in healthy older adults, older adults with functional limitations and neurodegenerative diseases such as cognitive impairment, Parkinson's disease and multiple sclerosis (336,337,416,417,419–421).

Previous work has used seed-based connectivity analysis involving cross correlating a region of interest with the remaining voxels in the brain to find other regions which may be correlated or connected (228). This method of analysis can improve the issues around multiple comparisons but is subject to potential bias in selection of ROIs (418–421). Additionally in seed-based analysis, the signal is likely to a mix a signal and noise, masking true activation (384,385,387). On the other hand, ICA is a data driven approach, limiting researcher bias in ROI selection (228). Additionally, ICA separates physiological noise components from components of interest (423,424). Given the exploratory nature of this study independent component analysis was used to identify networks of interest. ICA analysis decomposed resting state fMRI data into 128 components. Well established resting state network maps (426) were used to identify components of interest rather than manual classification of components.

Seven components of interest corresponding to default mode, sensorimotor, dorsal attention, limbic and visual resting state networks were identified.

When exploring the relationship between mean functional connectivity of each component and static and dynamic balance performance, contrary to previous work in healthy older adults and older adults with MCI (415–417,419–421), intra and inter network connectivity were not significantly associated with static or dynamic balance. Examining the regression analyses in more detail, a potential signal in the data was noted for intra connectivity of the limbic network, specifically the orbitofrontal cortex (see IC_1 in figure 24) and TUG performance (β= -2.75, p= 0.06, 95% C.I: -1.14, 66.50). Increased connectivity of the orbitofrontal cortex may be associated with slower TUG speed. The orbitofrontal cortex is a key node within the limbic network, with subcortical regions of this network, such as the hippocampus, affected by dementia related pathology (246,249,280). Additionally, the orbitofrontal cortex has a key role in planning, decision making, sensory processing and control of body movement (427,428). In younger populations, decreased activation of orbitofrontal cortex has been noted during walking (93), whereas aging has been associated with increased activation of the orbitofrontal cortex during walking (370). It is important to note that this association of increased orbitofrontal cortex connectivity with poorer dynamic balance performance, fell just outside the standard threshold for significance ($p<.05$), therefore these findings need to be interpreted with caution and further investigation is needed to establish whether this potential association is indeed present in larger samples.

When exploring the relationship between inter network connectivity and balance again the regression models were non-significant. A potential signal was noted between visual network-SMN connectivity and TUG performance, in that increased connectivity between visual and sensorimotor network may be associated with faster TUG speed. Again, this association was also just outside the prespecified threshold for significance ($p<.05$) and therefore difficult to draw firm conclusions, warranting further investigation. Previous work by Hsu et al. (419) reported disrupted connectivity between SMA a key region in the SMN and visual areas in healthy older adult fallers. Specifically, slower gait speed was associated with increased connectivity between supplementary motor area and bilateral ventral visual cortex and decreased connectivity between supplementary motor area and bilateral frontal eye fields and bilateral superior lateral occipital cortex. The findings of the present study are potentially contradictory to the association between slow gait speed and increased supplementary motor area and bilateral ventral visual cortex connectivity but possibly confirmatory for the latter associations between slow gait speed and decreased connectivity between motor and visual cortical areas. The differences in findings may be attributable to differences in analysis methods and balance measures used. Hsu et al. (419) used a region of interest analysis approach while the present study adopted a data driven approach, Additionally, the presented study used the Timed Up and Go assessment, a widely used clinical tool to assess dynamic balance and mobility whilst the previous work only assessed the relationship between motor visual connectivity and gait speed.

Increased visual network and SMN connectivity and better TUG performance suggests older adults with early-stage dementia, may engage in compensatory activation of multiple networks to maintain balance performance (419,421). Additionally, the potential association between visual network-SMN connectivity and balance performance may be indicative of increased reliance on visual input and to maintain balance during more complex tasks. Similar findings were noted in a task fMRI study by Zwergal et al. (346) who found that older adults displayed greater multisensory integration comparted to younger adults in response to an imagined movement task.

It is important to note that ICA is not without its limitations. ICA uses an iterative optimisation approach which means rerunning analysis on the same data set could produce different number of components each time it is run, raising a potential issue around reliability of identifying components (429). Prespecifying dimensionality can also influence ICA results, inputting low dimensionality estimates enables identification of large-scale networks, however, inputting larger dimensionality estimates may split networks into sub networks and nodes (Wang et al. 2015). To mitigate this, the number of components were not prespecified. The strengths and limitations of this study are discussed in greater detail in the next chapter (see chapter 8).

7.5 Conclusions

Contrary to previous work and the present study's hypotheses, intra or inter network connectivity was not significantly associated with static or dynamic balance performance, using standard alpha threshold $p<.05$. There were associations that were just outside of the threshold that may indicate a potential

signal of interest in the data. However further investigation is needed in larger samples to ascertain if this potential signal is still present.

Part III: General discussion

8. General discussion and conclusions

This chapter provides an overview of the initial aims of the thesis and planned studies to address the aims and research questions. This chapter also discusses the timeline and impact of the COVID-19 pandemic and related restrictions to the PrAISED RCT and subsequently to the MRI sub-study which formed part of this thesis. Considering the pandemic and restrictions the changes made to thesis aims and research questions are discussed. A summary of the key findings from each chapter are provided and what the findings mean in the context of previous work is discussed. The strengths and limitations of the studies presented in previous chapters are discussed and potential future directions from the work presented in this thesis are proposed.

8.1 Pre COVID-19 thesis aims and proposed studies

The initial aims of this thesis were 1) to use fMRI better understand the impact of dementia-related pathology on the functional neuroanatomy of balance control and 2) to explore the use of fMRI as an intermediate outcome in exercise and activity interventions to determine optimal intervention duration and intensity.

Additional aims of this thesis were:

3) To pilot a novel virtual reality-based balance task in healthy volunteers, comparing task-related activation in young healthy adults and healthy older adults.

4) To use systematic review methodology to review currently available literature exploring the effects of exercise on fMRI outcomes in older adults with MCI and dementia.

To address these aims, the following studies were planned and set up:

- Systematic review of exercise interventions and fMRI outcomes in dementia.
- Piloting an fMRI stimulus task in healthy participants, comparing activation between younger and older adults.
- A cross sectional study exploring the relationship between task related activity, functional connectivity, and balance in dementia.
- A 12-month longitudinal follow up study to explore the effects of the PrAISED exercise programme (compared with a control condition) on task related activity and functional connectivity.

At the start of the pandemic in March 2020 the status of these studies was:

- Systematic review. Searches had been conducted and title and abstract screening had been completed. The second reviewer had commenced title and abstract screening.
- Healthy volunteer pilot study. Prior to the first lockdown on 23rd March 2020, 10 healthy younger adults had been recruited and was permissions were in place to commence recruitment of 10 healthy older adults.
- PrAISED longitudinal MRI study. Prior to 23rd March 2020, n = 49 were recruited from the PrAISED RCT to take part in the MRI study, of which n = 45 completed baseline scanning. Recruitment was planned to continue until June 2020. Additionally, from 1st February 2020 12-month follow-up scans for these participants had commenced. Between 1st February 2020 and 23rd March 2020, n= 6 follow up scans were completed. Due to the

pandemic and resulting lockdowns, n= 2 baseline scans were cancelled and n = 5 follow up scans were cancelled.

8.2 Impact of COVID-19 pandemic

8.2.1 COVID-19 pandemic and UK restrictions timeline

In March 2020, due to rapid transmission of the coronavirus worldwide, WHO declared COVID-19 to be a global pandemic on 11th March 2020. On 16th March 2020, the Prime Minister announced that the UK would be entering a nationwide lockdown on the 23rd of March 2020. During this time, the UK population was ordered to stay at home. Additionally, the Chief Medical Officer announced that all non-COVID-19 related research was to be suspended unless "discontinuing research would have detrimental effects on the ongoing care of participants involved in those studies". NHS and NIHR staff were instructed to prioritise COVID-19 research and NIHR clinical research networks ceased work on new and existing studies (430).

On 23rd March 2020, the University of Nottingham, School of Medicine, and the Sir Peter Mansfield Imaging Centre in Queen's Medical Centre were closed. All staff and students were instructed to work from home. Although the formal lockdown ended in May 2020, many of the restrictions remained in place across the summer of 2020 and in autumn of 2020 a tier system was introduced whereby lockdowns were introduced locally rather than nationally. In November 2020, the UK entered a second "circuit breaker" lockdown returning to the tier system in December 2020. In January 2021, the UK entered a third national lockdown whereby people were instructed to stay at home. In March 2021, the UK embarked on the 'roadmap out of lockdown', with a phased re-opening of

schools, non-essential businesses and reducing restrictions on social contact between March and June 2021. During this time, the advice from the UK government was to continue to work from home if possible. Formal COVID-19 restrictions ceased on 19th July 2021, but many vulnerable individuals, including older people, remained cautious about social contact.

8.2.2 COVID-19 related changes to PrAISED RCT and MRI sub study

In line with the announcement from the Chief Medical Officer and Health Secretary on 16th March 2020, to stop all 'non-essential' research activity, the PrAISED RCT suspended recruitment, face-to-face delivery of the intervention and face to face follow-up data collection on 17th March 2020. In line with the announcement, PrAISED RCT and closure of the Sir Peter Mansfield Imaging Centre at Queen's Medical Centre, recruitment, baseline and follow up scanning for the PrAISED MRI sub study and the recruitment and scanning of healthy older adults for the healthy volunteer pilot study was suspended.

At the start of the pandemic, to ensure participant safety and attempt to mitigate some of the impacts of the lockdown and social distancing on participants, the PrAISED research team rapidly redesigned the therapy intervention, so that those participants in the active intervention arm, were able to continue with therapy remotely, via video or phone call coaching from therapists. This meant during the lockdown and restrictions on face-to-face contact, the intervention could not be delivered as initially intended. As part the planned studies for this thesis, prior to the pandemic, a longitudinal MRI study alongside PrAISED was set up and running, which aimed to explore the effects of the intervention on balance task-related activity and resting connectivity. Prior to the pandemic 6

participants had completed both baseline and follow up scans, 11 were randomised to the treatment as usual arm, and 16 were randomised to the active intervention, receiving the intervention as planned. Participants who were still enrolled on PrAISED and part of the MRI sub study as of 17th March 2020 and randomised to the treatment arm received a remote version of the intervention, thus addressing the initial research questions were not possible. Additionally, due to the very small number of participants completing the intervention as intended prior to the lockdown in March 2020 and lack of follow up of the remaining participants due to ongoing restrictions, it was also not possible to compare the effects of both trial intervention arms on task related and resting state fMRI signal.

The PrAISED RCT recommenced recruitment in October 2020, briefly paused in December 2020, resuming in January 2021, and concluding in June 2021. At the time of re-opening to recruitment post lockdown in 2020, face-to-face contact and social distancing guidance were still in place. Therapy and research staff were both required to wear PPE and engage in social distancing when meeting with participants face to face. Recommencing recruitment from the PrAISED RCT to the MRI study was not feasible as it required participants to travel into the SPMIC in the Medical School, which is attached to the Queen's Medical Centre. Potential participants were likely to be worried about the risk of COVID and decline to take part. Resuming follow-up scans was also not possible as many participants completed their time in the PrAISED RCT during the UK lockdowns and between lockdowns the SPMIC-QMC 3T MRI scanner was upgraded.

8.2.3 Risk factors for COVID-19 related adverse outcomes

At the beginning of the pandemic in March 2020, people who were classified as "clinically vulnerable", defined as aged 70 and over, aged 70 and under with an underlying health condition or pregnant, were contacted by their GP's and told to "shield". Shielding restrictions involved staying at home and limit their face-to-face contact with others. Shielding guidance was officially withdrawn in July 2021, and clinically vulnerable people were advised to follow the same guidance as the public.

During the pandemic, rapidly accumulating evidence showed that the risk of COVID-19 related severe ill health, hospitalisation and mortality increased exponentially with age (431–434). Additional risk factors for COVID-19 related severe ill health, hospitalisation and mortality were ethnicity, deprivation, body mass index, and comorbidities such as diabetes, hypertension, chronic heart disease, chronic respiratory disease, asthma, cancer, kidney disease, chronic neurological conditions (e.g. dementia), immunosuppression, learning disability or severe mental illness (433–437).

The population of interest for this thesis, were older adults, aged 65 and over (mean age = 81.8, S.D = 6.68) with MCI and dementia. Given that ageing is associated with increased risk for comorbidities (438), dementia and COVID-19 related complications (431–434), the population of interest for this thesis, were likely to be classified as clinically vulnerable and requiring to shield for a large part of the pandemic. This meant that it was not practical or safe to commence recruitment of healthy older volunteers or continue recruitment and follow up scanning of PrAISED participants during the pandemic.

8.3 Post COVID-19 adapted thesis aims

Due to the first national lockdown and subsequent closure of the imaging centre the healthy volunteer study and PrAISED MRI sub study were suspended. Ongoing restrictions, further lockdowns (in November 2020 and January 2021), shielding of clinically vulnerable people, working from home directives, restricted access to the medical school during this time combined with a scanner upgrade and the constraints of PhD timelines meant it was not possible to resume the studies that were running prior to the first lockdown in March 2020. This meant it was not possible to address the initial aims of my thesis. After consultation with the supervisory team for this thesis and previous literature the thesis aims, and proposed studies were reworked to be able to address the new research aim.

The new, overall aim of the thesis was to use both task fMRI and resting state fMRI to explore neural correlates of balance and exercise in older adults with MCI and dementia.

To address this aim the following studies were conducted:

- As initially planned pre-pandemic, a systematic review and narrative synthesis of the effects of exercise on task related activity and functional connectivity in older adults with cognitive impairments was conducted.
- A novel VR based balance task designed for older adults with cognitive impairments was piloted with healthy young adults.
- The VR based balance task was piloted with a subset of the PrAISED cohort, who were all older adults with MCI or dementia.

- Lastly, a cross sectional resting state fMRI study, using ICA to explore the relationship between functional connectivity of large-scale resting state networks and balance in a subset of the PrAISED cohort was conducted.

8.4 Summary of findings

Exercise is a promising intervention in improving balance and mobility and reducing the risk of falls in people with dementia. However, use of fMRI to study neural mechanisms involved in exercise in this population is limited and to date no comprehensive review of the literature had been completed. To address this gap, a systematic review and narrative synthesis was conducted, reported in chapter 4, to understand the current landscape of the research, review what we currently know about how exercise influences brain activity and connectivity in dementia and identify gaps in the knowledge that need to be explored by future research. The literature search found 12 papers from 6 studies, including healthy older adults as controls and older adults with MCI. Exercise interventions were diverse across the studies and involved either aerobic exercise, dancing, progressive resistance training and mind body exercise. Intervention duration ranged from 12 weeks to 12 months, with average duration of the intervention lasting around 6 months. Exercise alters task-related brain activity and connectivity in people with MCI. The mechanisms through which exercise alters brain function appears complex and depends on exercise type and the duration of the intervention. Aerobic exercise appears to have different effects to resistance training, with the former shown to increase task related activity and resting state connectivity, whilst the latter has been shown to decrease connectivity (317–320). This review found no studies that included

people with a dementia diagnosis, therefore results are only generalisable to older adults with MCI.

In chapters 5 and 6, balance related brain activity was explored using task fMRI. In chapter 5, a novel virtual reality balance task was piloted with healthy young adults. Scanning procedures were well tolerated by young healthy adults (mean score 4.8/5 for overall experience). Task experience feedback from this group showed that participants could see the videos in the scanner, however the pace of the tasks was too slow for the participants. fMRI data collected were pre-processed and analysed to explore whole brain activation during each condition and compared activation between conditions. During walking, obstacle navigation and postural instability task conditions, activation was noted in cerebellum, visual cortex, middle frontal gyrus and precuneus. Additionally, this study enabled refinement of scanning and experimental task procedures before piloting the task in people with dementia.

In chapter 6, the VR based balance task was piloted with older adults with MCI and dementia. MRI tolerability questionnaire scores show that overall scanning experience was well tolerated (4/5 for overall experience). Twenty-five participants provided written feedback on their experience of the task. Participants reported that the videos were clear to see, some participants reported finding the task easy, whilst others reported find the task quite difficult. One participant felt the videos helped make the scanning experience feel less claustrophobic. In this chapter task related activation during each task condition and differences in activation between the conditions was explored. The relationship between activation during walking, obstacle navigation, and

postural instability conditions in postural control related regions of interest and performance on static and dynamic balance tasks in older adults with MCI and dementia was investiagated. For each of the task conditions activation was noted in visual and motor regions, however no significant differences in activation were noted between conditions, even at a lenient, uncorrected alpha threshold. The differences in activation between the task conditions were explored for specific regions of interest thought to be involved in postural control, mainly SMA, PMC, ACC, PFC and PIVC, again there were no significant differences in activation in the regions between the task conditions. Finally multiple linear regression analyses were used to explore the relationship between activation in regions of interest for each task condition and performance on measures of static and dynamic balance. In the walking condition, activation in bilateral PMC was significantly associated with better dynamic balance but poorer static balance, whilst activation in the left SMA was significantly associated with poorer dynamic and static balance. During the obstacle avoidance condition, the left SMA and right ACC were significantly associated with better dynamic balance, the right premotor cortex was significantly associated with poorer static balance while the right ACC was significantly associated with better static balance. For the postural instability condition, left SMA activation was associated with poorer dynamic balance, the left SMA and right PMC were associated with poorer static balance whilst the right SMA was associated with better static balance.

In chapter 7 resting state fMRI and ICA were used to identify large scale resting state networks and explore the relationship between connectivity of these networks and balance performance in people with MCI and dementia. No

significant relationships between intra or inter network connectivity and timed up and go (a measure of functional mobility) or BBS (a balance performance scale) were identified, however the associations between limbic network, specifically the orbitofrontal cortex and TUG performance (β=32.68, p=0.06, 95% CI= -1.14, 66.50) and visual-SMN connectivity and TUG performance (β=-2.75, p=0.07, 95% CI= -5.76,0.26), fell just outside the prespecified alpha threshold (p<.05), indicating a potential signal in the data. More specifically the trends might indicate that increased orbitofrontal cortex connectivity may be associated with poorer TUG performance whilst increased visual-SMN connectivity may be associated better TUG performance.

8.5 What do the findings mean?

Exercise is a promising intervention for older adults with cognitive impairments and fMRI can detect changes in both task-related and spontaneous activity and connectivity. The findings from the systematic review show that the exercise exerts different effects on task-related and resting neural activity and connectivity. Specifically, task related activity and connectivity decreased post intervention in people with MCI indicating that exercise may improve neural efficiency, requiring less activation of key networks to maintain performance (316,318,319). Exercise increased resting activity in frontal regions (321,322), which suggests that exercise may increase the ability to recruit additional neural networks to meet task demands (69). Exercise also appeared to increase resting connectivity of hippocampus and posterior cingulate (317,320,322,324,325). Hippocampus atrophy is key feature of Alzheimer's disease and precedes cognitive impairments (124,248). The posterior cingulate is a key hub within the

default mode network (229), which is vulnerable to AD pathology (439). Increased connectivity of both these key regions suggest that exercise may improve plasticity of these regions and related networks at the early stages of cognitive impairment (440). My systematic review has also highlighted that this area of research has received limited attention to date, with studies included in the review using small samples with healthy older adults and older adults with mild cognitive impairment. The effects of exercise on brain activity and connectivity in dementia are still unknown.

The work presented in chapter 6 is the first to use a VR based balance paradigm to investigate brain activity associated with balance and walking in people with MCI and dementia. The application of a VR based balance task alongside fMRI to study the neural correlates of postural control in older adults with memory problems is feasible as scanning procedures were well tolerated, and participants were able to see and complete the task. In the walking and postural instability condition, activation of motor regions was associated with static and dynamic balance performance, suggesting that walking and responding to external perturbations requires greater involvement of cortical regions involved in cognitive processing and motor planning in the early stages of dementia. In the obstacle navigation condition, the anterior cingulate cortex, as well as motor regions were associated with static and dynamic balance performance. The anterior cingulate cortex is known to play a key role in executive functions such as set shifting and error detection (411). This region may play a key role in maintaining postural stability in contexts where planning is required such as the obstacle navigation condition of the task.

Previous research has shown notable and consistent changes in resting state functional connectivity of the default mode network (see section 3.2.4.1) due to the presence of dementia related pathology (232,284,290,291,441). Further studies have highlighted that altered DMN connectivity is linked to mobility, gait, and balance in older adults with MCI (419–421). The work presented in chapter 7 did not replicate these findings, however a potential association was noted between increased orbitofrontal cortex connectivity and poorer dynamic balance performance. Increased orbitofrontal cortex connectivity suggests that postural control during walking requires greater top-down processing in the early stages of dementia. The increased visual-sensorimotor network connectivity and potential association with improved balance performance suggests that there may also be compensatory mechanisms at play for some people with early stages of cognitive impairment, requiring consolidation of visual and sensorimotor input to maintain postural control abilities (69,346,371).

The notion of compensatory mechanisms has emerged from the observation that the level of brain damage observed in people with dementia did not match levels of deterioration of cognitive and functional abilities (332). This discrepancy between observed level of brain damage and relatively preserved cognitive and functional abilities gave rise to the cognitive reserve hypothesis which refers to the brain's ability to maintain performance in the presence of a certain level of brain damage (332). High levels of cognitive reserve have been linked to delayed onset of dementia symptoms. Previous studies found that older adults with fewer years of education presented with dementia symptoms earlier (332). Research has also found that cognitive reserve can be improved through various

lifestyle factors such as exercise, social involvement, leisure activities and education attainment (333). There are two neural mechanisms underpinning cognitive reserve; neural reserve and neural compensation. Neural reserve refers to the efficiency, capacity and flexibility of neural networks and neural compensation refers to the ability to compensate for brain damage by recruiting additional neural networks to complete a task or maintain performance (442).

Neuroimaging studies have explored the link between measures of cognitive reserve such as educational attainment and quantitative brain measure such as functional connectivity and white matter network integrity (332,442). Yoo et al. (443) found positive associations between education attainment and white matter network flow in healthy controls with the inverse in participants with AD, providing support for the role of cognitive reserve and its underlying mechanisms. A systematic review of cross sectional studies looking at functional imaging studies of cognitive reserve in healthy older adults, older adults with MCI or Alzheimer's disease found that increased activation in medial temporal regions, posterior and anterior cingulate cortex were associated neural reserve while activation in frontal regions and dorsal attention network were associated with neural compensation. Additionally, increased frontal activity in older adults with MCI or Alzheimer's disease was linked to high cognitive reserve (444).

The systematic review presented in this thesis has found that exercise may increase the capacity for compensatory mechanisms as well as increasing the brains threshold to cope with damage before it needs to employ these strategies to maintain performance. Also, the findings from the resting state fMRI study have highlighted a potential association between connectivity strength within

the orbitofrontal cortex and between motor and visual networks with balance performance. The underlying mechanisms of cognitive reserve, neural reserve and neural compensation mechanisms may also play a role in maintaining postural control abilities in the early stages of dementia. Further exploration of these mechanisms in exercise and postural control in dementia is warranted and may help to understand the neural mechanisms involved.

8.6 Strengths and limitations of studies presented

It is important to note the strengths and limitations of the studies presented in this thesis that should be considered when interpreting the findings. The systematic review inclusion criteria for study design were broad, this combined with heterogeneity in interventions, analysis methods and outcomes meant a meta-analysis was not feasible. Additionally, no study in the review included people with dementia. This means that the generalisability of findings is limited to people with MCI only.

The sample sizes in the studies presented in this thesis were relatively small. Additionally, the sample for the studies presented in chapter 6 and 7 consisted of participants that were less cognitively impaired and more physically able than their peers given their ability to undergo MRI. A major limitation of fMRI is that it is very sensitive to any type of movement, which can reduce data quality. Four task-related datasets and one resting state dataset were excluded due to excessive movement or poor data quality.

The pilot task fMRI studies presented in this thesis are the first studies to use a novel VR-based balance task to explore the neural correlates of walking, obstacle avoidance and postural instability in healthy young adults and older adults with

MCI or dementia. However, there are a few notable limitations of these studies. First, the postural instability condition, of the fMRI task included a sideways stumble which may have increased motion artifacts in the data. The present work did not explore the relationship between the task conditions and movement related artifacts in the functional imaging data. This is something that warrants further exploration to identify threshold for postural instability simulations before they introduce motion artifacts in the data. It is possible that including a forward stumble rather than a sideway stumble may have resulted in different effects in both healthy young adults and older adults with MCI and dementia. Future work should look to compare differences in motion artifacts in fMRI data for sideway and forward stumbles.

Second, due to small sample sizes and three trials per condition, whole brain, ROI and regression analyses are likely to be underpowered so findings are uncertain. When exploring differences in activation between the task conditions, in both healthy volunteers and PrAISED participants, I found no significant differences at a corrected threshold for multiple comparisons or at an uncorrected threshold. The lack of effect, in this case, does not mean the task was not able to measure what was intended, the small number of participants and small number of trials used will have reduced statistical power to detect a true effect.

Third, the lack of differences noted between conditions especially in older adults with MCI or dementia could be attributed to impairments of individual differences in imagery ability. From task feedback, some participants reported that they found it difficult to imagine themselves in the task. Previous work has shown that perceived imagery ability mediates the amplitude of neural activity

during a motor imagery-based task (117,445,446). A recent narrative review found imagery ability to be relatively preserved in ageing but hypothesise that imagery ability may be more affected by cognitive decline (447). However, I did not measure imagery ability in either task fMRI studies. Measuring imagery ability and including this as variable of interest in the analysis to explore how it affected between condition contrasts would have been useful to understand whether this influenced task-related activity.

In chapter 6, the sample were mildly cognitively impaired (mean MoCA score 20/30) and more physically able (mean Berg Balance score 47/52), thus the balance fMRI task may not have been challenging enough, and the response to the task did not change with increasing task complexity. It would be expected that older adults with MCI and dementia, who are more cognitively impaired and less physically able would respond differently to the task.

The templates used for ROI analysis in chapter 6 were based on cytoarchitecture maps of the brain at post-mortem of health individuals. It is well established during ageing the brain undergoes atrophy and this is accelerated in dementia. Using templates based on healthy adults in a region of interest analysis could mean study results do not represent the true effect or activation for people with dementia as the parts of the brain corresponding to template areas may be impacted by dementia related pathology. Future work should explore development of dementia sub type specific templates for ROI analysis. As well as this, future work should also explore whether an anatomical approach or a data driven approach to defining ROIs will be more appropriate and accurate in dementia functional MRI studies (448)

The regression analyses exploring the relationships between ROI task related activation in each task condition (walking, obstacle avoidance and postural instability), functional network connectivity and balance in chapters 6 and 7, were not corrected for multiple comparisons due to the exploratory nature of the analyses, thus increasing the risk of type 1 error. Additionally, the sample used in these analyses were from the same group of participants and the sample was relatively small. For regression analysis, a rule of thumb is to include 10 observations per variable of interest, thus the analyses are likely to be underpowered and there is risk of the R^2 risk of being overinflated (413).

8.7 Future directions

Findings from the systematic review highlighted knowledge gaps that need to be addressed by future work. The review found that studies exploring neural effects of exercise using fMRI only included participants with MCI. Studies including people with dementia are needed to explore how exercise can benefit brain function once dementia pathology is well established in the brain and notable clinical manifestation of the underlying brain diseases is present. Further exploration of the effects of exercise type (e.g. aerobic exercise, resistance training, balance training, and mind body type interventions like yoga) on brain function in dementia is needed to develop our understanding of how different types of exercise alter brain function and how this translates clinically in terms of functional abilities, cognition, and mood. This will also be useful for researchers and clinicians in developing and tailoring interventions to the individual based on their concerns, goals, and symptom profile. Understanding how long the effects of exercise last can help researchers to further tailor

interventions and activity programmes for the best results, for the patient, whilst being more cost effective for research and health services.

The work presented in this thesis has shown that using VR-based balance tasks in older adults with MCI and dementia, to explore neural mechanisms of balance is feasible and well tolerated by patients. This method of task delivery is promising and may be able to bridge the practical issues around MRI scanning during whole-body movements. Additionally, for people with dementia, the instructions for this task were relatively simple to follow, overcoming the issues around having to retain and understand often lengthy and complex task instructions in task-related fMRI studies. Future work needs to identify the minimum number of task trials needed to detect a reliable signal in response to the task and retain a degree of experimental control without becoming burdensome for participants with cognitive impairments. This could be one way of improving statistical power to detect a change in activation without needing to recruit large samples/more participants. Involvement of patients with lived experience and members of the public to co-produce balance fMRI tasks could aid researchers to improve the accessibility of experimental tasks for people with MCI and dementia. Additionally, the creation of a more realistic task paradigm in VR environments would enable researchers to measure brain activity closely relating to real-life contexts in which balance is often challenged for older people.

The task fMRI studies presented in this thesis did not measure the effects of imagery ability activation in response to the walking, obstacle avoidance and postural instability task conditions. Also, task experience feedback in the pilot

study with older adults with MCI and dementia highlighted that some participants found the task more challenging than others, which may have impacted how well they were able to imagine themselves in the task. Future work needs to explore the effects of imagery ability in this population. For instance, studies could ask participants to complete questionnaires such as the vividness of movement imagery questionnaire (449) after completing fMRI tasks and scanning procedures and explore whether imagery ability scores mediated task related activation (117). This would enable further development and refinement of VR balance fMRI tasks and improve accessibility. Conversely, some participants reported finding the task to be easy, given the sample of participants included in the study were relatively able individuals, it is conceivable that for some of the group, the task was not challenging enough. Development of the VR task to include a mechanism through which the walking speed is tailored to individual ability may evoke a neural response that is more representative of how the brain responds to challenges to balance in daily life.

Future research needs to address the issue around small and homogenous samples. Participants recruited from the PrAISED RCT to take part in the studies presented in this thesis were predominately older white males with an average of 12 of years of education, indicating higher socioeconomic status. Thus, findings presented in this thesis may not be representative of older adults with memory problems from underserved communities. To improve recruitment and diversity of participants, future studies need to investigate the reasons why older adults with cognitive impairments, specifically those from lower socioeconomic

and ethnic minority communities, tend to decline to participate in neuroimaging studies.

The task fMRI videos, and the use of a filler video (David Attenborough's 'Planet Earth') during MRI scans with participants from the PrAISED cohort may have improved the scanning experience and reduced feelings of claustrophobia. The MRI scanner company Phillips is currently working with Disney to produce child-friendly MRI videos as a way of improving the scanning experiences for paediatric populations (450). To improve recruitment, retention and improve scanning experience, future work should look to explore how best practices in paediatric neuroimaging research can be adapted for older adults with dementia.

Studies presented in this thesis were pilot work, using more exploratory analysis procedures and cross-sectional studies designs. Future work should look to build on this, using case control designs to compare differences in activation in response to the VR balance task between healthy older adults, older adults with MCI and older adults with differing severity of dementia, to map how balance related brain activity differs between the groups. Additionally future work should also look to employ more longitudinal designs to map progression of balance dysfunction and how the underlying neural processes change as dementia progresses.

The COVID-19 pandemic lockdowns and restrictions disproportionately affected older adults and older adults with cognitive impairments. Additionally, the pandemic and related restrictions increased social isolation, exacerbated cognitive impairments, reduced physical activity contributing to deconditioning (451), leading to increased postural instability and increased falls risk in this

population (452). During and post pandemic, exercise-based interventions are more important than ever to improve and maintain, physical, mental, and emotional wellbeing for people living with dementia. This further highlights the need for more high-quality research studying the neural mechanism involved in exercise and postural stability in dementia.

Participants that took part in the studies presented in chapters 6 and 7 were recruited from the PrAISED RCT. This RCT provided the opportunity to use fMRI to test the feasibility of the VR based postural control task and explore functional connectivity relating to exercise and postural control in older adults with dementia. The PRAISED RCT tested the efficacy of a multifactorial intervention aimed at promoting activity, independence and stability in MCI and early dementia and included balance challenging exercises and 150 minutes of activity per week (37). The PrAISED trial found that the intervention did not improve activities of daily living, quality of life, cognition, falls or other health status outcomes in people with MCI and dementia (453). Although the PrAISED RCT found no differences in outcomes the intervention group, the process evaluation work showed that the intervention was well received by participants, it filled a much needed gap in support, and participants felt the intervention helped them in their day to day life (453,454).

Large RCTs like PrAISED testing efficacy of exercise interventions in dementia have yielded mixed results (26,453). These RCTs have often focused on focused on cognition, mobility and functional abilities-related outcomes. These outcomes are often subject to ceiling or flooring effects and are not sensitive enough to detect to slow progression of symptoms in the early stages of dementia and may

not be sensitive to subtle changes in symptoms in response to activity based interventions (194,195). Additionally some of the outcome measures used to assess activities of daily living and quality of life are often self-reported by the individual or their carer, which relies on the individuals ability to accurately recall events, often challenging for someone with memory impairments (195). It is possible that current outcome measures used in dementia trials are not relevant to participants. The GREAT study tested a cognitive rehabilitation intervention for older adults with dementia and used a goal-based outcome that was meaningful to the individual and reported improved outcomes for participants in response to the intervention (455).

A recent report from Alzheimer's Association research roundtable meetings has highlighted that there is currently no consensus across stakeholders on what a clinically meaningful outcome is for Alzheimer's disease trials (195). Given current outcome measures used in dementia trials may lack sensitivity in the early stages of dementia, researchers have acknowledged the potential for additional biomarker based outcomes such as neuroimaging to compliment these measures (194). Future RCTs testing the efficacy of exercise and activity-based interventions in dementia are needed to uncover how exercise is of benefit and should look to explore what a meaningful outcome would look like for people with dementia and include that as a trial outcome. The inclusion of additional neuroimaging outcomes such as fMRI would complement widely used cognition, mobility and functional abilities outcomes and enable researchers to measure more subtle changes in brain function and connectivity in response to complex interventions before they are clinically detectable whilst improving the

knowledge base of the underlying neural mechanisms involved in exercise and postural control in dementia.

8.8 Conclusions

To date there has been little neuroimaging research exploring neural correlates of balance and exercise in dementia. The systematic review presented in this thesis had identified exercise related changes in task based and spontaneous activity and connectivity in people with MCI. Exercise may improve neural efficiency in response to tasks and increase capacity for compensatory activation to maintain performance. Due to limited number of studies, small samples size and no studies available including people with dementia, generalisability of findings is limited.

VR based balance tasks are novel solution to address the limitations of movement during fMRI. The work presented in this thesis has shown that using VR based balance tasks in older adults with memory problems is possible and well tolerated. The association between motor regions, static and dynamic balance during walking and postural instability task conditions, suggests that postural control in these contexts may become less automatic and an increasingly conscious process during the early stages of dementia. The relationship between motor regions, ACC and balance performance during the obstacle navigation condition suggests that in motor anticipatory postural control tasks, the brain recruits regions involved in higher order cognitive processes during the early stages of cognitive impairment.

Increased functional connectivity within the orbitofrontal cortex may underpin changes in postural stability when walking, whilst increased functional

connectivity of visual and sensorimotor networks may be a compensatory multisensory approach to maintain relatively normal balance abilities. This thesis demonstrates that VR based balance fMRI tasks and resting state fMRI are useful techniques to help advance the knowledge gap around neural correlates of balance and exercise in dementia.

9 References

1. Kaur R. the sun and her flowers. Simon & Schuster Ltd;

2. World Health Organization. World report on ageing and health [Internet]. Geneva: World Health Organization; 2015. Available from: https://apps.who.int/iris/handle/10665/186463

3. Ageing and health [Internet]. [cited 2022 Aug 5]. Available from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

4. Living longer - how our population is changing and why it matters. :53.

5. Nations U. Ageing [Internet]. United Nations. United Nations; [cited 2022 Aug 5]. Available from: https://www.un.org/en/global-issues/ageing

6. Living too long. EMBO Rep. 2015 Feb;16(2):137–41.

7. Khan HTA. Population ageing in a globalized world: Risks and dilemmas? J Eval Clin Pract. 2019;25(5):754–60.

8. 1m more living with multiple conditions by 2020 | Latest press | Age UK [Internet]. [cited 2021 Sep 16]. Available from: https://www.ageuk.org.uk/latest-press/archive/one-million-more-older-people-will-be-living-with-multiple-long-term-conditions/

9. Pyo IS, Yun S, Yoon YE, Choi JW, Lee SJ. Mechanisms of Aging and the Preventive Effects of Resveratrol on Age-Related Diseases. Molecules. 2020 Jan;25(20):4649.

10. Mc Auley MT, Guimera AM, Hodgson D, Mcdonald N, Mooney KM, Morgan AE, et al. Modelling the molecular mechanisms of aging. Biosci Rep. 2017 Feb 23;37(1):BSR20160177.

11. Aunan JR, Watson MM, Hagland HR, Søreide K. Molecular and biological hallmarks of ageing. Br J Surg. 2016 Jan 1;103(2):e29–46.

12. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimers Dement. 2015 May;11(6):718–26.

13. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. The Lancet. 2006 Apr;367(9518):1262–70.

14. Petersen R. Mild Cognitive Impairment. N Engl J Med. 2011;364(23):2227–34.

15. What is Mild cognitive impairment? [Internet]. Alzheimer's Research UK. [cited 2022 Aug 11]. Available from: https://www.alzheimersresearchuk.org/dementia-information/types-of-dementia/mild-cognitive-impairment/

16. Dunne RA, Aarsland D, O'Brien JT, Ballard C, Banerjee S, Fox NC, et al. Mild Cognitive Impairment: the Manchester consensus. Age Ageing. 2021 Jan 1;50(1):72–80.

17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®) [Internet]. Washington, UNITED STATES: American Psychiatric Publishing; 2013 [cited 2022 Aug 9]. Available from: http://ebookcentral.proquest.com/lib/nottingham/detail.action?docID=1811753

18. Wahl D, Solon-Biet SM, Cogger VC, Fontana L, Simpson SJ, Le Couteur DG, et al. Aging, lifestyle and dementia. Neurobiol Dis. 2019 Oct 1;130:104481.

19. The top 10 causes of death [Internet]. [cited 2022 Aug 9]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

20. Numbers of people in the UK [Internet]. Dementia Statistics Hub. [cited 2022 Aug 11]. Available from: https://www.dementiastatistics.org/statistics/numbers-of-people-in-the-uk-2/

21. Prince M, Knapp M, Guerchet M, McCrone P, Prina M, Comas-Herrera A, et al. Dementia UK: Second Edition - Overview. Alzheimer's Society; 2014.

22. What are the costs of dementia care in the UK? | Alzheimer's Society [Internet]. [cited 2022 Aug 11]. Available from: https://www.alzheimers.org.uk/about-us/policy-and-influencing/dementia-scale-impact-numbers

23. Delbaere K, Kochan NA, Close JC, Menant JC, Sturnieks DL, Brodaty H, et al. Mild cognitive impairment as a predictor of falls in community-dwelling older people. Am J Geriatr Psychiatry. 2012;20(10):845–53.

24. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. Age Ageing. 2012 Mar;41(3):299–308.

25. Kallin K, Gustafson Y, Sandman PO, Karlsson S. Factors associated with falls among older, cognitively impaired people in geriatric care settings: A population-based study. Am J Geriatr Psychiatry. 2005;13(6):501–9.

26. Burton E, Cavalheri V, Adams R, Browne CO, Bovery-Spencer P, Fenton AM, et al. Effectiveness of exercise programs to reduce falls in older people with dementia living in the community: A systematic review and meta-analysis. Vol. 10, Clinical Interventions in Aging. Dove Medical Press Ltd.; 2015. p. 421–34.

27. Introduction | Falls in older people: assessing risk and prevention | Guidance | NICE [Internet]. NICE; [cited 2022 Aug 12]. Available from: https://www.nice.org.uk/guidance/cg161/chapter/introduction

28. Lamb SE, Sheehan B, Atherton N, Nichols V, Collins H, Mistry D, et al. Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. BMJ. 2018;361:k1675.

29. Pitkala KH, Poysti MM, Laakkonen ML, Tilvis RS, Savikko N, Kautiainen H, et al. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. JAMA Intern Med. 2013;173(10):894–901.

30. Groot C, Hooghiemstra AM, Raijmakers PGHM, van Berckel BNM, Scheltens P, Scherder EJA, et al. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. Ageing Res Rev. 2016 May;25:13–23.

31. Cancela JM, Ayán C, Varela S, Seijo M. Effects of a long-term aerobic exercise intervention on institutionalized patients with dementia. J Sci Med Sport. 2016 Apr 1;19(4):293–8.

32. Holthoff VA, Marschner K, Scharf M, Steding J, Meyer S, Koch R, et al. Effects of Physical Activity Training in Patients with Alzheimer's Dementia: Results of a Pilot RCT Study. PLOS ONE. 2015 May;10(4):e0121478.

33. De Wit L, O'Shea D, Chandler M, Bhaskar T, Tanner J, Vemuri P, et al. Physical exercise and cognitive engagement outcomes for mild neurocognitive disorder: a group-randomized pilot trial. Trials. 2018 Apr;19(1):573.

34. Halloway S, Wilbur JE, Schoeny ME, Arfanakis K. Effects of Endurance-Focused Physical Activity Interventions on Brain Health: A Systematic Review. Vol. 19, Biological Research for Nursing. SAGE Publications Inc.; 2017. p. 53–64.

35. Jahn K, Deutschländer A, Stephan T, Strupp M, Wiesmann M, Brandt T. Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging. NeuroImage. 2004 Aug;22(4):1722–31.

36. la Fougère C, Zwergal A, Rominger A, Förster S, Fesl G, Dieterich M, et al. Real versus imagined locomotion: A [18F]-FDG PET-fMRI comparison. NeuroImage. 2010 May;50(4):1589–98.

37. Booth V, Harwood RH, Hood-Moore V, Bramley T, Hancox JE, Robertson K, et al. Promoting activity, independence and stability in early dementia and mild cognitive impairment (PrAISED): development of an intervention for people with mild cognitive impairment and dementia. Clin Rehabil. 2018;32(7):855–64.

38. Winter D. Human balance and posture control during standing and walking. Gait Posture. 1995 Dec 1;3(4):193–214.

39. Le Huec JC, Saddiki R, Franke J, Rigal J, Aunoble S. Equilibrium of the human body and the gravity line: the basics. Eur Spine J. 2011 Aug 2;20(5):558.

40. Williams HarrietG, Ho L. Balance and Postural Control across the Lifespan. In: Developmental Motor Disorders: A Neuropsychological Perspective [Internet]. The Guildford Press; 2004. Available from: https://books.google.co.uk/books?hl=en&lr=&id=MiLbuT6KV9wC&oi=fnd&pg=PA211&dq=Williams&ots=fAjfDruL6e&sig=fK8LNQQlG9XLR4I1SpXhAwsgfBY&redir_esc=y#v=onepage&q=Williams&f=false

41. Pollock AS, Durward BR, Rowe PJ, Paul JP. What is balance? Clin Rehabil. 2000 Aug 1;14(4):402–6.

42. Cech DJ, Martin S “Tink”. Chapter 12 - Posture and Balance. In: Cech DJ, Martin S “Tink”, editors. Functional Movement Development Across the Life Span (Third Edition) [Internet]. Saint Louis: W.B. Saunders; 2012 [cited 2022 Aug 11]. p. 263–87. Available from: https://www.sciencedirect.com/science/article/pii/B9781416049784000120

43. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing. 2006 Sep 1;35(suppl_2):ii7–11.

44. Maki BE, McIlroy WE. The role of limb movements in maintaining upright stance: the ‘change-in-support’ strategy. Phys Ther. 1997 May;77(5):488–507.

45. Iqbal K. Mechanisms and models of postural stability and control. In: 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2011. p. 7837–40.

46. Kell C. Posture and balance. In: Human Movement: An Introductory Text [Internet]. Elsevier Health Sciences; 2010. Available from: https://ebookcentral.proquest.com/lib/nottingham/reader.action?docID=1721697

47. Chiba R, Takakusaki K, Ota J, Yozu A, Haga N. Human upright posture control models based on multisensory inputs; in fast and slow dynamics. Neurosci Res. 2016 Mar 1;104:96–104.

48. Takakusaki K. Functional Neuroanatomy for Posture and Gait Control. J Mov Disord. 2017 Jan;10(1):1–17.

49. Dietz V. Human neuronal control of automatic functional movements: interaction between central programs and afferent input. Physiol Rev. 1992 Jan;72(1):33–69.

50. Satterthwaite WR, Talbott RE, Brookhart JM. Changes in canine postural control after injury to anterior vermal cerebellum. Brain Res. 1979 Mar 23;164(1):269–77.

51. Deliagina TG, Orlovsky GN. Comparative neurobiology of postural control. Curr Opin Neurobiol. 2002;12(6).

52. Deliagina TG, Orlovsky GN, Zelenin PV, Beloozerova IN. Neural Bases of Postural Control. Physiology. 2006 Jun 1;21(3):216–25.

53. Deliagina TG, Zelenin PV, Orlovsky GN. Physiological and circuit mechanisms of postural control. Curr Opin Neurobiol. 2012;22(4).

54. Sosnoff JJ, Broglio SP, Shin S, Ferrara MS. Previous Mild Traumatic Brain Injury and Postural-Control Dynamics. J Athl Train. 2011 Jan 1;46(1):85–91.

55. Degani AM, Santos MM, Leonard CT, Rau TF, Patel SA, Mohapatra S, et al. The effects of mild traumatic brain injury on postural control. Brain Inj. 2017 Jan 2;31(1):49–56.

56. Buckley TA, Oldham JR, Caccese JB. Postural control deficits identify lingering post-concussion neurological deficits. J Sport Health Sci. 2016 Mar 1;5(1):61–9.

57. Murray NG, Szekely B, Moran R, Ryan G, Powell D, Munkasy BA, et al. Concussion history associated with increased postural control deficits after subsequent injury. Physiol Meas. 2019 Feb;40(2):024001.

58. Lin YH, Tang PF, Wang YH, Eng JJ, Lin KC, Lu L, et al. Reactive Postural Control Deficits in Patients with Posterior Parietal Cortex Lesions After Stroke and the Influence of Auditory Cueing. Am J Phys Med Rehabil. 2014 Oct;93(10):849–59.

59. Postural Alignment Is Altered in People With Chronic Stroke... : Journal of Neurologic Physical Therapy [Internet]. [cited 2022 Aug 10]. Available from: https://journals.lww.com/jnpt/fulltext/2014/10000/Postural_Alignment_Is_Altered_in_People_With.6.aspx

60. Nieuwboer A, Leuven KU, Boisgontier MP, Beets IAM, Duysens J, Krampe RT, et al. Age-related differences in attentional cost associated with postural dual tasks: Increased recruitment of generic cognitive resources in older adults. Neurosci Biobehav Rev. 2013;37:1824–37.

61. Yogev-Seligmann G, Giladi N, Gruendlinger L, Hausdorff JM. The contribution of postural control and bilateral coordination to the impact of dual tasking on gait. Exp Brain Res. 2013 Apr 1;226(1):81–93.

62. Smith E, Cusack T, Cunningham C, Blake C. The Influence of a Cognitive Dual Task on the Gait Parameters of Healthy Older Adults: A Systematic Review and Meta-Analysis. J Aging Phys Act. 2017 Oct 1;25(4):671–86.

63. Lanzarin M, Parizzoto P, Libardoni T de C, Sinhorim L, Tavares GMS, Santos GM. The influence of dual-tasking on postural control in young adults. Fisioter E Pesqui. 2015 Mar;22:61–8.

64. Ruffieux J, Keller M, Lauber B, Taube W. Changes in Standing and Walking Performance Under Dual-Task Conditions Across the Lifespan. Sports Med. 2015 Dec 1;45(12):1739–58.

65. Petrigna L, Gentile A, Mani D, Pajaujiene S, Zanotto T, Thomas E, et al. Dual-Task Conditions on Static Postural Control in Older Adults: A Systematic Review and Meta-Analysis. J Aging Phys Act. 2020 Aug 12;29(1):162–77.

66. Bolton DAE. The role of the cerebral cortex in postural responses to externally induced perturbations. Neurosci Biobehav Rev. 2015 Oct;57:142–55.

67. Park DC, Reuter-Lorenz P. The adaptive brain: Aging and neurocognitive scaffolding [Internet]. Vol. 60, Annual Review of Psychology. NIH Public Access; 2009. p. 173–96. Available from: /pmc/articles/PMC3359129/

/pmc/articles/PMC3359129/?report=abstract
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3359129/

68. Deture MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease [Internet]. Vol. 14, Molecular Neurodegeneration. BioMed Central Ltd.; 2019. p. 1–18. Available from: https://doi.org/10.1186/s13024-019-0333-5

69. Kahya M, Moon S, Ranchet M, Vukas RR, Lyons KE, Pahwa R, et al. Brain activity during dual task gait and balance in aging and age-related neurodegenerative conditions: A systematic review. Exp Gerontol. 2019 Dec 1;128:110756.

70. Slobounov S, Hallett M, Stanhope S, Shibasaki H. Role of cerebral cortex in human postural control: an EEG study. Clin Neurophysiol. 2005 Feb 1;116(2):315–23.

71. Mierau A, Pester B, Hülsdünker T, Schiecke K, Strüder HK, Witte H. Cortical Correlates of Human Balance Control. Brain Topogr. 2017 Jul 1;30(4):434–46.

72. Solis-Escalante T, van der Cruijsen J, de Kam D, van Kordelaar J, Weerdesteyn V, Schouten AC. Cortical dynamics during preparation and execution of reactive balance responses with distinct postural demands. NeuroImage. 2019 Mar 1;188:557–71.

73. Hülsdünker T, Mierau A, Neeb C, Kleinöder H, Strüder HK. Cortical processes associated with continuous balance control as revealed by EEG spectral power. Neurosci Lett. 2015 Apr 10;592:1–5.

74. Goel R, Nakagome S, Rao N, Paloski WH, Contreras-Vidal JL, Parikh PJ. Fronto-Parietal Brain Areas Contribute to the Online Control of Posture during a Continuous Balance Task. Neuroscience. 2019 Aug 10;413:135–53.

75. Chen M, Pillemer S, England S, Izzetoglu M, Mahoney JR, Holtzer R. Neural correlates of obstacle negotiation in older adults: An fNIRS study. Gait Posture. 2017 Oct 1;58:130–5.

76. Eaves DL, Riach M, Holmes PS, Wright DJ. Motor imagery during action observation: A brief review of evidence, theory and future research opportunities. Front Neurosci. 2016 Nov;10(NOV):514.

77. Macintyre TE, Madan CR, Moran AP, Collet C, Guillot A. Motor imagery, performance and motor rehabilitation. 2018; Available from: https://doi.org/10.1016/bs.pbr.2018.09.010

78. Moran A, O'Shea H. Motor Imagery Practice and Cognitive Processes. Front Psychol. 2020 Mar;0:394.

79. Porro CA, Francescato MP, Cettolo V, Diamond ME, Baraldi P, Zuiani C, et al. Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study. J Neurosci. 1996 Dec 1;16(23):7688–98.

80. Hétu S, Grégoire M, Saimpont A, Coll MP, Eugène F, Michon PE, et al. The neural network of motor imagery: An ALE meta-analysis. Neurosci Biobehav Rev. 2013 Jun 1;37(5):930–49.

81. Hardwick RM, Caspers S, Eickhoff SB, Swinnen SP. Neural correlates of action: Comparing meta-analyses of imagery, observation, and execution. Neurosci Biobehav Rev. 2018 Nov;94:31–44.

82. Mulder T. Motor imagery and action observation: Cognitive tools for rehabilitation. In: Journal of Neural Transmission. 2007. p. 1265–78.

83. Rizzolatti G, Fogassi L, Gallese V. Neurophysiological mechanisms underlying the understanding and imitation of action. Nat Rev Neurosci. 2001 Sep;2(9):661–70.

84. Caspers S, Zilles K, Laird AR, Eickhoff SB. ALE meta-analysis of action observation and imitation in the human brain. NeuroImage. 2010 Apr 15;50(3):1148–67.

85. Ge S, Liu H, Lin P, Gao J, Xiao C, Li Z. Neural Basis of Action Observation and Understanding From First- and Third-Person Perspectives: An fMRI Study. Front Behav Neurosci [Internet]. 2018 [cited 2022 Aug 5];12. Available from: https://www.frontiersin.org/articles/10.3389/fnbeh.2018.00283

86. Talha Iftikhar M, Mallett CJ, Javed MA. Imagery Improves Reaction Time in Elite Sprinters. 2018;

87. Battaglia C, D'Artibale E, Fiorilli G, Piazza M, Tsopani D, Giombini A, et al. Use of video observation and motor imagery on jumping performance in national rhythmic gymnastics athletes. Hum Mov Sci. 2014 Dec;38:225–34.

88. Kumar VK, Chakrapani M, Kedambadi R. Motor Imagery Training on Muscle Strength and Gait Performance in Ambulant Stroke Subjects-A Randomized Clinical Trial. J Clin Diagn Res JCDR. 2016;10(3):YC01.

89. Sharma N, Pomeroy VM, Baron JC. Motor imagery: a backdoor to the motor system after stroke? Stroke. 2006 Jul;37(7):1941–52.

90. Guerra ZF, Lucchetti G, Fernandes Guerra Z, Lucchetti ALG. Motor Imagery Training After Stroke: A Systematic Review and Meta-analysis of Randomized Controlled Trials Functioning of informal caregivers: limitations and barriers. View project CIF NA GRADUAÇÃO EM FISIOTERAPIA View project Motor Imagery Training Afte. Artic J Neurol Phys Ther [Internet]. 2017; Available from: http://links.lww.com/JNPT/A188

91. Tong Y, Pendy JT, Li WA, Du H, Zhang T, Geng X, et al. Motor Imagery-Based Rehabilitation: Potential Neural Correlates and Clinical Application for Functional Recovery of Motor Deficits after Stroke. Aging Dis. 2017;8(3):364.

92. Borges LR, Fernandes AB, Melo LP, Guerra RO, Campos TF. Action observation for upper limb rehabilitation after stroke. Cochrane Database Syst Rev [Internet]. 2018 Oct;2018(10). Available from:

https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011887.pub2/full
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011887.pub2/abstract

93. Hamacher D, Herold F, Wiegel P, Hamacher D, Schega L. Brain activity during walking: A systematic review. Neurosci Biobehav Rev. 2015 Oct;57:310–27.

94. Jahn K, Zwergal A. Imaging supraspinal locomotor control in balance disorders. Restor Neurol Neurosci. 2010 Jan 1;28(1):105–14.

95. Ferraye MU, DebÛ B, Heil L, Carpenter M, Bloem BR, Toni I. Using motor imagery to study the neural substrates of dynamic balance. PLoS ONE. 2014 Mar;9(3).

96. Fung J, Guimarães RP, Paquette C, Bhatt T, Patel PJ, Deldonno SR, et al. Examining Neural Plasticity for Slip-Perturbation Training: An fMRI Study. Front Neurol Wwwfrontiersinorg. 2019;1:1181.

97. Labriffe M, Annweiler C, Amirova LE, Gauquelin-Koch G, Ter Minassian A, Leiber LM, et al. Brain Activity during Mental Imagery of Gait Versus Gait-Like Plantar Stimulation: A Novel Combined Functional MRI Paradigm to Better Understand Cerebral Gait Control. Front Hum Neurosci [Internet]. 2017 [cited 2022 Aug 11];11. Available from: https://www.frontiersin.org/articles/10.3389/fnhum.2017.00106

98. Bürki CN, Bridenbaugh SA, Reinhardt J, Stippich C, Kressig RW, Blatow M. Imaging gait analysis: An fMRI dual task study. Brain Behav. 2017;7(8):e00724.

99. Wei P, Zou T, Lv Z, Fan Y. Human locomotion-control brain networks detected with independent component analysis Nanomaterials Biocompatibility View project Cognitive screening View project Human locomotion-control brain networks detected with independent component analysis. Artic J Integr Neurosci. 2021;20(3):695–701.

100. Dyer E, Swartzlander BJ, Gugliucci MR. Using virtual reality in medical education to teach empathy. J Med Libr Assoc JMLA. 2018 Oct;106(4):498–500.

101. Izard SG, Juanes JA, García Peñalvo FJ, Estella JMG, Ledesma MJS, Ruisoto P. Virtual Reality as an Educational and Training Tool for Medicine. J Med Syst. 2018 Feb 1;42(3):50.

102. Clark R, Baum N. Applications of Virtual Reality in Modern Medicine. J Med Pract Manag MPM. 2019 Feb;34(4):226–30.

103. Desselle MR, Brown RA, James AR, Midwinter MJ, Powell SK, Woodruff MA. Augmented and Virtual Reality in Surgery. Comput Sci Eng. 2020 May;22(3):18–26.

104. Ang SP, Montuori M, Trimba Y, Maldari N, Patel D, Chen QC. Recent Applications of Virtual Reality for the Management of Pain in Burn and Pediatric Patients. Curr Pain Headache Rep. 2021 Jan 14;25(1):4.

105. Riva G, Baños RM, Botella C, Mantovani F, Gaggioli A. Transforming Experience: The Potential of Augmented Reality and Virtual Reality for Enhancing Personal and Clinical Change. Front Psychiatry [Internet]. 2016 [cited 2022 Aug 5];7. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2016.00164

106. Mazurek J, Kiper P, Cieślik B, Rutkowski S, Mehlich K, Turolla A, et al. Virtual reality in medicine: a brief overview and future research directions. Hum Mov. 2019;20(3):16–22.

107. Mekbib DB, Han J, Zhang L, Fang S, Jiang H, Zhu J, et al. Virtual reality therapy for upper limb rehabilitation in patients with stroke: a meta-analysis of randomized clinical trials. Brain Inj. 2020 Mar 20;34(4):456–65.

108. Maggio MG, Latella D, Maresca G, Sciarrone F, Manuli A, Naro A, et al. Virtual Reality and Cognitive Rehabilitation in People With Stroke: An Overview. J Neurosci Nurs. 2019 Apr;51(2):101–5.

109. Lei C, Sunzi K, Dai F, Liu X, Wang Y, Zhang B, et al. Effects of virtual reality rehabilitation training on gait and balance in patients with Parkinson's disease: A systematic review. PLOS ONE. 2019 Nov 7;14(11):e0224819.

110. Kim O, Pang Y, Kim JH. The effectiveness of virtual reality for people with mild cognitive impairment or dementia: a meta-analysis. BMC Psychiatry. 2019 Jul 12;19(1):219.

111. Thapa N, Park HJ, Yang JG, Son H, Jang M, Lee J, et al. The Effect of a Virtual Reality-Based Intervention Program on Cognition in Older Adults with Mild Cognitive Impairment: A Randomized Control Trial. J Clin Med. 2020 May;9(5):1283.

112. Bohil CJ, Alicea B, Biocca FA. Virtual reality in neuroscience research and therapy. Nat Rev Neurosci. 2011 Dec;12(12):752–62.

113. Parsons TD, Gaggioli A, Riva G. Virtual Reality for Research in Social Neuroscience. Brain Sci. 2017 Apr;7(4):42.

114. Parsons TD. Virtual Reality for Enhanced Ecological Validity and Experimental Control in the Clinical, Affective and Social Neurosciences. Front Hum Neurosci [Internet]. 2015 [cited 2022 Aug 10];9. Available from: https://www.frontiersin.org/articles/10.3389/fnhum.2015.00660

115. Reggente N, Essoe JKY, Aghajan ZM, Tavakoli AV, McGuire JF, Suthana NA, et al. Enhancing the ecological validity of fMRI memory research using virtual reality. Front Neurosci. 2018 Jun;12(JUN):408.

116. Adamovich SV, August K, Merians A, Tunik E. A virtual reality-based system integrated with fmri to study neural mechanisms of action observation-

execution: A proof of concept study. Restor Neurol Neurosci. 2009 Jan 1;27(3):209–23.

117. van der Meulen M, Allali G, Rieger SW, Assal F, Vuilleumier P. The influence of individual motor imagery ability on cerebral recruitment during gait imagery. Hum Brain Mapp. 2014 Feb;35(2):455–70.

118. Yang HD, Kim DH, Lee SB, Young LD. History of Alzheimer's Disease. Dement Neurocognitive Disord. 2016 Dec;15(4):115–21.

119. Assal F. History of Dementia. Front Neurol Neurosci. 2019;44:118–26.

120. Giebel CM, Sutcliffe C, Stolt M, Karlsson S, Renom-Guiteras A, Soto M, et al. Deterioration of basic activities of daily living and their impact on quality of life across different cognitive stages of dementia: a European study. Int Psychogeriatr. 2014;26(8):1283–93.

121. Statistical commentary: dementia profile, March 2021 update [Internet]. GOV.UK. [cited 2022 Nov 9]. Available from: https://www.gov.uk/government/statistics/dementia-profile-updates/statistical-commentary-dementia-profile-march-2021-update

122. Cooper C, Sommerlad A, Lyketsos CG, Livingston G. Modifiable Predictors of Dementia in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. Am J Psychiatry. 2015 Apr;172(4):323–34.

123. Bothongo PLK, Jitlal M, Parry E, Waters S, Foote IF, Watson CJ, et al. Dementia risk in a diverse population: A single-region nested case-control study in the East End of London. Lancet Reg Health - Eur. 2022 Apr 1;15:100321.

124. Tondelli M, Wilcock GK, Nichelli P, de Jager CA, Jenkinson M, Zamboni G. Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. Neurobiol Aging. 2012;33(4):825.e25-825.e36.

125. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild Cognitive Impairment: Clinical Characterization and Outcome. Arch Neurol. 1999 Mar 1;56(3):303–8.

126. Petersen RC. Mild Cognitive Impairment. Contin Lifelong Learn Neurol. 2016 Apr;22(2 Dementia):404–18.

127. Ganguli M, Jia Y, Hughes TF, Snitz BE, Chang CCH, Berman SB, et al. Mild Cognitive Impairment that Does Not Progress to Dementia: A Population-Based Study. J Am Geriatr Soc. 2019;67(2):232–8.

128. Maestú F, Yubero R, Moratti S, Campo P, Gil-Gregorio P, Paul N, et al. Brain Activity Patterns in Stable and Progressive Mild Cognitive Impairment During Working Memory as Evidenced by Magnetoencephalography. J Clin Neurophysiol. 2011 Apr;28(2):202.

129. Li Y, Wang X, Li Y, Sun Y, Sheng C, Li H, et al. Abnormal Resting-State Functional Connectivity Strength in Mild Cognitive Impairment and Its Conversion to Alzheimer's Disease. Neural Plast. 2015 Dec 30;2016:e4680972.

130. Soman SM, Raghavan S, Rajesh PG, Mohanan N, Thomas B, Kesavadas C, et al. Does resting state functional connectivity differ between mild cognitive impairment and early Alzheimer's dementia? J Neurol Sci. 2020 Nov;418:117093.

131. Perl DP. Neuropathology of Alzheimer's disease. Mt Sinai J Med N Y. 2010 Jan;77(1):32–42.

132. Braak H, Braak E. Staging of alzheimer's disease-related neurofibrillary changes. Neurobiol Aging. 1995 May 1;16(3):271–8.

133. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Tredici KD. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol (Berl). 2006 Oct;112(4):389.

134. van Oostveen WM, de Lange ECM. Imaging Techniques in Alzheimer's Disease: A Review of Applications in Early Diagnosis and Longitudinal Monitoring. Int J Mol Sci. 2021 Feb;22(4):2110.

135. Jellinger KA, Attems J. Neuropathological approaches to cerebral aging and neuroplasticity. Dialogues Clin Neurosci. 2013 Mar;15(1):29.

136. Bir SC, Khan MW, Javalkar V, Toledo EG, Kelley RE. Emerging Concepts in Vascular Dementia: A Review. J Stroke Cerebrovasc Dis [Internet]. 2021 Aug 1 [cited 2022 Jul 27];30(8). Available from: https://www.strokejournal.org/article/S1052-3057(21)00267-6/fulltext#seccesectitle0024

137. Olney NT, Spina S, Miller BL. Frontotemporal Dementia. Neurol Clin. 2017 May;35(2):339–74.

138. Recommendations | Dementia: assessment, management and support for people living with dementia and their carers | Guidance | NICE [Internet]. NICE; [cited 2022 Jul 20]. Available from: https://www.nice.org.uk/guidance/ng97/chapter/Recommendations#diagnosis

139. Borsje P, Wetzels RB, Lucassen PL, Pot AM, Koopmans RT. The course of neuropsychiatric symptoms in community-dwelling patients with dementia: a systematic review. Int Psychogeriatr. 2015 Mar;27(3):385–405.

140. Cerejeira J, Lagarto L, Mukaetova-Ladinska E. Behavioral and Psychological Symptoms of Dementia. Front Neurol [Internet]. 2012 May;3. Available from: https://www.frontiersin.org/articles/10.3389/fneur.2012.00073/full http://files/251/Cerejeira et al. - 2012 - Behavioral and Psychological Symptoms of Dementia.pdf

141. Tible OP, Riese F, Savaskan E, von Gunten A. Best practice in the management of behavioural and psychological symptoms of dementia. Ther Adv Neurol Disord. 2017 Aug 1;10(8):297–309.

142. Cheng ST. Dementia Caregiver Burden: a Research Update and Critical Analysis. Curr Psychiatry Rep. 2017 Aug 10;19(9):64.

143. Albert MS. Changes in cognition. Neurobiol Aging. 2011 Dec 1;32:S58–63.

144. Hugo J, Ganguli M. Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment. Clin Geriatr Med. 2014 Aug;30(3):421–42.

145. Muir-Hunter SW, Clark J, McLean S, Pedlow S, Van Hemmen A, Montero Odasso M, et al. Identifying Balance and Fall Risk in Community-Dwelling Older Women: The Effect of Executive Function on Postural Control. Physiother Can. 2014;66(2):179–86.

146. Demnitz N, Zsoldos E, Mahmood A, Mackay CE, Kivimäki M, Singh-Manoux A, et al. Associations between Mobility, Cognition, and Brain Structure in Healthy Older Adults. Front Aging Neurosci [Internet]. 2017 [cited 2022 May 4];9. Available from: https://www.frontiersin.org/article/10.3389/fnagi.2017.00155

147. Fernando E, Fraser M, Hendriksen J, Kim CH, Muir-Hunter SW. Risk Factors Associated with Falls in Older Adults with Dementia: A Systematic Review. Physiother Can. 2017 May;69(2):161–70.

148. Diamond A. Executive Functions. Annu Rev Psychol. 2013;64:135.

149. Educating executive function - Blair - 2017 - WIREs Cognitive Science - Wiley Online Library [Internet]. [cited 2022 Aug 2]. Available from: https://wires.onlinelibrary.wiley.com/doi/full/10.1002/wcs.1403

150. Cognition C. CANTAB Cognitive Assessments [Internet]. Cambridge; 2015. Available from: http://www.cambridgecognition.com/

151. Ferguson HJ, Brunsdon VEA, Bradford EEF. The developmental trajectories of executive function from adolescence to old age. Sci Rep. 2021 Jan 14;11(1):1382.

152. Harada CN, Natelson Love MC, Triebel K. Normal Cognitive Aging. Clin Geriatr Med. 2013 Nov;29(4):737–52.

153. Stanley ML, Simpson SL, Dagenbach D, Lyday RG, Burdette JH, Laurienti PJ. Changes in Brain Network Efficiency and Working Memory Performance in Aging. PLOS ONE. 2015 Apr 13;10(4):e0123950.

154. Kirova AM, Bays RB, Lagalwar S. Working Memory and Executive Function Decline across Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease. BioMed Res Int. 2015 Oct 15;2015:e748212.

155. Brandt J, Link to external site this link will open in a new window, Aretouli E, Neijstrom E, Samek J, Manning K, et al. Selectivity of executive function deficits in mild cognitive impairment. Neuropsychology. 2009 Sep;23(5):607–18.

156. Zheng D, Dong X, Sun H, Xu Y, Ma Y, Wang X. The overall impairment of core executive function components in patients with amnestic mild cognitive impairment: a cross-sectional study. BMC Neurol. 2012 Nov 20;12(1):138.

157. Sudo FK, Amado P, Alves GS, Laks J, Engelhardt E. A continuum of executive function deficits in early subcortical vascular cognitive impairment: A systematic review and meta-analysis. Dement Neuropsychol. 2017 Dec;11:371–80.

158. Voss SE, Bullock RA. Executive Function: The Core Feature of Dementia? Dement Geriatr Cogn Disord. 2004;18(2):207–16.

159. Stopford CL, Thompson JC, Neary D, Richardson AMT, Snowden JS. Working memory, attention, and executive function in Alzheimer's disease and frontotemporal dementia. Cortex. 2012 Apr 1;48(4):429–46.

160. Firbank M, Kobeleva X, Cherry G, Killen A, Gallagher P, Burn DJ, et al. Neural correlates of attention-executive dysfunction in lewy body dementia and Alzheimer's disease. Hum Brain Mapp. 2016;37(3):1254–70.

161. Valkanova V, Ebmeier KP. What can gait tell us about dementia? Review of epidemiological and neuropsychological evidence. Gait Posture. 2017 Mar 1;53:215–23.

162. Mc Ardle R, Pratt S, Buckley C, Del Din S, Galna B, Thomas A, et al. Balance Impairments as Differential Markers of Dementia Disease Subtype. Front Bioeng Biotechnol [Internet]. 2021 [cited 2022 Mar 21];9. Available from: https://www.frontiersin.org/article/10.3389/fbioe.2021.639337

163. Lach HW, Harrison BE, Phongphanngam S. Falls and Fall Prevention in Older Adults With Early-Stage Dementia: An Integrative Review. Res Gerontol Nurs. 2017 May;10(3):139–48.

164. Bortoli CG, Piovezan MR, Piovesan EJ, Zonta MB. Balance, falls and functionality among elderly persons with cognitive function impairment. Rev Bras Geriatr E Gerontol. 2015 Sep;18:587–97.

165. Szczepańska-Gieracha J, Cieślik B, Chamela-Bilińska D, Kuczyński M. Postural Stability of Elderly People With Cognitive Impairments. Am J Alzheimers Dis Dementias®. 2016 May 1;31(3):241–6.

166. Tangen GG, Engedal K, Bergland A, Moger TA, Mengshoel AM. Relationships Between Balance and Cognition in Patients With Subjective Cognitive Impairment, Mild Cognitive Impairment, and Alzheimer Disease. Phys Ther. 2014 Aug 1;94(8):1123–34.

167. Taylor ME, Lord SR, Delbaere K, Kurrle SE, Mikolaizak AS, Close JCT. Reaction Time and Postural Sway Modify the Effect of Executive Function on Risk of Falls in Older People with Mild to Moderate Cognitive Impairment. Am J Geriatr Psychiatry. 2017 Apr 1;25(4):397–406.

168. Hunter SW, Divine A, Madou E, Omana H, Hill KD, Johnson AM, et al. Executive function as a mediating factor between visual acuity and postural stability in cognitively healthy adults and adults with Alzheimer's dementia. Arch Gerontol Geriatr. 2020 Jul 1;89:104078.

169. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020 Dec 1;54(24):1451–62.

170. WHO guidelines on physical activity and sedentary behaviour [Internet]. [cited 2022 Jul 23]. Available from: https://www.who.int/publications-detail-redirect/9789240015128

171. WHO | Physical Activity and Adults. WHO. 2015;

172. WHO | Physical Activity. WHO. 2017;

173. Penedo FJ, Dahn JR. Exercise and well-being: a review of mental and physical health benefits associated with physical activity. Curr Opin Psychiatry. 2005 Mar;18(2):189–93.

174. Reiner M, Niermann C, Jekauc D, Woll A. Long-term health benefits of physical activity – a systematic review of longitudinal studies. BMC Public Health. 2013 Dec;13(1):813.

175. Warburton DER, Bredin SSD. Health benefits of physical activity. Curr Opin Cardiol. 2017 Sep;32(5):541–56.

176. Santos L, Elliott-Sale KJ, Sale C. Exercise and bone health across the lifespan. Biogerontology. 2017 Dec;18(6):931–46.

177. Trombetti A, Hars M, Herrmann FR, Kressig RW, Ferrari S, Rizzoli R. Effect of Music-Based Multitask Training on Gait, Balance, and Fall Risk in Elderly People: A Randomized Controlled Trial. Arch Intern Med. 2011 Mar;171(6):525–33.

178. Rhodes RE, Janssen I, Bredin SSD, Warburton DER, Bauman A. Physical activity: Health impact, prevalence, correlates and interventions. Psychol Health. 2017 May;32(8):942–75.

179. Chapman S, Aslan S, Spence J, DeFina L, Keebler M, Didehbani N, et al. Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. Front Aging Neurosci [Internet]. 2013 [cited 2022 Aug 13];5. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2013.00075

180. Bherer L, Erickson KI, Liu-Ambrose T. A Review of the Effects of Physical Activity and Exercise on Cognitive and Brain Functions in Older Adults

[Internet]. Journal of Aging Research. 2013. Available from: https://www.hindawi.com/journals/jar/2013/657508/abs/ http://files/126/Bherer et al. - 2013 - A Review of the Effects of Physical Activity and E.pdf http://www.ncbi.nlm.nih.gov/pubmed/24102028 http://files/127/abs.html

181. Frederiksen KS, Verdelho A, Madureira S, Bazner H, O'Brien JT, Fazekas F, et al. Physical activity in the elderly is associated with improved executive function and processing speed: The LADIS study. Study L, Aarsland Baker, Buchman, Colcombe, Devore, Fazekas, Ferris, Ihara, Johnson, Jokinen, Kivipelto, Kramer, Krarup, Lawton, Lindsay, Lindwall, Liu-Ambrose, MacLeod, Madureira, Middleton, Nagamatsu, Netz, Pantoni, Pantoni, Pohjasvaara, Reitan, Sabia, Van Praa A, editors. Int J Geriatr Psychiatry. 2015;30(7):744–50.

182. Guure CB, Ibrahim NA, Adam MB, Said SM. Impact of Physical Activity on Cognitive Decline, Dementia, and Its Subtypes: Meta-Analysis of Prospective Studies [Internet]. BioMed Research International. 2017. Available from: https://www.hindawi.com/journals/bmri/2017/9016924/abs/ http://files/183/Guure et al. - 2017 - Impact of Physical Activity on Cognitive Decline, .pdf http://files/182/abs.html

183. Haeger A, Costa AS, Schulz JB, Reetz K. Cerebral changes improved by physical activity during cognitive decline: A systematic review on MRI studies. NeuroImage Clin. 2019 Jan;23.

184. Öhman H, Savikko N, Strandberg TE, Pitkälä KH. Effect of Physical Exercise on Cognitive Performance in Older Adults with Mild Cognitive Impairment or Dementia: A Systematic Review. Dement Geriatr Cogn Disord. 2014;38(5–6):347–65.

185. Guitar NA, Connelly DM, Nagamatsu LS, Orange JB, Muir-Hunter SW. The effects of physical exercise on executive function in community-dwelling older adults living with Alzheimer's-type dementia: A systematic review. Ageing Res Rev. 2018 Nov 1;47:159–67.

186. Langoni C da S, Resende T de L, Barcellos AB, Cecchele B, da Rosa JN, Knob MS, et al. The effect of group exercises on balance, mobility, and depressive symptoms in older adults with mild cognitive impairment: a randomized controlled trial. Clin Rehabil. 2019 Mar 1;33(3):439–49.

187. de Souto Barreto P, Demougeot L, Pillard F, Lapeyre-Mestre M, Rolland Y. Exercise training for managing behavioral and psychological symptoms in people with dementia: A systematic review and meta-analysis. Ageing Res Rev. 2015 Nov;24:274–85.

188. Schwenk M, Zieschang T, Englert S, Grewal G, Najafi B, Hauer K. Improvements in gait characteristics after intensive resistance and functional training in people with dementia: a randomised controlled trial. BMC Geriatr. 2014 Dec;14(1):73.

189. Pitkälä K, Savikko N, Poysti M, Strandberg T, Laakkonen ML. Efficacy of physical exercise intervention on mobility and physical functioning in older

people with dementia: A systematic review. Exp Gerontol. 2013 Jan 1;48(1):85–93.

190. Blankevoort CG, van Heuvelen MJ, Boersma F, Luning H, de Jong J, Scherder EJ. Review of effects of physical activity on strength, balance, mobility and ADL performance in elderly subjects with dementia. Dement Geriatr Cogn Disord. 2010;30(5):392–402.

191. Lam FM, Huang MZ, Liao LR, Chung RC, Kwok TC, Pang MY. Physical exercise improves strength, balance, mobility, and endurance in people with cognitive impairment and dementia: a systematic review. J Physiother. 2018 Jan 1;64(1):4–15.

192. Guo JL, Tsai YY, Liao JY, Tu HM, Huang CM. Interventions to reduce the number of falls among older adults with/without cognitive impairment: an exploratory meta-analysis. Int J Geriatr Psychiatry. 2014 Jul;29(7):661–9.

193. Sherrington C, Michaleff ZA, Fairhall N, Paul SS, Tiedemann A, Whitney J, et al. Exercise to prevent falls in older adults: an updated systematic review and meta-analysis. Br J Sports Med. 2017;51(24):1750–8.

194. Cohen S, Cummings J, Knox S, Potashman M, Harrison J. Clinical Trial Endpoints and Their Clinical Meaningfulness in Early Stages of Alzheimer's Disease. J Prev Alzheimers Dis. 2022;9(3):507–22.

195. Rentz DM, Wessels AM, Annapragada AV, Berger AK, Edgar CJ, Gold M, et al. Building clinically relevant outcomes across the Alzheimer's disease spectrum. Alzheimers Dement Transl Res Clin Interv. 2021 Jan;7(1):e12181.

196. Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF. Exercise, brain, and cognition across the life span. J Appl Physiol. 2011 Nov;111(5):1505–13.

197. Hashimoto M, Araki Y, Takashima Y, Nogami K, Uchino A, Yuzuriha T, et al. Hippocampal atrophy and memory dysfunction associated with physical inactivity in community-dwelling elderly subjects: The Sefuri study. Brain Behav. 2017;7(2):e00620.

198. Bugg JM, Head D. Exercise moderates age-related atrophy of the medial temporal lobe. Adlard Ang, Baltes, Barnes, Baron, Bissig, Bookstein, Bowles, Braak, Buckner, Burns, Colcombe, Colcombe, Colcombe, Cotman, Cotman, Davatzikos, Desikan, Fabel, Fischl, Fischl, Fotenos, Gomez-Pinilla, Gordon, Greenwood, Head, Hillman, Hollingshead, Honea, A, editor. Neurobiol Aging. 2011;32(3):506–14.

199. Varma VR, Chuang YF, Harris GC, Tan EJ, Carlson MC. Low-intensity daily walking activity is associated with hippocampal volume in older adults. Hippocampus. 2015;25(5):605–15.

200. Dougherty RJ, Ellingson LD, Schultz SA, Boots EA, Meyer JD, Lindheimer JB, et al. Meeting physical activity recommendations may be protective against temporal lobe atrophy in older adults at risk for Alzheimer's disease. Alzheimers Dement Diagn Assess Dis Monit. 2016;4(1):14–7.

201. Tan ZS, Spartano NL, Beiser AS, DeCarli C, Auerbach SH, Vasan RS, et al. Physical Activity, Brain Volume, and Dementia Risk: The Framingham Study. J Gerontol A Biol Sci Med Sci. 2017;72(6):789–95.

202. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Black Burdette, Colcombe, Colcombe, Colcombe, Cotman, Creer, Erickson, Erickson, Erickson, Figurov, Hackert, Heo, Hillman, Holmes, Honea, Jack, Kang, Kramer, Lee, Li, Moser, Neeper, Oldfield, Pang, Patenaude, Pencea, Pereira, Raji, Rasmussen, Raz, Redila B, editor. PNAS Proc Natl Acad Sci U S Am. 2011;108(7):3017–22.

203. Bolandzadeh N, Tam R, Handy TC, Nagamatsu LS, Hsu CL, Davis JC, et al. Resistance Training and White Matter Lesion Progression in Older Women: Exploratory Analysis of a 12-Month Randomized Controlled Trial. J Am Geriatr Soc. 2015;63(10):2052–60.

204. Burdette JH, Laurienti PJ, Espeland MA, Morgan AR, Telesford Q, Vechlekar CD, et al. Using network science to evaluate exercise-associated brain changes in older adults. Front Aging Neurosci [Internet]. 2010 May;2. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2010.00023/full#B25 http://files/191/Burdette et al. - 2010 - Using network science to evaluate exercise-associa.pdf

205. Voss MW, Erickson KI, Prakash RS, Chaddock L, Malkowski E, Alves H, et al. Functional connectivity: A source of variance in the association between cardiorespiratory fitness and cognition? Aggleton Beckmann, Birn, Biswal, Black, Boly, Buckner, Buckner, Burgess, Byrne, Castelli, Celone, Chang, Christie, Clark, Colcombe, Colcombe, Colcombe, Cotman, Damoiseaux, De Luca, de Munck, Ding, Dolcos, Erickson, Fair, Fairchild, Farmer, Garrity, Green AH, editor. Neuropsychologia. 2010;48(5):1394–406.

206. Liu-Ambrose T, Nagamatsu LS, Voss MW, Khan KM, Handy TC. Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. Neurobiol Aging. 2012 Aug 1;33(8):1690–8.

207. Domingos C, Pêgo JM, Santos NC. Effects of physical activity on brain function and structure in older adults: A systematic review. Behav Brain Res. 2021 Mar 26;402:113061.

208. Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A, et al. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. Neurology. 2008 Jul 15;71(3):210–6.

209. Makizako H, Liu-Ambrose T, Shimada H, Doi T, Park H, Tsutsumimoto K, et al. Moderate-intensity physical activity, Hippocampal volume, and memory in older adults with mild cognitive impairment. Almeida Apostolova, Barrett, Brown, Buchman, Buchman, Burdette, Daviglus, Devanand, Erickson, Erickson, Folstein, Gates, Hagstromer, Hamer, Head, Hanninen, Kerr, Lezak, Makizako, Nelson, Ohkawara, Oshima, Pate, Patenaude, Petersen, Petersen, Petersen, Sa A, editor. J Gerontol A Biol Sci Med Sci. 2015;70(4):480–6.

210. Teixeira CVL, Rezende TJR, Weiler M, Nogueira MH, Campos BM, Pegoraro LFL, et al. Relation between aerobic fitness and brain structures in amnestic mild cognitive impairment elderly. Age Dordr Neth. 2016;38(3):51.

211. Doi T, Makizako H, Shimada H, Tsutsumimoto K, Hotta R, Nakakubo S, et al. Objectively measured physical activity, brain atrophy, and white matter lesions in older adults with mild cognitive impairment. Exp Gerontol. 2015 Feb 1;62:1–6.

212. Boyle CP, Raji CA, Erickson KI, Lopez OL, Becker JT, Gach HM, et al. Physical activity, body mass index, and brain atrophy in Alzheimer's disease. Ahlskog Belarbi, Benjamini, Blankevoort, Bryan, Bryan, Burdette, Burns, Calabrese, Chang, Chu, Chu, Colcombe, Colcombe, Cronk, Elosua, Erickson, Erickson, Erickson, Erickson, Folsom, Forbes, Forbes, Fried, Head, Ho, Ho, Ho, Honea, Hotting, Intlekofer, Ku B, editor. Neurobiol Aging. 2015;36(Suppl 1):S194–202.

213. Siddarth P, Rahi B, Emerson ND, Burggren AC, Miller KJ, Bookheimer S, et al. Physical Activity and Hippocampal Sub-Region Structure in Older Adults with Memory Complaints. J Alzheimers Dis. 2018 Jan;61(3):1089–96.

214. Perea RD, Vidoni ED, Morris JK, Graves RS, Burns JM, Honea RA. Cardiorespiratory fitness and white matter integrity in Alzheimer's disease. Alexander Alves, Anderson, Andersson, Bach, Berg, Boots, Bosch, Bouchard, Braak, Brun, Burggren, Burns, Burns, Burzynska, Colcombe, Colcombe, Erickson, Erickson, Fleg, Gold, Gons, Hayes, Hayes, Hollenberg, Honea, Hua, Johansen-Berg, Johnson, Keihaninejad A, editor. Brain Imaging Behav. 2016;10(3):660–8.

215. Reiter K, Nielson KA, Smith TJ, Weiss LR, Alfini AJ, Smith JC. Improved Cardiorespiratory Fitness Is Associated with Increased Cortical Thickness in Mild Cognitive Impairment. J Int Neuropsychol Soc. 2015 Nov;21(10):757–67.

216. Callow DD, Won J, Pena GS, Jordan LS, Arnold-Nedimala NA, Kommula Y, et al. Exercise Training-Related Changes in Cortical Gray Matter Diffusivity and Cognitive Function in Mild Cognitive Impairment and Healthy Older Adults. Front Aging Neurosci [Internet]. 2021 [cited 2022 Aug 13];13. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2021.645258

217. Teixeira CVL, Ribeiro de Rezende TJ, Weiler M, Magalhães TNC, Carletti-Cassani AFMK, Silva TQAC, et al. Cognitive and structural cerebral changes in amnestic mild cognitive impairment due to Alzheimer's disease after multicomponent training. Alzheimers Dement Transl Res Clin Interv. 2018 Jan;4(1):473–80.

218. Um YH, Wang SM, Kim NY, Kang DW, Na HR, Lee CU, et al. Effects of Moderate Intensity Exercise on the Cortical Thickness and Subcortical Volumes of Preclinical Alzheimer's Disease Patients: A Pilot Study. Psychiatry Investig. 2020 Jun 15;17(6):613–9.

219. Frederiksen KS, Larsen CT, Hasselbalch SG, Christensen AN, Hogh P, Wermuth L, et al. A 16-Week Aerobic Exercise Intervention Does Not Affect Hippocampal Volume and Cortical Thickness in Mild to Moderate Alzheimer's Disease. Front Aging Neurosci. 2018;10:293.

220. Eyre HA, Acevedo B, Yang H, Siddarth P, Van Dyk K, Ercoli L, et al. Changes in Neural Connectivity and Memory Following a Yoga Intervention for Older Adults: A Pilot Study. J Alzheimers Dis. 2016 Jan 1;52(2):673–84.

221. Alfini AJ, Weiss LR, Smith JC, Nielson KA, Verber MD, A.J. A, et al. Resting cerebral blood flow after exercise training in mild cognitive impairment. J Alzheimers Dis. 2019 Nov;67(2):671–84.

222. Boa Sorte Silva NC, Nagamatsu LS, Gill DP, Owen AM, Petrella RJ. Memory Function and Brain Functional Connectivity Adaptations Following Multiple-Modality Exercise and Mind–Motor Training in Older Adults at Risk of Dementia: An Exploratory Sub-Study. Front Aging Neurosci [Internet]. 2020 [cited 2022 Jul 6];12. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2020.00022

223. Bajwa RK, Goldberg SE, Van der Wardt V, Burgon C, Di Lorito C, Godfrey M, et al. A randomised controlled trial of an exercise intervention promoting activity, independence and stability in older adults with mild cognitive impairment and early dementia (PrAISED) - A Protocol. Trials. 2019 Dec 30;20(1):815.

224. Khanna N, Altmeyer W, Zhuo J, Steven A. Functional Neuroimaging: Fundamental Principles and Clinical Applications.

225. Ahmed RM, Paterson RW, Warren JD, Zetterberg H, O'Brien JT, Fox NC, et al. Biomarkers in dementia: Clinical utility and new directions. Vol. 85, Journal of Neurology, Neurosurgery and Psychiatry. BMJ Publishing Group; 2014. p. 1426–34.

226. Márquez F, Yassa MA. Neuroimaging Biomarkers for Alzheimer's Disease. Vol. 14, Molecular Neurodegeneration. BioMed Central Ltd.; 2019.

227. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. Magn Reson Med. 1995 Oct 1;34(4):537–41.

228. Lv XH, Wang XZ, Tong XE, Williams XLM, Zaharchuk XG, Zeineh XM, et al. Resting-State Functional MRI: Everything That Nonexperts Have Always Wanted to Know. 2018;

229. Cieri F, Esposito R. Neuroaging through the Lens of the Resting State Networks. BioMed Res Int. 2018;2018.

230. Soares JM, Magalhães R, Moreira PS, Sousa A, Ganz E, Sampaio A, et al. A Hitchhiker's guide to functional magnetic resonance imaging. Front Neurosci. 2016;10(November):1–35.

231. Seitzman BA, Snyder AZ, Leuthardt EC, Shimony JS. The State of Resting State Networks.

232. Badhwar A, Tam A, Dansereau C, Orban P, Hoffstaedter F, Bellec P. Resting-state network dysfunction in Alzheimer's disease: A systematic review and meta-analysis. Alzheimers Dement Diagn Assess Dis Monit. 2017 Mar;8:73–85.

233. Terry DP, Sabatinelli D, Puente AN, Lazar NA, Miller LS. A Meta-Analysis of fMRI Activation Differences during Episodic Memory in Alzheimer's Disease and Mild Cognitive Impairment. J Neuroimaging. 2015;25(6):849–60.

234. Nellessen N, Rottschy C, Eickhoff SB, Ketteler ST, Kuhn H, Shah NJ, et al. Specific and disease stage-dependent episodic memory-related brain activation patterns in Alzheimer's disease: a coordinate-based meta-analysis. Brain Struct Funct. 2015 May 1;220(3):1555–71.

235. Buckner RL. The brain's default network: origins and implications for the study of psychosis. Dialogues Clin Neurosci. 2013 Sep;15(3):351.

236. Buckner RL. The serendipitous discovery of the brain's default network. Vol. 62, NeuroImage. Academic Press; 2012. p. 1137–45.

237. Davey CG, Pujol J, Harrison BJ. Mapping the self in the brain's default mode network. NeuroImage. 2016 May;132:390–7.

238. Marek S, Dosenbach NUF. The frontoparietal network: Function, electrophysiology, and importance of individual precision mapping. Vol. 20, Dialogues in Clinical Neuroscience. Les Laboratoires Seriver; 2018. p. 133–41.

239. Kashou N. A Practical Guide to an fMRI Experiment. Adv Brain Neuroimaging Top Health Dis - Methods Appl. 2014 May 31;

240. Amaro E, Barker GJ. Study design in fMRI: Basic principles. Brain Cogn. 2006 Apr 1;60(3):220–32.

241. Lindquist MA, Wager TD. Principles of functional Magnetic Resonance Imaging.

242. Matthews PM. Functional magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 2004;75:6–12.

243. Rittman T. Neurological update: neuroimaging in dementia. J Neurol. 2020 Nov 1;267(11):3429–35.

244. Clinical use of neuroimaging in dementia: an international perspective. Int Psychogeriatr. 2011 Sep;23(S2):S3–5.

245. Staffaroni AM, Elahi FM, McDermott D, Marton K, Karageorgiou E, Sacco S, et al. Neuroimaging in Dementia. Semin Neurol. 2017 Oct;37(5):510–37.

246. Vernooij MW, Pizzini FB, Schmidt R, Smits M, Yousry TA, Bargallo N, et al. Dementia imaging in clinical practice: a European-wide survey of 193 centres

and conclusions by the ESNR working group. Neuroradiology. 2019;61(6):633–42.

247. Lombardi G, Crescioli G, Cavedo E, Lucenteforte E, Casazza G, Bellatorre A, et al. Structural magnetic resonance imaging for the early diagnosis of dementia due to Alzheimer's disease in people with mild cognitive impairment. Cochrane Database Syst Rev. 2020 Mar 2;2020(3).

248. Ausó E, Gómez-Vicente V, Esquiva G. Biomarkers for Alzheimer's Disease Early Diagnosis. J Pers Med. 2020;

249. Tabatabaei-Jafari H, Shaw ME, Cherbuin N. Cerebral atrophy in mild cognitive impairment: A systematic review with meta-analysis. Alzheimers Dement Diagn Assess Dis Monit. 2015 Dec 1;1(4):487.

250. Johnson KA, Fox NC, Sperling RA, Klunk WE. Brain imaging in Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(4).

251. Yang J, Pan P, Song W, Huang R, Li J, Chen K, et al. Voxelwise meta-analysis of gray matter anomalies in Alzheimer's disease and mild cognitive impairment using anatomic likelihood estimation. J Neurol Sci. 2012 May 15;316(1–2):21–9.

252. Talwar P, Kushwaha S, Chaturvedi M, Mahajan V. Systematic Review of Different Neuroimaging Correlates in Mild Cognitive Impairment and Alzheimer's Disease. Clin Neuroradiol 2021. 2021 Jul 23;1–15.

253. Zakzanis KK, Graham SJ, Campbell Z. A Meta-Analysis of Structural and Functional Brain Imaging in Dementia of the Alzheimer's Type: A Neuroimaging Profile. Neuropsychol Rev. 2003 Mar 1;13(1):1–18.

254. Vijayakumar A, Vijayakumar A. Comparison of Hippocampal Volume in Dementia Subtypes. Int Sch Res Not. 2013;

255. Pettigrew C, Soldan A, Zhu Y, Wang MC, Moghekar A, Brown T, et al. Cortical thickness in relation to clinical symptom onset in preclinical AD. NeuroImage Clin. 2016 Feb 1;12:116–22.

256. Singh V, Chertkow H, Lerch JP, Evans AC, Dorr AE, Kabani NJ. Spatial patterns of cortical thinning in mild cognitive impairment and Alzheimer's disease. Brain J Neurol. 2006 Nov;129(Pt 11):2885–93.

257. Bakkour A, Morris JC, Dickerson BC. The cortical signature of prodromal AD. Neurology. 2009 Mar 24;72(12):1048–55.

258. Duara R, Loewenstein DA, Potter E, Appel J, Greig MT, Urs R, et al. Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. Neurology. 2008 Dec 9;71(24):1986–92.

259. Frisoni GB, Fox NC, Jack CR, Jr, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol. 2010 Feb;6(2):67.

260. Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are White Matter Hyperintensities Made of? J Am Heart Assoc Cardiovasc Cerebrovasc Dis. 2015 Jun 23;4(6):e001140.

261. Mortamais M, Artero S, Ritchie K. Cerebral white matter hyperintensities in the prediction of cognitive decline and incident dementia. Int Rev Psychiatry Abingdon Engl. 2013;25(6):686–98.

262. Smith EE, Egorova S, Blacker D, Killiany RJ, Muzikansky A, Dickerson BC, et al. Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. Arch Neurol. 2008 Jan;65(1):94–100.

263. Brickman AM, Zahodne LB, Guzman VA, Narkhede A, Meier IB, Griffith EY, et al. Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. Neurobiol Aging. 2015 Jan 1;36(1):27–32.

264. Hu HY, Ou YN, Shen XN, Qu Y, Ma YH, Wang ZT, et al. White matter hyperintensities and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 36 prospective studies. Neurosci Biobehav Rev. 2021 Jan;120:16–27.

265. Martinez-Ramirez S, Greenberg SM, Viswanathan A. Cerebral microbleeds: overview and implications in cognitive impairment. Alzheimers Res Ther. 2014 Jun 11;6(3):33.

266. Lee J, Sohn EH, Oh E, Lee AY. Characteristics of Cerebral Microbleeds. Dement Neurocognitive Disord. 2018 Sep;17(3):73–82.

267. Akoudad S, Wolters FJ, Viswanathan A, de Bruijn RF, van der Lugt A, Hofman A, et al. Association of Cerebral Microbleeds With Cognitive Decline and Dementia. JAMA Neurol. 2016 Aug 1;73(8):934–43.

268. Abdullah KM, Zakieldin HM, Bayomy IM, Awadallah MY, Wahid El Din MM. Do cerebral microbleeds affect cognition in patients with symptomatic small vessel disease? Egypt J Neurol Psychiatry Neurosurg. 2020 Jan 9;56(1):7.

269. Romero JR, Beiser A, Himali JJ, Shoamanesh A, DeCarli C, Seshadri S. Cerebral Microbleeds and risk of Incident Dementia: The Framingham Heart Study. Neurobiol Aging. 2017 Jun;54:94–9.

270. Wang M, Hu HY, Wang ZT, Ou YN, Qu Y, Ma YH, et al. Association of cerebral microbleeds with risks of cognitive impairment and dementia: A systematic review and meta-analysis of prospective studies. Brain Disord. 2021 Jun 1;2:100010.

271. Sperling R. The potential of functional MRI as a biomarker in early Alzheimer's disease. Neurobiol Aging. 2011 Dec;32(SUPPL. 1).

272. McDonald AP, D'Arcy RCN, Song X. Functional MRI on executive functioning in aging and dementia: A scoping review of cognitive tasks. Aging Med. 2018 Sep 1;1(2):209–19.

273. Peelle JE, Powers J, Cook PA, Smith EE, Grossman M. Frontotemporal neural systems supporting semantic processing in Alzheimer's disease. Cogn Affect Behav Neurosci. 2014;14(1):37.

274. Corriveau-Lecavalier N, Mellah S, Clément F, Belleville S. Evidence of parietal hyperactivation in individuals with mild cognitive impairment who progressed to dementia: A longitudinal fMRI study. NeuroImage Clin. 2019 Jan 1;24:101958.

275. Staffen W, Ladurner G, Höller Y, Bergmann J, Aichhorn M, Golaszewski S, et al. Brain activation disturbance for target detection in patients with mild cognitive impairment: an fMRI study. Neurobiol Aging. 2012 May;33(5):1002.e1-1002.e16.

276. Paek EJ, Murray LL, Newman SD. Neural Correlates of Verb Fluency Performance in Cognitively Healthy Older Adults and Individuals With Dementia: A Pilot fMRI Study. Front Aging Neurosci. 2020 Mar;0:73.

277. Migo EM, Mitterschiffthaler M, O'Daly O, Dawson GR, Dourish CT, Craig KJ, et al. Alterations in working memory networks in amnestic mild cognitive impairment. Aging Neuropsychol Cogn. 2015 Jan 2;22(1):106–27.

278. Hohenfeld C, Werner CJ, Reetz K. Resting-state connectivity in neurodegenerative disorders: Is there potential for an imaging biomarker? NeuroImage Clin. 2018 Jan;18:849–70.

279. Wang L, Zang Y, He Y, Liang M, Zhang X, Tian L, et al. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: Evidence from resting state fMRI. NeuroImage. 2006 Jun;31(2):496–504.

280. Xue J, Guo H, Gao Y, Wang X, Cui H, Chen Z, et al. Altered Directed Functional Connectivity of the Hippocampus in Mild Cognitive Impairment and Alzheimer's Disease: A Resting-State fMRI Study. Front Aging Neurosci [Internet]. 2019 [cited 2022 Jul 21];11. Available from: https://www.frontiersin.org/articles/10.3389/fnagi.2019.00326

281. Dennis EL, Thompson PM. Functional brain connectivity using fMRI in aging and Alzheimer's disease. Neuropsychol Rev. 2014 Mar;24(1):49–62.

282. Dai Z, Yan C, Li K, Wang Z, Wang J, Cao M, et al. Identifying and Mapping Connectivity Patterns of Brain Network Hubs in Alzheimer's Disease. Achard Alexander-Bloch, Ashburner, Attwell, Bero, Bero, Birn, Biswal, Brier, Buckner, Buckner, Bullmore, Bullmore, Bunge, Cabeza, Chang, Chen, Collignon, Crossley, Curtis, D'Amelio, Dai, de Haan, de Haan, de Reus, Deen, Delbeuck, Drzezga, Dubois, Dubois, A, editor. Cereb Cortex. 2015 Oct;25(10):3723–42.

283. Sheline YI, Raichle ME. Resting State Functional Connectivity in Preclinical Alzheimer's Disease. Biol Psychiatry. 2013 Sep 1;74(5):340–7.

284. Binnewijzend MAA, Schoonheim MM, Sanz-Arigita E, Wink AM, van der Flier WM, Tolboom N, et al. Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging. 2012 Sep;33(9):2018–28.

285. Damoiseaux JS, Prater KE, Miller BL, Greicius MD. Functional connectivity tracks clinical deterioration in Alzheimer's disease. Neurobiol Aging. 2012 Apr;33(4):828.e19-828.e30.

286. Pievani M, de Haan W, Wu T, Seeley WW, Frisoni GB. Functional network disruption in the degenerative dementias. Vol. 10, The Lancet Neurology. Elsevier; 2011. p. 829–43.

287. Lee ES, Yoo K, Lee YB, Chung J, Lim JE, Yoon B, et al. Default mode network functional connectivity in early and late mild cognitive impairment: Results from the Alzheimer's disease neuroimaging initiative. Initiative ADN, Aisen Ashburner, Bai, Balthazar, Cavanna, Cha, Crane, Damoiseaux, Gibbons, Greicius, Hedden, Jicha, Klunk, Koch, Landau, Lee, Lim, Lim, Machulda, McKhann, Nir, Petrella, Rombouts, Sala-Llonch, Schopf, Shim, Sohn, Sperling, Sperling, Vogt, Wang, Weiner, W A, editors. Alzheimer Dis Assoc Disord. 2016;30(4):289–96.

288. Kim HJ, Cha J, Lee JM, Shin JS, Jung NY, Kim YJ, et al. Distinctive Resting State Network Disruptions Among Alzheimer's Disease, Subcortical Vascular Dementia, and Mixed Dementia Patients. Im K, editor. J Alzheimers Dis. 2016 Feb;50(3):709–18.

289. Zhou J, Greicius MD, Gennatas ED, Growdon ME, Jang JY, Rabinovici GD, et al. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. Brain. 2010 May;133(5):1352–67.

290. Eyler LT, Elman JA, Hatton SN, Gough S, Mischel AK, Hagler DJ, et al. Resting State Abnormalities of the Default Mode Network in Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. J Alzheimers Dis. 2019;70(1):107–20.

291. Agosta F, Pievani M, Geroldi C, Copetti M, Frisoni GB, Filippi M. Resting state fMRI in Alzheimer's disease: Beyond the default mode network. Neurobiol Aging. 2012 Aug;33(8):1564–78.

292. Wang Z, Xia M, Dai Z, Liang X, Song H, He Y, et al. Differentially disrupted functional connectivity of the subregions of the inferior parietal lobule in Alzheimer's disease. Agosta Allen, Ashburner, Ashburner, Bai, Barrantes, Becker, Binkofski, Biswal, Braak, Brier, Buckner, Buckner, Busatto, Caspers, Caspers, Caspers, Caspers, Cavada, Cavada, Chai, Crone, Dai, Dai, Desikan, Dickerson, Dosenbach, Downar, Dubois, Dubois, Eick A, editor. Brain Struct Funct. 2015;220(2):745–62.

293. Zheng W, Liu X, Song H, Li K, Wang Z. Altered functional connectivity of cognitive-related cerebellar subregions in Alzheimer's disease. Agosta Ashburner, Bai, Bai, Bas, Biswal, Bokde, Braak, Brier, Buckner, Buckner,

Busatto, Castellazzi, Chao-Gan, Chetelat, Ciavardelli, Cronin-Golomb, Dai, Dickerson, Diedrichsen, Dubois, Dubois, Fox, Frisoni, Greicius, Habas, Hauser, He, Kandimalla, Kand A, editor. Front Aging Neurosci [Internet]. 2017;9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc14&NEWS=N&AN=2017-23977-001

294. Zhu H, Zhou P, Alcauter S, Chen Y, Cao H, Tian M, et al. Changes of intranetwork and internetwork functional connectivity in Alzheimer's disease and mild cognitive impairment. J Neural Eng. 2016 Jun;13(4):046008.

295. Hafkemeijer A, Möller C, Dopper EGP, Jiskoot LC, Schouten TM, van Swieten JC, et al. Resting state functional connectivity differences between behavioral variant frontotemporal dementia and Alzheimer's disease. Front Hum Neurosci. 2015 Sep;9(September):474.

296. Orrell M, Brayne C. Dementia prevention: Call to action. Vol. 386, The Lancet. Lancet Publishing Group; 2015. p. 1625.

297. Wahl D, Solon-Biet SM, Ribeiro RV, Cogger VC, Fontana L, Simpson SJ, et al. The role of nutrition in brain health View project The Concord Health and Ageing in Men Project (CHAMP) View project Aging, lifestyle and dementia. 2019;

299. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. Age Ageing. 2012 Mar 7;41(3):299–308.

300. Farina N, Rusted J, Tabet N. The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review. Int Psychogeriatr. 2014 Jan 20;26(1):9–18.

301. Potter R, Ellard D, Rees K, Thorogood M. A systematic review of the effects of physical activity on physical functioning, quality of life and depression in older people with dementia. Int J Geriatr Psychiatry. 2011;26(10):1000–11.

302. Frederiksen KS, Gjerum L, Waldemar G, Hasselbalch SG. Effects of Physical Exercise on Alzheimer's Disease Biomarkers: A Systematic Review of Intervention Studies. Burns J, editor. J Alzheimers Dis. 2017 Nov 28;61(1):359–72.

303. Huang P, Fang R, Li BY, Chen SD. Exercise-Related Changes of Networks in Aging and Mild Cognitive Impairment Brain. Front Aging Neurosci. 2016 Apr 24;8.

304. Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, et al. Plasticity of Brain Networks in a Randomized Intervention Trial of Exercise Training in Older Adults. Front Aging Neurosci. 2010 Mar 7;2.

305. Ruffieux J, Mouthon A, Keller M, Mouthon M, Annoni JM, Taube W. Balance Training Reduces Brain Activity during Motor Simulation of a Challenging

Balance Task in Older Adults: An fMRI Study. Front Behav Neurosci. 2018 Jan 24;12:10.

306. Hötting K, Röder B. Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci Biobehav Rev. 2013 Mar 7;37(9, Part B):2243–57.

307. Voelcker-Rehage C, Niemann C. Structural and functional brain changes related to different types of physical activity across the life span. Neurosci Biobehav Rev. 2013 Mar 14;37(9):2268–95.

308. Bray NW, Pieruccini-Faria F, Bartha R, Doherty TJ, Nagamatsu LS, Montero-Odasso M. The effect of physical exercise on functional brain network connectivity in older adults with and without cognitive impairment. A systematic review. Mech Ageing Dev. 2021 Jun 1;196:111493.

309. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and Cognition: A Complementary Approach to Understanding Brain Function and the Risk of Falling. J Am Geriatr Soc. 2012 May 12;60(11):2127–36.

310. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009 Jul 21;339(7716):332–6.

311. Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP, Johansen-Berg H. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. NeuroImage. 2016 May 5;131:81–90.

312. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 May 5;343:d5928.

313. Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. World J Meta-Anal. 2017;5(4):80.

314. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the Conduct of Narrative Synthesis in Systematic Reviews. :93.

315. Smith JC, Nielson KA, Woodard JL, Seidenberg M, Verber MD, Durgerian S, et al. Does physical activity influence semantic memory activation in amnestic mild cognitive impairment? Psychiatry Res - Neuroimaging. 2011 Jul 30;193(1):60–2.

316. Carson Smith J, Nielson KA, Antuono P, Lyons JA, Hanson RJ, Butts AM, et al. Semantic memory functional mri and cognitive function after exercise intervention in mild cognitive impairment. J Alzheimers Dis. 2013;37(1):197–215.

317. Chirles TJ, Reiter K, Weiss LR, Alfini AJ, Nielson KA. Exercise Training and Functional Connectivity Changes in Mild Cognitive Empairment and Healthy Elders. 2017;57:28.

318. Hsu CL, Best JR, Wang S, Voss MW, Hsiung RGY, Munkacsy M, et al. The Impact of Aerobic Exercise on Fronto-Parietal Network Connectivity and Its Relation to Mobility: An Exploratory Analysis of a 6-Month Randomized Controlled Trial. Front Hum Neurosci. 2017 Mar 7;11.

319. Hsu CL, Best JR, Davis JC, Nagamatsu LS, Wang S, Boyd LA, et al. Aerobic exercise promotes executive functions and impacts functional neural activity among older adults with vascular cognitive impairment. Br J Sports Med. 2018 May 5;52(3):184–91.

320. Suo C, Singh MF, Gates N, Wen W, Sachdev P, Brodaty H, et al. Therapeutically relevant structural and functional mechanisms triggered by physical and cognitive exercise. Ahlskog Chodzko-Zajko, Bai, Barnes, Barnes, Best, Braak, Breteler, Cassilhas, Castaneda, Clare, Clare, Coen, Colcombe, Cotman, Cotman, Damoiseaux, Damoiseaux, Debette, Engvig, Engvig, Erickson, Erickson, Fiatarone Singh, Frisoni, Gates, Gates, Gates, Gat A, editor. Mol Psychiatry. 2016 Nov 22;21(11):1633–42.

321. Qi M, Zhu Y, Zhang L, Wu T, Wang J. The effect of aerobic dance intervention on brain spontaneous activity in older adults with mild cognitive impairment: A resting-state functional MRI study. Exp Ther Med. 2018 Nov 23;17(1):715–22.

322. Tao J, Liu J, Chen X, Xia R, Li M, Huang M, et al. Mind-body exercise improves cognitive function and modulates the function and structure of the hippocampus and anterior cingulate cortex in patients with mild cognitive impairment. NeuroImage Clin. 2019;23:101834.

323. Xia R, Qiu P, Lin H, Ye B, Wan M, Li M, et al. The Effect of Traditional Chinese Mind-Body Exercise (Baduanjin) and Brisk Walking on the Dorsal Attention Network in Older Adults With Mild Cognitive Impairment. Front Psychol. 2019 Sep 10;10(SEP):2075.

324. Won J, Callow DD, Pena GS, Jordan LS, Arnold-Nedimala NA, Nielson KA, et al. Hippocampal Functional Connectivity and Memory Performance After Exercise Intervention in Older Adults with Mild Cognitive Impairment. J Alzheimers Dis. 2021 Jan 1;82(3):1015–31.

325. Broadhouse KM, Singh MF, Suo C, Gates N, Wen W, Brodaty H, et al. Hippocampal plasticity underpins long-term cognitive gains from resistance exercise in MCI. NeuroImage Clin. 2020 Jan 1;25:102182.

326. Liu J, Tao J, Xia R, Li M, Huang M, Li S, et al. Mind-Body Exercise Modulates Locus Coeruleus and Ventral Tegmental Area Functional Connectivity in Individuals With Mild Cognitive Impairment. Front Aging Neurosci. 2021 Jun 14;0:295.

327. Study designs — Centre for Evidence-Based Medicine (CEBM), University of Oxford [Internet]. [cited 2023 May 5]. Available from: https://www.cebm.ox.ac.uk/resources/ebm-tools/study-designs

328. Wells G, Shea B, O'Connell D, Peterson J, Welch V. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000;

329. Smith JC, Nielson KA, Antuono P, Verber MD, Cogbill E, Greene A, et al. Effects of Exercise Training on fMRI Activation and Hippocampal Blood Flow in Mild Cognitive Impairment. Med Sci Sports Exerc. 2011 May 2;43(Suppl 1):617–8.

330. Chhatwal JP, Sperling RA. Functional MRI of mnemonic networks across the spectrum of normal aging, mild cognitive impairment, and Alzheimer's disease. Vol. 31, Journal of Alzheimer's Disease. IOS Press; 2012. p. S155.

331. Reitz C, Mayeux R. Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. Vol. 88, Biochemical Pharmacology. Elsevier Inc.; 2014. p. 640–51.

332. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 2012 Nov 1;11(11):1006–12.

333. Cheng ST. Cognitive Reserve and the Prevention of Dementia: the Role of Physical and Cognitive Activities. Curr Psychiatry Rep. 2016 May 5;18(9):85.

334. Castellazzi G, Palesi F, Casali S, Vitali P, Wheeler-Kingshott CAM, Sinforiani E, et al. A comprehensive assessment of resting state networks: Bidirectional modification of functional integrity in cerebro-cerebellar networks in dementia. Front Neurosci. 2014 Jul 30;8(8 JUL):223.

335. Wang P, Zhou B, Yao H, Zhan Y, Zhang Z, Cui Y, et al. Aberrant intra- and inter-network connectivity architectures in Alzheimer's disease and mild cognitive impairment. Sci Rep. 2015 Dec 6;5(1):14824.

336. Lo OY, Halko MA, Devaney KJ, Wayne PM, Lipsitz LA, Manor B. Gait Variability Is Associated With the Strength of Functional Connectivity Between the Default and Dorsal Attention Brain Networks: Evidence From Multiple Cohorts. Newman AB, editor. J Gerontol Ser A. 2021 Sep;76(10):e328–34.

337. Lo OY, Halko MA, Zhou J, Harrison R, Lipsitz LA, Manor B. Gait speed and gait variability are associated with different functional brain networks. Front Aging Neurosci. 2017 Nov;9(NOV):390.

338. Aime S, Alberich A, Almen A, Arthurs OJ, Barthel H, Clément O, et al. Strategic research agenda for biomedical imaging. Insights Imaging. 2019 May 13;10(1):7.

339. Sonkusare S, Breakspear M, Guo C. Naturalistic Stimuli in Neuroscience: Critically Acclaimed. Trends Cogn Sci. 2019 Aug 1;23(8):699–714.

340. Godde B, Voelcker-Rehage C. More automation and less cognitive control of imagined walking movements in high- versus low-fit older adults. Front Aging Neurosci. 2010;2(SEP).

341. Taube W, Mouthon M, Leukel C, Hoogewoud HM, Annoni JM, Keller M. Brain activity during observation and motor imagery of different balance tasks: An fMRI study. Cortex. 2015 Mar;64:102–14.

342. Helmich RC, de Lange FP, Bloem BR, Toni I. Cerebral compensation during motor imagery in Parkinson's disease. Neuropsychologia. 2007 Jan 1;45(10):2201–15.

343. Snijders AH, Leunissen I, Bakker M, Overeem S, Helmich RC, Bloem BR, et al. Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait. Brain. 2011 Jan 1;134(1):59–72.

344. Peterson DS, Pickett KA, Duncan R, Perlmutter J, Earhart GM. Gait-Related Brain Activity in People with Parkinson Disease with Freezing of Gait. PLOS ONE. 2014 Mar;9(3):e90634.

345. Ferraye MU, DebÛ B, Heil L, Carpenter M, Bloem BR, Toni I. Using motor imagery to study the neural substrates of dynamic balance. PLoS ONE. 2014 Mar 24;9(3).

346. Zwergal A, Linn J, Xiong G, Brandt T, Strupp M, Jahn K. Aging of human supraspinal locomotor and postural control in fMRI. Neurobiol Aging. 2012 Mar 7;33(6):1073–84.

347. Dijkstra BW, Bekkers EMJ, Gilat M, de Rond V, Hardwick RM, Nieuwboer A. Functional neuroimaging of human postural control: A systematic review with meta-analysis. Neurosci Biobehav Rev. 2020 Aug 1;115:351–62.

348. Vemuri P, Jones DT, Jack CR. Resting state functional MRI in Alzheimer's disease. Vol. 4, Alzheimer's Research and Therapy. BioMed Central; 2012. p. 2.

349. Wollman DE, Beeri MS, Weinberger M, Cheng H, Silverman JM, Prohovnik I. Tolerance of MRI procedures by the oldest old. Magn Reson Imaging. 2004 Nov 1;22(9):1299–304.

350. Peirce J, Gray JR, Simpson S, MacAskill M, Höchenberger R, Sogo H, et al. PsychoPy2: Experiments in behavior made easy. Behav Res Methods 2019 511. 2019 Feb 7;51(1):195–203.

351. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol. 2013 Sep 18;13(1):117.

352. Poldrack RA, Mumford JA, Nichols TE. Handbook of Functional MRI Data Analysis. Cambridge University Press; 2011. 239 p.

353. Friston KJ, Jezzard P, Turner R. Analysis of functional MRI time-series. Hum Brain Mapp. 1994;1(2):153–71.

354. Worsley KJ, Friston KJ. Analysis of fMRI Time-Series Revisited—Again. NeuroImage. 1995 Sep 1;2(3):173–81.

355. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. NeuroImage. 2002 Jan 1;15(1):273–89.

356. Zhan M, Goebel R, de Gelder B. Ventral and Dorsal Pathways Relate Differently to Visual Awareness of Body Postures under Continuous Flash Suppression. eNeuro. 2018 Feb 13;5(1):ENEURO.0285-17.2017.

357. Lindquist MA, Mejia A. Zen and the Art of Multiple Comparisons. Psychosom Med. 2015;77(2):114–25.

358. Meulen M van der, Allali G, Rieger SW, Assal F, Vuilleumier P. The influence of individual motor imagery ability on cerebral recruitment during gait imagery. Hum Brain Mapp. 2014 Feb 1;35(2):455–70.

359. Zhang W, Low LF, Schwenk M, Mills N, Gwynn JD, Clemson L. Review of Gait, Cognition, and Fall Risks with Implications for Fall Prevention in Older Adults with Dementia. Dement Geriatr Cogn Disord. 2019 Dec 1;48(1–2):17–29.

360. Kearney FC, Harwood RH, Gladman JRF, Lincoln N, Masud T. The Relationship between Executive Function and Falls and Gait Abnormalities in Older Adults: A Systematic Review. Dement Geriatr Cogn Disord. 2013;36(1–2):20–35.

361. Beauchet O, Annweiler C, Callisaya ML, De Cock AM, Helbostad JL, Kressig RW, et al. Poor Gait Performance and Prediction of Dementia: Results From a Meta-Analysis. Vol. 17, Journal of the American Medical Directors Association. Elsevier Inc.; 2016. p. 482–90.

362. Kikkert LHJ, Vuillerme N, van Campen JP, Hortobágyi T, Lamoth CJ. Walking ability to predict future cognitive decline in old adults: A scoping review. Ageing Res Rev. 2016 May 1;27:1–14.

363. Montero-Odasso M, Oteng-Amoako A, Speechley M, Gopaul K, Beauchet O, Annweiler C, et al. The Motor Signature of Mild Cognitive Impairment: Results From the Gait and Brain Study. J Gerontol Ser A. 2014 Nov 1;69(11):1415–21.

364. Tian Q, Chastan N, Bair WN, Resnick SM, Ferrucci L, Studenski SA. The brain map of gait variability in aging, cognitive impairment and dementia—A systematic review. Neurosci Biobehav Rev. 2017 Mar;74:149–62.

365. Wennberg AMV, Savica R, Mielke MM. Association between Various Brain Pathologies and Gait Disturbance. Dement Geriatr Cogn Disord. 2017;43(3–4):128–43.

366. Wilson J, Allcock L, Mc Ardle R, Taylor JP, Rochester L. The neural correlates of discrete gait characteristics in ageing: A structured review. Neurosci Biobehav Rev. 2019 May 1;100:344–69.

367. Lee YW, Lee H, Chung IS, Yi HA, Hu CJ. Relationship between postural instability and subcortical volume loss in Alzheimer's disease. Medicine (Baltimore) [Internet]. 2017 Jun;96(25). Available from: /pmc/articles/PMC5484251/ /pmc/articles/PMC5484251/?report=abstract https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5484251/

368. Surgent OJ, Dadalko OI, Pickett KA, Travers BG. Balance and the brain: A review of structural brain correlates of postural balance and balance training in humans. Gait Posture. 2019 Jun 1;71:245–52.

369. Allali G, Blumen HM, Devanne H, Pirondini E, Delval A, Van De Ville D. Brain imaging of locomotion in neurological conditions. Neurophysiol Clin. 2018 Dec 1;48(6):337–59.

370. Allali G, van der Meulen M, Beauchet O, Rieger SW, Vuilleumier P, Assal F. The Neural Basis of Age-Related Changes in Motor Imagery of Gait: An fMRI Study. J Gerontol Ser A. 2014 Nov;69(11):1389–98.

371. Mouthon A, Ruffieux J, Mouthon M, Hoogewoud HM, Annoni JM, Taube W. Age-Related Differences in Cortical and Subcortical Activities during Observation and Motor Imagery of Dynamic Postural Tasks: An fMRI Study. Neural Plast. 2018 Mar 11;2018:e1598178.

372. Gilat M, Dijkstra BW, D'Cruz N, Nieuwboer A, Lewis SJG. Functional MRI to Study Gait Impairment in Parkinson's Disease: a Systematic Review and Exploratory ALE Meta-Analysis. Curr Neurol Neurosci Rep. 2019 Jun 18;19(8):49.

373. Abidi M, de Marco G, Grami F, Termoz N, Couillandre A, Querin G, et al. Neural Correlates of Motor Imagery of Gait in Amyotrophic Lateral Sclerosis. J Magn Reson Imaging. 2021;53(1):223–33.

374. Nouri FM, Lincoln NB. An extended activities of daily living scale for stroke patients. Clin Rehabil. 1987;1(4):301–5.

375. Gelinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: The disability assessment for dementia. Am J Occup Ther. 1999;53(5):471–81.

376. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc. 2005 Apr;53(4):695–9.

377. CANTAB® [Cognitive assessment software]. Cambridge Cognition; 2019.

378. Berg K, Norman KE. Functional assessment of balance and gait. Vol. 12, Clinics in Geriatric Medicine. W.B. Saunders; 1996. p. 705–23.

379. Bogle Thorbahn LD, Newton RA. Use of the Berg Balance Test to Predict Falls in Elderly Persons. Phys Ther. 1996;76(6):576–83.

380. Podsiadlo D, Richardson S. The timed ‘Up & Go’: a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142–8.

381. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved Assessment of Significant Activation in Functional Magnetic Resonance Imaging (fMRI): Use of a Cluster-Size Threshold. Magn Reson Med. 1995;33(5):636–47.

382. Woo CW, Krishnan A, Wager TD. Cluster-extent based thresholding in fMRI analyses: Pitfalls and recommendations. NeuroImage. 2014 May 1;91:412–9.

383. Degryse J, Seurinck R, Durnez J, Gonzalez-Castillo J, Bandettini PA, Moerkerke B. Introducing alternative-based thresholding for defining functional regions of interest in fMRI. Front Neurosci. 2017 Apr;11(APR):222.

384. Poldrack RA. Region of interest analysis for fMRI. Soc Cogn Affect Neurosci. 2007 Mar;2(1):67–70.

385. Mitsis GD, Iannetti GD, Smart TS, Tracey I, Wise RG. Regions of interest analysis in pharmacological fMRI: How do the definition criteria influence the inferred result? NeuroImage. 2008 Mar 1;40(1):121–32.

386. Kriegeskorte N, Simmons WK, Bellgowan PSF, Baker CI. Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci. 2009 May;12(5):535–40.

387. Vul E, Harris C, Winkielman P, Pashler H. Puzzlingly High Correlations in fMRI Studies of Emotion, Personality, and Social Cognition. Perspect Psychol Sci. 2009 May 1;4(3):274–90.

388. Poldrack RA, Halchenko YO, Hanson SJ. Decoding the Large-Scale Structure of Brain Function by Classifying Mental States Across Individuals. Psychol Sci. 2009 Nov 1;20(11):1364–72.

389. Gentili C, Cecchetti L, Handjaras G, Lettieri G, Cristea IA. The case for preregistering all region of interest (ROI) analyses in neuroimaging research. Eur J Neurosci. 2021;53(2):357–61.

390. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. . New York: Thieme; 1988.

391. Amunts K, Zilles K. Architectonic Mapping of the Human Brain beyond Brodmann. Neuron. 2015 Dec 16;88(6):1086–107.

392. Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage. 2005 May;25(4):1325–35.

393. Eickhoff SB, Paus T, Caspers S, Grosbras MH, Evans AC, Zilles K, et al. Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. NeuroImage. 2007 Jul 1;36(3):511–21.

394. Eickhoff SB, Heim S, Zilles K, Amunts K. Testing anatomically specified hypotheses in functional imaging using cytoarchitectonic maps. NeuroImage. 2006 Aug 15;32(2):570–82.

395. Bhatt T, Patel P, Dusane S, DelDonno SR, Langenecker SA. Neural mechanisms involved in mental imagery of slip-perturbation while walking: A preliminary fMRI study. Front Behav Neurosci. 2018 Sep;12:203.

396. Noohi F, Kinnaird C, De Dios Y, Kofman I, Wood SJ, Bloomberg JJ, et al. Deactivation of somatosensory and visual cortices during vestibular stimulation is associated with older age and poorer balance. Masani K, editor. PLOS ONE. 2019 Sep;14(9):e0221954.

397. Wittenberg E, Thompson J, Nam CS, Franz JR. Neuroimaging of human balance control: A systematic review [Internet]. Vol. 11, Frontiers in Human Neuroscience. Frontiers Media S. A; 2017. p. 170. Available from: www.frontiersin.org

398. Field A. Discovering statistics using IBM SPSS statistics. 5th Edition. London, UNITED KINGDOM: SAGE Publications Inc.; 2018.

399. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis, Second Edition: A Regression-Based Approach [Internet]. New York, UNITED STATES: Guilford Publications; 2017 [cited 2022 May 6]. Available from: http://ebookcentral.proquest.com/lib/nottingham/detail.action?docID=5109647

400. Munn Z, Moola S, Lisy K, Riitano D, Murphy F. Claustrophobia in magnetic resonance imaging: A systematic review and meta-analysis. Radiography. 2015 May 1;21(2):e59–63.

401. Philips, Disney Join Forces to Improve Children's MRI Experience - ProQuest [Internet]. [cited 2022 May 6]. Available from: https://www.proquest.com/docview/2496530932?pq-origsite=gscholar&fromopenview=true

402. Shimokawa K, Matsumoto K, Yokota H, Kobayashi E, Hirano Y, Masuda Y, et al. Anxiety relaxation during MRI with a patient-friendly audiovisual system. Radiography [Internet]. 2022 Apr 13 [cited 2022 May 6]; Available from: https://www.sciencedirect.com/science/article/pii/S1078817422000475

403. Greene DJ, Koller JM, Hampton JM, Wesevich V, Van AN, Nguyen AL, et al. Behavioral interventions for reducing head motion during MRI scans in children. NeuroImage. 2018 May 1;171:234–45.

404. Huff T, Mahabadi N, Tadi P. Neuroanatomy, Visual Cortex. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2022 May 9]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK482504/

405. Hosman T, Hynes JB, Saab J, Wilcoxen KG, Buchbinder BR, Schmansky N, et al. Auditory cues reveal intended movement information in middle frontal gyrus

neuronal ensemble activity of a person with tetraplegia. Sci Rep. 2021 Jan 11;11:98.

406. Bookheimer SY. Precentral Gyrus. In: Volkmar FR, editor. Encyclopedia of Autism Spectrum Disorders [Internet]. New York, NY: Springer; 2013 [cited 2022 May 9]. p. 2334–5. Available from: https://doi.org/10.1007/978-1-4419-1698-3_203

407. Husain M, Nachev P. Space and the parietal cortex. Trends Cogn Sci. 2007 Jan 1;11(1):30–6.

408. Baker DH, Vilidaite G, Lygo FA, Smith AK, Flack TR, Gouws AD, et al. Power contours: Optimising sample size and precision in experimental psychology and human neuroscience. Psychol Methods. 2021 Jun;26(3):295–314.

409. IJmker T, Lamoth CJC. Gait and cognition: The relationship between gait stability and variability with executive function in persons with and without dementia. Gait Posture. 2012 Jan 1;35(1):126–30.

410. Deschamps T, Beauchet O, Annweiler C, Cornu C, Mignardot JB. Postural control and cognitive decline in older adults: Position versus velocity implicit motor strategy. Gait Posture. 2014 Jan 1;39(1):628–30.

411. Lavin C, Melis C, Mikulan E, Gelormini C, HUEPE D, Ibanez A. The anterior cingulate cortex: an integrative hub for human socially-driven interactions. Front Neurosci [Internet]. 2013 [cited 2022 May 9];7. Available from: https://www.frontiersin.org/article/10.3389/fnins.2013.00064

412. Sparto PJ, Rosso AL, Divecha AA, Metti AL, Rosano C. Shared neural substrates of cognitive function and postural control in older adults. Alzheimers Dement. 2020;16(4):621–9.

413. Austin PC, Steyerberg EW. The number of subjects per variable required in linear regression analyses. J Clin Epidemiol. 2015 Jun 1;68(6):627–36.

414. Jalilianhasanpour R, Beheshtian E, Sherbaf G, Sahraian S, Sair HI. Functional Connectivity in Neurodegenerative Disorders: Alzheimer's Disease and Frontotemporal Dementia. Top Magn Reson Imaging. 2019 Dec;28(6):317–24.

415. Di Scala G, Dupuy M, Guillaud E, Doat E, Barse E, Dillhareguy B, et al. Efficiency of Sensorimotor Networks: Posture and Gait in Young and Older Adults. Exp Aging Res. 2019 Jan;45(1):41–56.

416. Yuan J, Blumen HM, Verghese J, Holtzer R. Functional connectivity associated with gait velocity during walking and walking-while-talking in aging: A resting-state fMRI study. Hum Brain Mapp. 2015 Apr;36(4):1484–93.

417. Zhou J, Poole V, Wooten T, Lo OY, Iloputaife I, Manor B, et al. Multiscale Dynamics of Spontaneous Brain Activity Is Associated With Walking Speed in Older Adults. J Gerontol Ser A. 2020 Jul 13;75(8):1566–71.

418. Hsu CL, Voss MW, Handy TC, Davis JC, Nagamatsu LS, Chan A, et al. Disruptions in Brain Networks of Older Fallers Are Associated with Subsequent Cognitive Decline: A 12-Month Prospective Exploratory Study. Maurits NM, editor. PLoS ONE. 2014 Apr;9(4):e93673.

419. Hsu CL, Best JR, Voss MW, Handy TC, Beauchet O, Lim C, et al. Functional Neural Correlates of Slower Gait Among Older Adults With Mild Cognitive Impairment. J Gerontol Ser A. 2019 Mar;74(4):513–8.

420. Crockett RA, Hsu CL, Best JR, Liu-Ambrose T. Resting State Default Mode Network Connectivity, Dual Task Performance, Gait Speed, and Postural Sway in Older Adults with Mild Cognitive Impairment. Front Aging Neurosci. 2017 Dec;9(DEC):423.

421. Crockett RA, Hsu CL, Best JR, Beauchet O, Liu-Ambrose T. Head over heels but I forget why: Disruptive functional connectivity in older adult fallers with mild cognitive impairment. Behav Brain Res. 2019 Dec;376:112104.

422. BRC_Pipeline/BRC_functional_pipeline at master · SPMIC-UoN/BRC_Pipeline · GitHub [Internet]. [cited 2020 Oct 22]. Available from: https://github.com/SPMIC-UoN/BRC_Pipeline/tree/master/BRC_functional_pipeline

423. Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc B Biol Sci. 2005 May 29;360(1457):1001–13.

424. Murphy K, Birn RM, Bandettini PA. Resting-state fMRI confounds and cleanup. NeuroImage. 2013 Oct 15;80:349–59.

425. Nickerson LD, Smith SM, Öngür D, Beckmann CF. Using Dual Regression to Investigate Network Shape and Amplitude in Functional Connectivity Analyses. Front Neurosci [Internet]. 2017 [cited 2022 May 8];11. Available from: https://www.frontiersin.org/article/10.3389/fnins.2017.00115

426. Thomas Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 2011 Sep;106(3):1125.

427. Rudebeck PH, Rich EL. Orbitofrontal cortex. Curr Biol. 2018 Sep;28(18):R1083–8.

428. El-Baba RM, Schury MP. Neuroanatomy, Frontal Cortex. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2022 May 9]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554483/

429. Cole D, Smith S, Beckmann C. Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. Front Syst Neurosci [Internet]. 2010 [cited 2022 May 13];4. Available from: https://www.frontiersin.org/article/10.3389/fnsys.2010.00008

430. DHSC issues guidance on the impact of COVID-19 on research funded or supported by NIHR [Internet]. [cited 2022 Jun 17]. Available from: https://www.nihr.ac.uk/news/dhsc-issues-guidance-on-the-impact-of-covid-19-on-research-funded-or-supported-by-nihr/24469

431. Vahey GM, McDonald E, Marshall K, Martin SW, Chun H, Herlihy R, et al. Risk factors for hospitalization among persons with COVID-19—Colorado. PLOS ONE. 2021 Sep 2;16(9):e0256917.

432. Ko JY, Danielson ML, Town M, Derado G, Greenlund KJ, Kirley PD, et al. Risk Factors for Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization: COVID-19-Associated Hospitalization Surveillance Network and Behavioral Risk Factor Surveillance System. Clin Infect Dis Off Publ Infect Dis Soc Am. 2021 Jun 1;72(11):e695–703.

433. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020 Aug;584(7821):430–6.

434. Beaney T, Neves AL, Alboksmaty A, Ashrafian H, Flott K, Fowler A, et al. Trends and associated factors for Covid-19 hospitalisation and fatality risk in 2.3 million adults in England. Nat Commun. 2022 Apr 29;13(1):2356.

435. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2020 May;94:91–5.

436. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet Lond Engl. 2020 Mar 28;395(10229):1054–62.

437. Semenzato L, Botton J, Drouin J, Cuenot F, Dray-Spira R, Weill A, et al. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. Lancet Reg Health – Eur [Internet]. 2021 Sep 1 [cited 2022 Jun 20];8. Available from: https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00135-6/fulltext#seccesectitle0026

438. Kingston A, Robinson L, Booth H, Knapp M, Jagger C, Project for the M. Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. Age Ageing. 2018 May 1;47(3):374–80.

439. Mutlu J, Landeau B, Tomadesso C, de Flores R, Mézenge F, de La Sayette V, et al. Connectivity Disruption, Atrophy, and Hypometabolism within Posterior Cingulate Networks in Alzheimer's Disease. Front Neurosci [Internet]. 2016 [cited 2022 Jul 11];10. Available from: https://www.frontiersin.org/articles/10.3389/fnins.2016.00582

440. Lin TW, Tsai SF, Kuo YM. Physical Exercise Enhances Neuroplasticity and Delays Alzheimer's Disease. Brain Plast. 2018 Jan 1;4(1):95–110.

441. Lee ES, Yoo K, Lee YB, Chung J, Lim JE, Yoon B, et al. Default Mode Network Functional Connectivity in Early and Late Mild Cognitive Impairment. Initiative ADN, Aisen Ashburner, Bai, Balthazar, Cavanna, Cha, Crane, Damoiseaux, Gibbons, Greicius, Hedden, Jicha, Klunk, Koch, Landau, Lee, Lim, Lim, Machulda, McKhann, Nir, Petrella, Rombouts, Sala-Llonch, Schopf, Shim, Sohn, Sperling, Sperling, Vogt, Wang, Weiner, W A, editors. Alzheimer Dis Assoc Disord. 2016 Oct;30(4):289–96.

442. Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. Trends Cogn Sci. 2013 Oct 1;17(10):502–9.

443. Yoo SW, Han C, Shin J, Seo S, Na D, Kaiser M, et al. A Network Flow-based Analysis of Cognitive Reserve in Normal Ageing and Alzheimer's Disease. Sci Rep. 2015 May 20;5:10057.

444. Anthony M, Lin F. A Systematic Review for Functional Neuroimaging Studies of Cognitive Reserve Across the Cognitive Aging Spectrum. Arch Clin Neuropsychol. 2017 Dec 13;33(8):937–48.

445. Lorey B, Pilgramm S, Bischoff M, Stark R, Vaitl D, Kindermann S, et al. Activation of the Parieto-Premotor Network Is Associated with Vivid Motor Imagery—A Parametric fMRI Study. PLOS ONE. 2011 May 31;6(5):e20368.

446. Zabicki A, de Haas B, Zentgraf K, Stark R, Munzert J, Krüger B. Subjective vividness of motor imagery has a neural signature in human premotor and parietal cortex. NeuroImage. 2019 Aug 15;197:273–83.

447. Passarello N, Liparoti M, Padulo C, Sorrentino P, Alivernini F, Fairfield B, et al. Motor Imagery as a Key Factor for Healthy Ageing: A Review of New Insights and Techniques. Brain Sci. 2022 Nov;12(11):1492.

448. Binney RJ, Pankov A, Marx G, He X, McKenna F, Staffaroni AM, et al. Data-driven regions of interest for longitudinal change in three variants of frontotemporal lobar degeneration. Brain Behav. 2017;7(4):e00675.

449. Roberts R, Callow N, Hardy L, Markland D, Bringer J. Movement Imagery Ability: Development and Assessment of a Revised Version of the Vividness of Movement Imagery Questionnaire. Vol. 30, Journal of Sport & Exercise Psychology. 2008 p. 200–21.

450. Survey cites enhanced patient experience and anxiety reduction as top benefits of Philips Ambient Experience [Internet]. Philips. [cited 2022 Jul 8]. Available from: https://www.philips.com/a-w/about/news/archive/standard/news/press/2021/20210303-survey-cites-enhanced-patient-experience-and-anxiety-reduction-as-top-benefits-of-philips-ambient-experience.html

451. Di Lorito C, Masud T, Gladman J, Godfrey M, Dunlop M, Bosco A, et al. Deconditioning in people living with dementia during the COVID-19 pandemic: qualitative study from the Promoting Activity, Independence and Stability in Early Dementia (PrAISED) process evaluation. BMC Geriatr. 2021 Oct 7;21(1):529.

452. Santy-Tomlinson J. The musculoskeletal implications of deconditioning in older adults during and following COVID-19. Int J Orthop Trauma Nurs. 2021 Jul;42:100882.

453. Harwood RH, Goldberg SE, Brand A, Wardt V van D, Booth V, Lorito CD, et al. Promoting Activity, Independence and Stability in early dementia and mild cognitive impairment (PrAISED): A randomised controlled trial [Internet]. medRxiv; 2023 [cited 2023 Feb 9]. p. 2022.12.20.22283699. Available from: https://www.medrxiv.org/content/10.1101/2022.12.20.22283699v2

454. Lorito CD, Wardt V van der, Pollock K, Howe L, Booth V, Logan P, et al. The facilitators and barriers to improving functional activity and wellbeing in people with dementia: A qualitative study from the Process Evaluation of Promoting Activity, Independence and Stability in Early Dementia [Internet]. medRxiv; 2022 [cited 2023 May 5]. p. 2022.12.20.22283555. Available from: https://www.medrxiv.org/content/10.1101/2022.12.20.22283555v1

455. Clare L, Kudlicka A, Oyebode JR, Jones RW, Bayer A, Leroi I, et al. Individual goal-oriented cognitive rehabilitation to improve everyday functioning for people with early-stage dementia: A multicentre randomised controlled trial (the GREAT trial). Int J Geriatr Psychiatry. 2019 May;34(5):709–21.

10 Appendices

A. Search Strategy

1. Dementia/ or Dementia, Vascular/ or Dementia, Multi-Infarct/
2. Alzheimer Disease
3. Cognition Disorders
4. Memory Disorders
5. Mild cognitive impairment
6. Mild cogniti* impair*
7. Cognitive impairment
8. Cogniti* impair*
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp Exercise Therapy/ or exp Exercise/
11. Physical activity.mp.
12. Leisure Activities/
13. Resistance Training/
14. Dual task training.mp.
15. Functional activities.mp.
16. 10 or 11 or 12 or 13 or 14 or 15
17. Magnetic Resonance Imaging/
18. functional magnetic resonance imaging.mp.
19. MRI.mp.
20. fMRI.mp.
21. Neuroimaging/ or Functional Neuroimaging/
22. 17 or 18 or 19 or 20 or 21
23. 9 and 16 and 22

fMRI Development Study

1.1. Gender:	1 Male	2 Female
1.2. D.O.B	DD/MM/YYYY	

2.0 MRI Tolerability Questionnaire

The following statements are about your experience in the scanner. Please answer by selecting <u>one</u> option for each question.

	Very Uncomfortable (1)				**Very comfortable (5)**
2.1 Overall experience	1	2	3	4	5
2.2 Lying flat on the MRI table	1	2	3	4	5
2.3 Having the technician position you in the MRI	1	2	3	4	5
2.4 Moving into the Machine	1	2	3	4	5
2.5 Confinement inside the MRI	1	2	3	4	5
2.6 Not moving during the scan	1	2	3	4	5
2.7 Noise of the machine	1	2	3	4	5
	Very unpleasant (1)				**Very Pleasant (5)**

2.8 Being alone in the scanner	1	2	3	4	5
2.9 Length of time in the scanner	1	2	3	4	5
2.10 Scanner temperature	1	2	3	4	5
2.11 Scanner smell	1	2	3	4	5
2.12 Post scan dizziness upon sitting	1	2	3	4	5
	Very difficult (1)				**Very easy (5)**
2.13 Ability to see clearly.	1	2	3	4	5

3.0 Do you have any feedback on the video task you completed whilst having your MRI scan? (e.g. how easy it was to imagine it was you, how clear the video was?)

C. PrAISED RCT consent form.

Nottinghamshire Healthcare NHS
NHS Foundation Trust

University of Nottingham
UK | CHINA | MALAYSIA

Nottingham University Hospitals NHS
NHS Trust

PrAISED 2 Consent form MRI
Version: 1.2 Date: 04-04-2019
Promoting Activity, Independence and Stability in Early Dementia (PrAISED2) - MRI study.

Principal Investigator: Dr Kehinde Junaid
IRAS Project Identification Number: 236099

Patient Study ID: _ _ _ _ Patient initials:.....

The participant should initial each box if in agreement. Initial here:

1. I confirm that I have read and understand the information sheet regarding the MRI scan dated 4th April 2019 (version 1.2) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my agreement to undergo the additional MRI scans is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. ☐
3. I understand that even if I withdraw from the MRI part of the above study, the data collected from me will be used in analysing the results of the study, unless I specifically withdraw consent for this. ☐
4. I consent to the storage including electronic, of personal information for the purposes of this study. I understand that any information that could identify me will be kept confidential and that no personal information will be included in the study report or other publication. ☐
5. I understand that the Sir Peter Mansfield Imaging Centre is not a clinical diagnostic facility and so does not routinely inspect images for abnormalities. I understand that my MRI scans will NOT routinely be reviewed by a radiologist (or any other medically qualified person) to look for any signs of disease, and it is unlikely that any abnormalities that may be present will be detected. ☐

PrAISED2 MRI Participant Consent Form V1.2 04-04-2019

Initial here:

6. However, in the event that an unexpected finding is identified on my brain scan by one of the investigators, I agree to my MRI scan data being reviewed by an NHS clinical radiologist and for them to liaise with my general practitioner so that further appropriate tests or treatments can be arranged. In this eventuality, the scan images would be made available to the relevant medical practitioners. ☐

7. I agree to take part in the study. ☐

Name of patient:	Date:	Patient's signature:

Name of researcher:	Date:	Researcher's signature:

When completed: 1 to be kept in care record, 1 copy for patient and 1 copy for researcher site file.

D. NHS/HRA ethical approval

NHS
Health Research Authority

Yorkshire & The Humber - Bradford Leeds Research Ethics Committee

NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Tel: 0207 1048 088

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

01 August 2018

Ms Clare Burgon
Research Assistant
School of Medicine
University of Nottingham
B58 (correspondence to: B114)
Medical School, QMC
Nottingham
NG7 2UH

Dear Ms Burgon

Study title:	**Promoting Activity, Independence and Stability in Early Dementia and Mild Cognitive Impairment 2**
REC reference:	**18/YH/0059**
Amendment number:	**Substantial Amendment 1, 10/07/18**
Amendment date:	**17 July 2018**
IRAS project ID:	**236099**

The above amendment was reviewed at the meeting of the Sub-Committee held by correspondence.

Summary of amendment

This amendment was submitted in order to make various changes relating to: data collection forms, 6 month time point, and MRI sub-study. The study protocol and information sheets have also been update accordingly.

Ethical opinion

The members of the Committee taking part in the review gave a **favourable** ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

A Research Ethics Committee established by the Health Research Authority

E. Amendment approval

NHS
Health Research Authority
Yorkshire & The Humber - Bradford Leeds Research Ethics Committee
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Tel: 0207 104 8079

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

24 January 2019

Ms Rupinder Kaur Bajwa
Research Assistant
Division of Rehabilitation and Ageing
School of Medicine
University of Nottingham
Room B114, Queen's Medical Centre
Nottingham
NG7 2UH

Dear Ms Bajwa

Study title:	**Promoting Activity, Independence and Stability in Early Dementia and Mild Cognitive Impairment 2**
REC reference:	**18/YH/0059**
Amendment number:	**Substantial Amendment 3, 17/12/2018**
Amendment date:	**20 December 2018**
IRAS project ID:	**236099**

The above amendment was reviewed by the Sub-Committee in correspondence.

Summary of Amendment

Submission of this amendment was to make changes to the protocol to provide information on the new recruitment procedure. The recruitment procedure for the MRI sub study had been updated to enable participants to provide consent at the MRI scan appointment.
The MRI participant information sheet had been updated to reflect the change under 'What will happen to me if i take part?'. Contact details had been updated in the participant information sheet and duplicated information had been removed to avoid repetition.
The MRI consent form had been updated to include the most recent version number of MRI participant information sheet.

A Research Ethics Committee established by the Health Research Authority

F. PrAISED MRI information sheet

Nottinghamshire Healthcare NHS
NHS Foundation Trust

University of Nottingham
UK | CHINA | MALAYSIA

Nottingham University Hospitals NHS
NHS Trust

Participant Information Sheet – MRI study

Title of Study: Promoting Activity, Independence and Stability in Early Dementia (PrAISED2) - MRI study.

Principal Investigator: Dr Kehinde Junaid

IRAS Project Identification Number: 236099

PrAISED
Promoting Activity, Independence and Stability in Early Dementia and Mild Cognitive Impairment

You have already been participating in the PrAISED study. As part of this study, we would now like to invite you to have a magnetic resonance imaging (MRI) scan of your brain. Before you decide whether to have the MRI scan, you need to know why we want to do this, and what it will involve.

This information sheet tells you the purpose of the MRI scan, and what will happen if you take part. Take time to decide if you want to take part or not. Discuss it with others if you wish. Please ask us if there is anything that is not clear, or if you need more information.

Why do we want to do an MRI scan as part of the PrAISED study?

The PrAISED team want to find out whether exercise programmes can be beneficial for helping to maintain activity and independence and reduce falls in people with memory problems. We think that some of the positive effects of exercise that we expect to see are due to its positive effects on brain health and functioning. To help us to understand whether this is the case, we would like to perform a MRI scan of the brain. It is important that we scan people who are participating in exercise and those who are not, in order to compare the effect of exercise on the brain. MRI scanning is a widely used and safe method for scanning the brain. We can use MRI to look at both the structure and function of the brain. We think that if exercise has beneficial effects on the brain, then MRI provides a useful way to allow us to see these changes.

In 2018, we tested this type of MRI scan in people taking part in a similar study. We found that participants were happy with the overall scanning experience, and that we could take the measurements that we needed. We now want to test whether the MRI measures of the brain relate to activity, independence and reduction in falls people with memory problems. We will also use this scan to look at brain activity related to walking and balance. This will give us a better understanding of the areas of the brain involved in balance correction when walking.

Why have I been invited to take part?

You have been invited to take part because you are participating in the PrAISED study.

Do I have to take part?

No. It is up to you whether you want to have the MRI scan or not. If you decide to take part, we will ask you to sign an additional consent form to say that you agree to have the MRI scan, and understand what is involved. You are free to withdraw from this part of the study at any time without giving a reason. If you withdraw, we will still use your MRI data, unless you object. If you decide not

to take part, or if you withdraw, this will not affect the quality of any care you receive, and will not affect your participation in the PrAISED study.

What will happen to me if I take part?

You already told the PrAISED researcher who visited you that you were willing to be contacted about the MRI scan. A researcher from the MRI team will be in touch to discuss the study and arrange an appointment for you to attend the Sir Peter Mansfield Imaging Centre **at the Queen's Medical Centre, Nottingham.**

At your appointment, the researcher will discuss the study with you in more detail and the radiographer will check your suitability for the MRI scan. If it is safe for you to have an MRI scan and you are happy to take part in this study, you will be asked to sign a consent form, before you have your scan.

We would like to perform two MRI scans. One will be at the beginning of your participation in the PrAISED study, and one will be 12 months later. By doing two MRI scans, we can look at the effects of the study (therapy package one or two, depending on which group you are in) by comparing the results of the first and the second scan.

This scan is harmless and has no side effects. It will last around 40 minutes in total. If you like, you can bring a family member or friend with you.

We will offer you the opportunity to practice the MRI scan procedure in our MRI simulator. Some people find that this helps them to prepare. Before the scan, the person who will be doing the scan will go through a detailed safety questionnaire with you. This is to make sure that you are safe to have the MRI scan. If there is any possibility that you could have metal fragments in your eyes, we will arrange for you to have an x-ray first.

Before you enter the room where the scanner is, the researcher will check that you have removed all jewellery and loose metal.

You will then have the MRI scan. The MRI scan involveslying on your back in the MRI scanner for around 40 minutes. It is best if you lie as still as possible.

During your scan, there will be a five minute period when we will ask you to imagine walking and keeping your balance. We will not ask you to do any walking tasks or balancing as part of the MRI study, we will just ask you to imagine you are doing this. To help you imagine walking and balancing while in the MRI scanner, we will show you short video clips filmed by someone walking along a corridor, walking around an object, or losing balance. You will watch the videos on a virtual reality headset, which we will ask you to wear throughout your scan. Before your MRI scan, the researcher will show you the video clips so that you have a chance to practice imagining walking and balancing. You can take your time and practice for as long as you need so that you are happy that you understand and feel able to do what we would like you to do during this part of the MRI scan.

Whilst in the scanner you will have protective earplugs on, as MRI scanners can be very noisy. Most people have MRI scans without any difficulty, but if you need to, you can use an emergency buzzer should you wish to stop the scan. **The scanner has an 'Intercom' system, which means you will be able to speak** to the person doing your scan whilst you are in the scanner, should you need to. After the MRI scan has finished, the researcher will ask you some questions about your experience of the scan.

What are the benefits of taking part?

There are no direct benefits for you in having the additional MRI scan. However, this will help us to show that we can use MRI scanning to make useful measurements of brain health in relation to exercise. Some people appreciate having the opportunity to contribute to the well-being of others through research.

What are the possible disadvantages and risks of taking part?

Provided you do not have a condition that prevents you from having an MRI scan, there are no risks associated with this study. Before you have the scan, we will check that you do not have conditions that would prevent you from having an MRI scan.

The MRI scanner is a relatively enclosed space and occasionally participants can feel claustrophobic. If you would like to come out of the scanner at any time, you can request this. If you know that you are claustrophobic, we would advise that you do not participate.

The Sir Peter Mansfield Imaging Centre is not a clinical diagnostic facility and so does not routinely inspect images for abnormalities. The scans in this study are not the same as those performed by specialist doctors for medical purposes. However, there is a chance that your brain scan may show something unexpected that is relevant to your health. If this happens, the scan will be reviewed by a fully qualified clinical radiologist external to the University of Nottingham, and your general practitioner (GP) will be informed so that further investigations can be arranged.

What if there is a problem?

If you have a concern about the MRI scan or what will happen, please speak with the researcher present on the day, or contact a member of the research team prior to your visit, who will do their best to answer your question. Rupinder Kaur Bajwa is a PhD student who can answer any questions you might have about the MRI and the study. Alternatively, you can contact the study manager Dr Sarah Goldberg (who is a nurse) or the main investigator, Professor Rowan Harwood (who is a doctor). Contact details can be found at the end of this information sheet.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Please contact Nottinghamshire Healthcare NHS Foundation Trust - the Patient Experience Team on 0115 993 4542, or email complaints@nottshc.nhs.uk . You can also write to: Patient Experience

Team, Moorgreen House, Highbury Hospital, Highbury Vale, Bulwell, Nottingham NG6 9DR.

In the unlikely event that something does go wrong and you are harmed during the research, there are no special compensation arrangements. If you are **harmed due to someone's negligence**, you may have grounds for legal action for compensation, but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you.

Will my information be kept confidential?

Yes. All the information about you and your participation in this study will be kept confidential. You will not be identified in any reports arising from this research. You will be given a study number, which will be used as a code to identify you on all study forms. The information will be held securely on paper and on computers at the University of Nottingham under the provisions of the General Data Protection Regulation 2018. For more information on how your data will be processed please refer to the Privacy statement at the end of this sheet.

PRIVACY STATEMENT

We will comply with the General Data Protection Regulation 2018. Information about your health is sensitive. We will hold and use the research information we collect from you and your medical records for medical and scientific research. We can use your information legally because a) it is used for scientific research b) it is used in the public interest c) you gave your permission.

We will protect your data using a number to identify you. Your name and address will be held separately and securely. We will use approved physical and computer security measures to keep it private. You have the right to ask us to show you the data we hold, and correct it if it is wrong. We will not use your data if you specifically ask us not to. We will not process the information automatically or use it for profiling. The information will be shared with the therapy team who see you, and the researchers who are collecting and

analysing it. It may also be seen by people working for the Research Sponsor, or the Research Ethics Committee, who are responsible for ensuring that the study is carried out correctly. We will not transfer your information outside the European Union.

At the end of the study, your information will be kept securely for a minimum of 15 years. We will then arrange for confidential disposal. Research information can be useful to other researchers. The research funding body (NIHR) requires us to put your data in a store (the UK Data Archive), where others can use it, in an anonymised form, which means that no-one will be able to identify or contact you if they use it.

We will comply with University of Nottingham privacy policies, which can be found at https://www.nottingham.ac.uk/utilities/privacy/privacy.aspx

Contact for further information

Rupinder Kaur Bajwa
PhD student and Research Assistant
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Email: sarah.goldberg@nottingham.ac.uk

G. PrAISED MRI consent form.

Nottinghamshire Healthcare NHS
NHS Foundation Trust

University of Nottingham
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Nottingham University Hospitals NHS
NHS Trust

PrAISED 2 Consent form MRI

Version: 1.2 Date: 04-04-2019

Promoting Activity, Independence and Stability in Early Dementia (PrAISED2) - MRI study.

Principal Investigator: Dr Kehinde Junaid
IRAS Project Identification Number: 236099

Patient Study ID: _ _ _ _ Patient initials:.....

The participant should initial each box if in agreement. Initial here:

1. I confirm that I have read and understand the information sheet regarding the MRI scan dated 4th April 2019 (version 1.2) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my agreement to undergo the additional MRI scans is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. ☐
3. I understand that even if I withdraw from the MRI part of the above study, the data collected from me will be used in analysing the results of the study, unless I specifically withdraw consent for this. ☐
4. I consent to the storage including electronic, of personal information for the purposes of this study. I understand that any information that could identify me will be kept confidential and that no personal information will be included in the study report or other publication. ☐
5. I understand that the Sir Peter Mansfield Imaging Centre is not a clinical diagnostic facility and so does not routinely inspect images for abnormalities. I understand that my MRI scans will NOT routinely be reviewed by a radiologist (or any other medically qualified person) to look for any signs of disease, and it is unlikely that any abnormalities that may be present will be detected. ☐

Initial here:

6. However, in the event that an unexpected finding is identified on my brain scan by one of the investigators, I agree to my MRI scan data being reviewed by an NHS clinical radiologist and for them to liaise with my general practitioner so that further appropriate tests or treatments can be arranged. In this eventuality, the scan images would be made available to the relevant medical practitioners. ☐

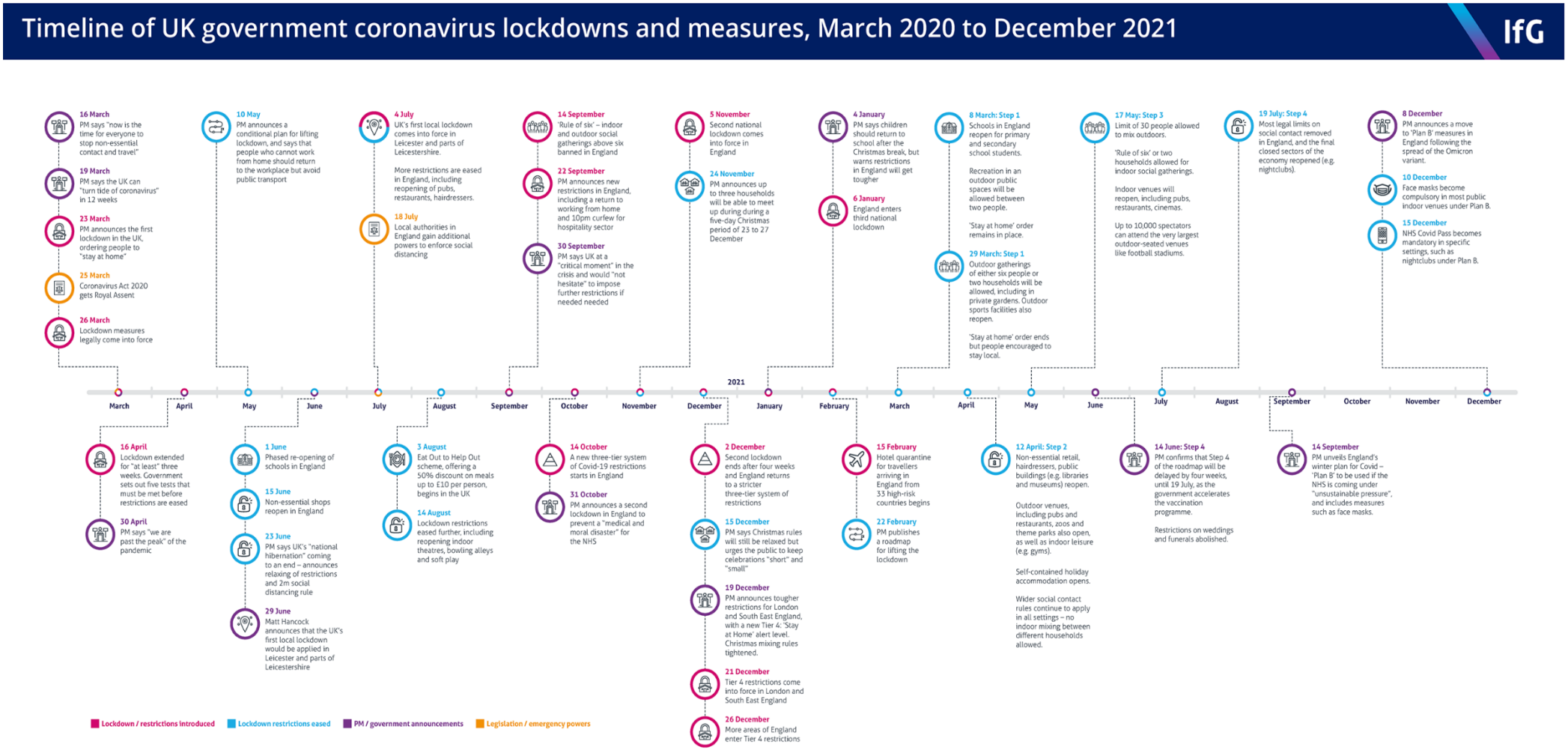
7. I agree to take part in the study. ☐

Name of patient:	Date:	**Patient's signature:**

Name of researcher:	Date:	**Researcher's signature:**

When completed: 1 to be kept in care record, 1 copy for patient and 1 copy for researcher site file.

H. Timeline of UK government COVID-19 lockdowns and measures



Source: Institute for Government analysis.