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Physical and Mental Coordination in the Elderly: A Causal Role for the Cerebellum?

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Abstract

The mechanisms underlying the progressive changes in tissues and organs that characterise normal ageing remain unclear. The cerebellum is known to play a major role in motor function, but recent research suggests it plays an equivalent role in cognition. Working with the hypothesis that cortico-cerebellar loops ensure smooth and coordinated activity in both domains, this thesis investigates the possible role of the cerebellum in normal ageing and in interventions to improve function, seeking to contribute to both theoretical and applied approaches to ageing.

Study one investigated relationships between motor and cognitive function using raw data from a national normative sample of adults aged 16 to 75, employing a test battery assessing motor and cognitive skills. Differences between age groups were demonstrated in some tests of complex processing speed, working memory and executive function, with suggestive evidence that senescence in tests is reflected in tests sensitive to cerebellar function.

Study two refined the battery, while including further measures of motor and memory performance to investigate linkages between cognitive and cerebellar function. Using a sample of 256 older adults, results were variable but provided evidence that pegboard performance could act as a predictor of some cognitive functions.

Study three investigated a proactive intervention for healthy older adults designed to improve cerebellar function, and therefore balance and executive function. This involved an 8-10 week self-administered, internet-based coordinative exercise intervention using a 'cerebellar challenge' suite of graded activities. Performance on a basket of tests was assessed before and after, and also compared with performance changes in a no-intervention control group. Significantly greater benefits for the intervention group than the controls were found for balance physical coordination and controlled information processing.

Overall, these studies support current research indicating cerebellar contribution to both cognitive and motor problems arising in old age, and present evidence that non-verbal memory and controlled speeded information problems may be alleviated through targeted activities affecting cerebellar function improving postural stability and physical coordination.

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1 Chapter 1: Introduction

1.1 Preview

There are many ways in which to describe ageing, but it is characterised by progressive changes in the tissues or organs of the body, leading to a decline in function and death (Balcombe and Sinclair, 2001). Ageing is a hot topic amongst governments worldwide. It is of particular importance here in the UK, with the post war baby boomers now reaching pensionable age, and an ever increasing need to fund pensions. The population is projected to grow by 5.5% over the next 10 years, with the number of people over 85 projected to double to 3.2 million by mid-2041 (Office for National Statistics, 2017). People are living longer, but are not necessarily living 'well' which brings with it an increased burden on NHS resources. Living well, or healthy ageing, can be defined as retaining both physical and mental abilities, to a standard which allows individuals to meet their own basic needs, stay mobile, and contribute to society (World Health Organisation, 2018). On the other end of the spectrum lies pathological ageing, such as seen in dementia, with huge human and economic costs (Prince et al., 2015) Age is a major risk factor for dementia (Launer et al., 1999). With continued pressure on public finances, there is an urgent need for this issue to be addressed. This is a growing concern in western societies that populations continue to age without the infrastructure to support the financial burdens that come with this change. Dementia and Alzheimer's disease not only remained the leading cause of death in England and Wales in 2017, but continued to increase, accounting for 12.7% of all registered deaths (Office for National Statistics, 2018a). While less successful ageing and dementia are separate conditions, they share protective and risk factors. Therefore, there is a strong need to improve diagnosis and treatment possibilities for such conditions in our society.

1.2 Theories of Ageing

Ageing is not a simple concept to define. Technically, we are all ageing from the day we are born, but what is of interest here are the changes which occur in the later years of life, which can be described as a collection of losses in physical, sensorimotor and some (but not all) cognitive abilities (Goodpaster et al., 2006; Schiffman, 1997; West, 1993). Ageing can be described from many perspectives, such as sociological (Joyce & Loe, 2010), psychological (Clarke, Marshall, Ryff, & Wheaton, 2001) or physical (St-Onge, 2005). Before we can describe pathological ageing, we must be able to describe normal ageing. Understanding the links between neural, behavioural, cognitive and social aspects of ageing is central for

modelling these interactions (Ballesteros, Nillson & Lemaire, 2009) and Balcombe and Sinclair (2001) highlighted the need for collaborative research to examine the interaction between different theories of ageing, something that this thesis aims to address. This will be done from the point of view of cerebellar contributions to cognition and ageing, the biological changes seen in the ageing brain, and the relationship of these changes to alterations in sensory, motor and cognitive coordination.

Ballesteros et al. (2009) described cognitive ageing as non-uniform across functions, instead following different patterns of decline, stability, or even gains in some cases across the lifespan. For example, verbal abilities and word knowledge are spared, implicit memory remains stable, but processing speed reduces and reaction times increase with age (Ballesteros et al., 2009). Furthermore, recent advances in neuroimaging techniques have allowed us to understand more about the changes in brain activation associated with ageing. As yet, no single theory has been able to fully account for the variance associated with cognitive ageing across all cognitive domains (Drag & Bueliauskas, 2010). In part, this could be due to the fact that inter-individual variability in cognitive ageing is vast (Cabeza et al., 2018). Several theories are described in this introductory chapter, from micro scale degeneration of brain structure, to functional changes as the human brain ages. While it is important to understand each of these theories in their own right, it is generally accepted that ageing occurs as a result of multiple causes, both environmental (extrinsic) and genetic (intrinsic), which interact with each other (Balcombe & Sinclair, 2001). Therefore, there is the pressing need for a single unifying theory that can explain the interrelated mechanisms of cognitive ageing (Drag & Bueliauskas, 2010).

1.2.1 Age-related Physical Changes in the Brain

Biological ageing involves age-related changes in brain structure at both the macroscopic and microscopic levels, including reductions in brain volume, changes in neuronal connectivity, alongside the accumulation of errors in genetic replication and repair (Baltes, Staudinger, & Lindenberger, 1999). It is generally accepted that the frontal cortex is most affected by these changes, though there is only weak evidence to suggest that other regions are not as vulnerable (Greenwood, 2000). A brief overview of these changes in terms of macro-scale, micro-scale and neurochemical changes is presented next.

1.2.1.1 Macro-scale Changes in Brain Structure

The human brain begins to shrink as we age, at a rate of approximately 5% volume loss per decade after the age of 50 (Trollor & Valenzuela, 2001). Although brain shrinkage is global, the most pronounced shrinkage is found in the frontal lobes; with Balcombe and Sinclair (2001) stating that daily neuronal loss in humans is estimated to lead to a reduction in brain weight of 20% by the age of 90. Atrophy is found in both grey and white mater, with anterior regions showing greater decline than posterior regions (Cabeza, Anderson, Locantore, & McIntosh, 2002; Ballesteros et al., 2009.) Raz et al. (2005) reported that shrinkage in the hippocampus and cerebellum accelerated with age. Theories for how the brain responds to this atrophy and the behavioural impact are discussed later in this chapter.

1.2.1.2 Micro-scale Changes in Brain Structure

At a microscopic level, physical changes in the brain include demyelination, , synaptic degeneration, blood flow reductions, white matter hyperintensities in MRI and neurochemical alterations, while senile plaques and neurofibrillary tangles signal pathological ageing (Trollor & Valenzuela, 2001; Cabeza, Anderson, Locantore, & Mcintosh, 2002; Charlton et al., 2006). Changes in relation to specific domains pertinent to motor performance have also been described in terms of normal ageing. For example, Sullivan, Rohlfing and Pfefferbaum (2010) reported greater transverse diffusivity of cerebellar fibre bundles, an index of myelin integrity, which they found contributed to slower finger movements. Rogalski et al. (2012) reported age-related micro-structural changes in parahippocampal white matter (PWM) fibres, important for memory performance. They reported that PWM volume (along with verbal recall and PWM fractional anisotropy) significantly predicted young or old group membership, suggesting that these age-related differences could be due to pruning of fibres, axonal loss or partial demyelination (Rogalski et al., 2012). Hughes et al (2012) report microstructural changes in the thalamus and thalamo-cortical networks, having found that the volume of thalamo-frontal projections decreased significantly with age and that the greatest shape change was in the anterior thalamus. They suggested that these changes could potentially lead to disorders of attention, working memory, and executive functioning (Hughes et al., 2012). This is by no means an extensive list; rather an illustration of the fact that the different types of degeneration (vs pathology) seen in the ageing brain is well established. What is less certain is what this means functionally for the ageing human brain.

1.2.1.3 Neurochemical Changes

The neurobiological mechanisms underlying progressive, variable cognitive decline remains uncertain (Charlton, McIntyre, Howe, Morris & Markus, 2007), though various chemical differences between older and younger adults have been characterised, which are briefly described here. Enna (1981) describes a number of age-related, brain region specific changes in ageing, citing differences in a number of neurotransmitter synthesizing enzymes such as choline acetyltransferase and glutamic acid decarboxylase, suggesting that this could lead to decreases in receptor binding in areas such as the cerebellum, brain stem and cerebral cortex. More recently, dopamine dysregulation (a dysfunction of the reward system), acetylcholine and calcium signalling have all been implied in declines in aspects of cognition in ageing (Drag and Bieliauskas, 2010; Agatonovic-Kustrin, Kustrin & Morton, 2019; Chandran et al., 2019). These neurochemical changes are widely supported as playing a role in age related cognitive decline, though Charlton et al. (2007) found no age related decline in N-acetylasperate, a marker of neuronal function, which argues against axonal loss with age. This suggests, as is often reported, that there is still a long way to go in understanding the neurochemical changes underlying functional deficits in ageing. What seems clearer however is that as we age, the transmission of information becomes less efficient due to declines in neuromodulation, and this has widespread repercussions for cognition (Drag & Bieliauskas, 2010). Nevertheless, this is not the case for everyone.

1.2.2 Models of Cognitive Ageing

The general consensus is that there is no single unifying model that fully explains cognitive ageing, but that there is desperate need for one. This section describes the competing theories that have been put forward, with a view to bring them together, in order to identify a single, testable predictor of cognitive decline.

1.2.2.1 The Frontal Lobe and Inhibitory Control Hypotheses.

The frontal lobe ageing hypothesis is based on the knowledge that this is the region that shows the most atrophy with ageing, and suggests that cognitive abilities supported by it decline earlier than functions supported by other regions (West, 1996). Many frontal- and prefrontal-based processes, such as strategy initiation and long-term memory retrieval, do indeed show marked decline in normal ageing (Drag & Bieliauskas, 2010). Albinet, Boucard, Bouquet, and Audiffren (2012) suggest that frontal lobe theories state that specific declines in

executive abilities lead to more general cognitive deficits, as a result of local structural and functional changes in frontal cortex areas

One explanation for this comes from the inhibitory control hypothesis, which suggests that while the frontal lobes are heavily involved in the ability to effectively inhibit or suppress irrelevant or distracting information to the present task; age-related deficits in this region mean that this is not carried out with enough efficiency in older age (Dempster, 1992). This difficulty means that tasks involving executive functions, such as problem solving or selective attention are more effortful, as the individual is required to sustain goal directed activity (Drag & Bieliauskas, 2010). Furthermore, this framework also fits in with the processing speed hypothesis (discussed in more detail later in this chapter) by suggesting that deficits in inhibition reflect the deficits in processing efficiency, to ignore irrelevant stimuli with increasing task complexity (Dempster, 1992).

The idea that frontal and prefrontal regions are most susceptible to the effects of ageing is challenged by Greenwood (2000) who states that the evidence to support this is weak, going on to suggest that functions such as visuospatial attention that is dependent on parietal or face recognition which is dependent on temporal cortices, and are largely independent of prefrontal areas, are also significantly impaired. It is this argument that has continued to gather strength over the last few decades, calling for multiple theories to be combined in order to provide a more holistic view.

1.2.2.2 Compensatory Ageing Models

As an alternative explanation for the cognitive changes associated with ageing, Greenwood (2000) argues that a network-based theory is advantageous over a localised approach—such as the frontal lobe theory—citing differences in activation patterns between older and younger adults in executive functioning tasks to support this approach.

Reuter-Lorenz and Cappell (2008) suggested that the age-related under-activation identified by brain imaging techniques is typically interpreted as a sign of impairment due to poor or underutilised strategies or due to structural changes, such as atrophy. They also go on to state that the over-activation seen in ageing is more ambiguous, asserting that as over-activation has been found across a range of brain regions and is not always related to age differences, that it is highly unlikely that the instances seen in cognitive ageing all stem from a single source (Reuter-Lorenz and Cappell, 2008). Ballesteros et al. (2009) suggest that the additional recruitment of anterior brain regions as identified by functional imaging studies

implies flexibility and reorganisation of neural networks with ageing, a marker of brain adaptation. However, Drag and Bueliauskas (2010) note that these frontal activation patterns tend to be less specific in older age, and when this is coupled with declines in neural integrity lead to reduced specialisation of task specific behaviours. This phenomenon is still not fully understood (Hubert et al., 2009) and several concepts to describe the patterns of under- and over-activation in ageing have been put forward. The leading theories will be discussed in the subsequent two subsections.

1.2.2.3 The HAROLD and CRUNCH Models

One of the models put forward to describe the changes in patterns of brain activation in ageing comes from Roberto Cabeza. He describes the hemispheric asymmetry reduction in older adults (HAROLD) model, and states that under similar circumstances, prefrontal activity during cognitive performances tends to be less lateralized in older adults than in younger adults (Cabeza, 2002). The idea here is that there is a type of compensatory process going on, to counter-act age-related cognitive decline, although Cabeza also points out that may be a dedifferentiation process occurring instead. That is, that older adults show more difficulty in recruiting specialized neural mechanisms. However, it is unclear as to whether this process reflects regional (local brain changes independent of task) or network (task-specific) mechanisms (Cabeza, 2002).

In response to the compensatory idea suggested by the HAROLD model, Berlingeri suggests that HAROLD-like patterns could be conceptualised as a special manifestation of age-related compensatory processes triggered by the specific task demands (Berlingeri, Danelli Bottini, Sberna & Paulesu, 2013). Her group found HAROLD-like effects outside of the prefrontal cortex, and suggested a more general model for the age-related activation changes found. The compensation-related utilisation of neural circuits hypothesis (CRUNCH) suggests that elderly subjects recruit additional brain regions that do not necessarily belong to the contralateral hemisphere as much as they rely on additional strategies to solve cognitive problems (Berlingeri et al., 2013).

1.2.2.4 The PASA Model

Furthering the idea of compensatory processes occurring in ageing, the posterior-anterior shift in ageing (PASA) model was also suggested by Cabeza's lab. They suggested that older adults recruit anterior regions to compensate for sensory processing deficits in

occipitotemporal regions (Davis, Dennis, Daselaar, Fleck & Cabeza, 2008). They suggested that this pattern is well established in the literature, and found to exist over a variety of cognitive functions, but also that PASA describes a pattern of deactivations as well as activations, something that cannot be overlooked. It is possible that greater anterior midline deactivations in older adults may free up processing resources for the engagement of greater frontal activity (Davis et al., 2008).

Understanding the patterns of change in activation that occur with ageing is crucial to designing suitable interventions to help stave off the cognitive declines associated with old age. As Reuter-Lorenz and Cappell (2008) point out, training, exercise and other interventions applied in older age or throughout the life course may increase available resources and compensatory potential.

1.2.2.5 Processing Speed Theory of Ageing

Processing speed refers to the efficiency with which a series of items with simple cognitive content can be completed (Deary, Johnson & Starr, 2010). The processing speed theory of ageing argues that age-related cognitive declines can be accounted for by a single, global mechanism: the generalized slowing of cognitive processes (Salthouse, 1996; Albinet et al., 2012). Ren, Wu, Chan and Yan (2013) attribute this slowing in processing speed to degradation of white matter in anterior parts of the brain. However, Yang, Bender and Raz (2015) found that in healthy adults, age differences in normal-appearing white matter diffusion properties are not a major contributor to age differences in speed of processing. So while ageing is reliably associated with a general slowing of processing speed, the neural substrates behind this remain unclear.

There is strong evidence to support the notion that deficits in processing speed can be associated with impairments in various cognitive functions, such as language deficits and working memory tasks (Drag & Bieliauskas, 2010; McKinlay, Darlymple-Alford, Grace, & Roger, 2009; Greenwood, 2000: Park, Lautenschlager, Heddon, Davidson, Smith, & Smith, 2002.) Salthouse (1996) suggested that this singular mechanism that has such wide reaching implications for cognition could be split in to two further mechanisms; limited time and simultaneity. The time-limited mechanism suggests that for brain processes that are time-limited, relevant operations cannot be executed efficiently enough within that time, which then means that products of earlier processing are not available when needed in later stages of processing (simultaneity; Salthouse, 1996). Therefore, the fact that the many compensatory

models of ageing fail to take this shortfall into account, perhaps in itself explains why no single unifying theory has been put forward that dully describes the effects of ageing with sufficient wholeness.

While both the compensatory-style and processing speed theories are plausible, a more holistic approach would be to include them both. Albinet, et al. (2012) reported that while they share mutual variance, processing speed and executive function measures were independently affected by age, and that the adverse effect of ageing was more important for processing speed than executive function. More than just explaining cognitive decline, Deary et al. (2010) conclude that processing speed should be considered as a biomarker of cognitive ageing, and that it could be seen as an indicator of a more general cognitive system state. Moreover, this is likely to be independent of education (Bellasteros et al., 2009). Caution is urged when interpreting these results, with several studies reporting that although speed changes still explain a large portion of the variance, by using cross-sectional rather than longitudinal data, this is likely to be overestimated, and additional factors must be taken into account (Sliwinski & Buschke, 1999; Lemke & Zimprich, 2005; Drag & Bueliauskas, 2010). Despite this caution, the evidence to date suggests a compelling argument for including the processing speed theory in any global theory of cognitive ageing.

1.2.2.6 Fronto-cerebellar Theory of Ageing

One of the most striking observations of the literature in this area is the general disregard for the cerebellum as an important structure in cognitive ageing, a view echoed by Hogan (2004), who reported that the cerebellum is often left out of imaging studies, despite it modulating sensorimotor and cognitive efficiency. For example, A diffusion tensor imaging (DTI) study investigating executive function, processing speed and memory did not look at cerebellar structures (Sasson, Doniger, Pasternak, Tarrasch & Assaf, 2012), and Cherubini, Peran, Caltagirone, Sabatini and Spalletta (2009) did not include the cerebellum in their investigation into the ageing of subcortical nuclei. Additionally, it can be argued that none of the compensatory models, or the frontal lobe theory, fully describes the neural decline experienced in ageing. Hogan's (2004) fronto-cerebellar theory of ageing attempts to provide a neural explanation for the differences experienced which includes the processing speed theory of ageing, and takes the cerebellum's contribution to cognition into account.

A cerebro-cerebellar circuit involving complex connectivity with multiple subcortical structures is well established (Buckner, 2013) and it could in fact be the degeneration of this

network with age that underlies some of the associated cognitive decline. Fjell, Sneve, Grydeland, Storsve and Walhovd (2017) found that executive decline with age was greater than what could be attributed to processing speed alone, and that the major part of this decline was explained by connectivity markers. They reported that 82.5% of the age-related executive function reductions they found could be explained by putamen-cortical resting state functional connectivity, diffusion-based structural connectivity and white matter volume combined (Fjell et al., 2017).

Frontal and cerebellar grey matter systems may predict age-related variation in processing speed (Eckert, 2011), but connectivity of the cerebellum with other brain regions could have far reaching implications for cognitive decline as we age. Koppelmans et al. (2015) reported that the more efficient neural organisation of the cerebellar hemispheric white matter, rather than volume, could result in better motor performance. The authors suggested that the structural connectivity between the cerebellum and other brain regions played a major role, and therefore opens the possibility of the same patterns being seen for cognitive functions as well. It is thought that the cerebellum mediates cortical information processing via closed cortico-cerebellar loops between the cortex, pons, cerebellum and thalamus, with strong connections between the lateral prefrontal cortex and cerebellum also reported (Bellebaum & Daum, 2007). The authors suggest that it is likely that these circuits are involved in processing for many cognitive domains, including memory and spatial perception (Bellebaum & Daum, 2007). Taken together, it could be surmised that cerebellar connections not only play a vital role in cognition, but that disruption of these networks can account for some of the difficulties experienced with advancing age. This is precisely the argument of the fronto-cerebellar theory of ageing; that cerebellar degeneration and disruption of fronto-cerebellar control loops may be of central importance to understanding age-related changes, not only in processing speed, but in cognitive functions as well (Hogan, 2004).

1.3 Domain Specific Ageing: Cognition

This section aims to provide an overview of age-related changes which occur in specific functional domains, moving away from a characterisation of general decline in physical and cognitive ability to look at distinct aspects of this decline in more detail. Some abilities are largely unaffected by the ageing process while others show sharp decline, and there are many variables, such as education, intelligence and sensory abilities, that can affect cognitive

ageing (Treitz, Heyder & Daum, 2007; Drag and Bieliauskas, 2010). Moreover, abilities that are independent in young adults tend to become interrelated in older age, and some aspects of cognitive ageing start between the ages of 20 and 30 (Drag & Bieliauskas, 2010; Salthouse, 2009).

1.3.1 Executive Functioning

Executive functions are general cognitive processes that support strategic organisation and control other processes important to complex, goal-oriented tasks (Buckner, 2004). Older adults have been found to have difficulty with task switching, problem solving and information manipulation (Drag & Bueliauskas, 2010; Troller & Valenzuela, 2001; Greenwood, 2000). Each of these functions are described in more detail in the following subsections. It is thought that executive functions use large amounts of information, and that decline in older age is a result of change in frontal-striatal circuits, consistent with the frontal lobe ageing hypothesis. (Drag & Bieliauskas, 2010; Buckner 2004). This was supported by Elderkin-Thompson, Ballmaier, Hellemann, Pham and Kumar (2008), who found that variability in executive function performance, was better explained by prefrontal structural brain volume than by chronological age. Drag and Bueliauskas (2010) suggest that aging reduces an already limited supply of cognitive processes, which is what results in deficits during demanding cognitive tasks. While it is agreed that executive functioning declines with age, quite how this manifests for each of the executive subcomponents is less clear (Treitz, Heyder & Daum, 2007).

1.3.1.1 Fluid and Crystallised Abilities

Cattell (1943) described adult mental capacity as two distinct types, 'fluid' and 'crystallised' abilities. "Fluid" intelligence refers to the ability to adapt to novel situations and problem solve, while "crystallised" intelligence refers to learned intellectual skills, and remains stable or shows minimal decline even up to the eighth decade of life. (Zec, 1995; Trollor & Valenzuela, 2001). On the other hand, fluid intelligence begins to decline from the age of 50, and as a result, speed of information processing, working memory, and complex attention are particularly affected (Trollor & Valenzuela 2001). In terms of cognitive conceptual structures, this distinction corresponds roughly to that between automatic (without conscious effort) and controlled (conscious control and attention) processes (Shiffrin & Schneider, 1977) and hence to cognitive resources. Cattell (1943) stressed the need to test

both fluid and crystallised abilities if performance in different situations is to be reliably predicted when it comes to adult intelligence.

Both fluid and crystallised abilities rely on the interplay between various other functions, such as memory and language, which are each discussed in turn below. As previously discussed, functional connectivity between brain regions may be the key to understanding cognitive decline, with cerebellar function again providing a potential explanation as to the age-related changes seen in these abilities. Leggio, Silveri, Petrosini and Molinari, (2000) demonstrated that cerebellar patients had difficulty with word tasks involving unusual and novel searching strategies, while tasks that relied on well-known and usually employed strategies performed as well as controls. These results mirror what is seen in normal ageing; declines in fluid intelligence, while crystallised intelligence is largely spared, thus providing support for the fronto-cerebellar theory of ageing.

1.3.1.2 Attention

Attention is required in order for us to carry out many everyday tasks, such as crossing the road, and is especially important if trying to do two things at once. Moreover, attentional declines in ageing are reflected in declines in working memory and executive functions (Rodrigues-Aranda et al., 2016). There are various aspects of attention, which are each affected by ageing in different ways. Sustained attention is relatively unaffected by normal ageing, while selective attention (the ability to ignore irrelevant information) is thought to be age-sensitive, and divided attention and task-switching also show age effects (Beradi, Parasuraman & Haxby, 2001; Plude & Doussard-Roosevelt, 1989; Kramer, Hahn & Gopher, 1999). However, it is generally believed that in situations with low attentional demands, older adults do not present any particular difficulties in comparison to their younger counterparts; it is instead the overall task complexity that is of importance (McDowd & Craik, 1988; Andres, Guerrini, Phillips & Perfect, 2008). This was supported by West (1996) who suggested that the ability to maintain focused attention over an extended time period in a resource-demanding task is susceptible to the effects of increasing age. Taken together, it is clear that declines in attentional control have wide reaching implications for cognition, with working memory and executive functions being particularly susceptible (Rodrigues-Aranda et al., 2016).

1.3.1.3 Working Memory

Memory deficits are one of the first functions people worry about in terms of pathological ageing, with the Alzheimer's Society specifically targeting their information to meet this concern (Alzheimer's Society, 2017). However, it is likely that more subtle deficits exist long before there are any noticeable changes, with high education acting as a cognitive reserve buffer. Cognitive reserve can be described as the brain's resilience to neuropathological damage, and describes a framework for understanding how the brain responds to challenge and pathology (Devita et al., 2020; Stern, 2002). Moreover, defining memory as a unitary construct is not particularly accurate, and ageing has differential effects on specific aspects of memory; it is likely that older adults have difficulty with both the encoding of new information, as well as the retrieval of previously experienced events and learned facts (Drag & Bueliauskas, 2010). Procedural memory (i.e. for of automatic processes, such as tying a shoelace) appears to be relatively spared with ageing (Ballesteros et al., 2009). Various parts of the brain have been implicated in these memory problems; the medial temporal lobes, prefrontal cortex, parietal regions, the middle and superior temporal gyrus, and of course the hippocampus (Ballesteros et al., 2009; and for a review of this literature, see Drag & Bueliauskas, 2010). Patterns of decreased functional activity (particularly in frontal regions), and bilateral activation in older adults (in comparison to unilateral activation in younger adults), lend support to both the frontal lobe and compensatory models of cognitive ageing (Drag and Bueliaskas, 2010). However, these theories do not fully explain the deficits seen in working memory, which can be classified as an executive function, but also relies on the processes of encoding and retrieval which has a memory component and is affected by slowed processing speed (Greenwood, 2000; Baddeley, 1992). Although imaging studies reveal prefrontal activation while information is held in working memory, posterior areas have also shown an association, highlighting the need for better understanding of the underlying circuitry that connects these regions (Greenwood, 2000).

Working memory is presented here as distinct from other types of memory process, as it comprises short term memory storage and manipulation of information which is where executive functions come in to play. It involves maintaining information for immediate processing (Reuter-Lorenz & Park, 2010), and is a system that is essential for complex planning and monitoring of actions (Strauss, Sherman & Spreen, 2006, cited in Rodriguez-Aranda et al., 2016). Working memory may be more sensitive than short-term memory to the effects of ageing (Bopp & Verhaeghen, 2005), possibly as a result of difficulties in both the

storage and (speed dependent) processing components needed simultaneously, as the older adult struggles to meet the complex demands on their mental capacity (Babcock & Salthouse, 1990).

It is thought that both the amount needing to be remembered and processing demands contribute to working memory independently (Salthouse, Babcock & Shaw, 1991), and that age-related declines in these processes can be attributed to both slowed processing speed and reduced visual acuity (Salthouse, Hancock, Meinz & Hambrick, 1996). The authors go on to suggest that this may be representative of an age-related general reduction in central nervous system functioning (Salthouse et al., 1996). This idea is supported by Charlton et al. (2006), who suggest that the complex network important for working memory may be particularly dependent on the integrity of white matter connections, and that degradation of any component of this network could lead to a reduction in working memory. A review by Greenwood (2000) concluded that regional activation patterns during working memory tasks consistently showed differences between young and old adults, suggesting that a network-based theory of cognitive ageing is perhaps more appropriate to describe age-related changes than the frontal ageing hypothesis. The aim of this review was to evaluate the frontal ageing hypothesis, and therefore no clear alternative is proposed, leaving the question as to what this network-based theory might look like.

Several issues are raised by the literature: firstly, that aspects of memory performance are unexplained by the current leading models; secondly, the need to identify memory difficulties before a tangible deficit is observed; and thirdly, that general intelligence (defined as representing general abilities that together constitute the intelligence quotient; Sternberg, 2000) may act as a buffer. The first point has been discussed in relation to working memory, and other aspects are discussed in the subsection below. The second issue is emphasised by the fact that a general, rather than localised, mechanism for decline is likely to underlie declines in working memory, which has wide reaching implications for all aspects of cognition and quality of life as we age. It highlights the importance of this thesis in working to create a predictive test battery, and providing interventions to appropriately support those in need. The third issue is something that needs to be taken into account as the battery and interventions are designed.

1.3.1.4 Memory

Memory is not a unitary construct, with each aspect differentially affected by the ageing process. Nilsson (2003) concludes that clear age deficits exist in episodic memory, but that the same cannot be said for semantic, short-term and perceptual representation systems. It is suggested that poor memory in older adults is partially reflective of deficient encoding strategies, and that the greatest effect is seen in long-term episodic memory (Reuter-Lorenz & Park, 2010). As previously discussed, fluid intelligence is age sensitive, while crystallised intelligence remains fairly stable. As a result, any impairment in semantic knowledge is usually reflective of problems with retrieval in older age (Drag & Bueliauskas, 2010).

Specific structures and connectivity has been associated with age-related changes in the memory domain. In addition to known age-related structural changes in the hippocampus (Drag & Bieliauskas 2010), Ballesteros et al. (2009) noted that although implicit memory appears stable and the structural perceptual object recognition system is spared with age, the episodic memory system that relies on the medial-temporal lobe is impaired. Rogalski et al. (2012) suggests that age-related decline in memory performance may partly be a consequence of a partial disconnection in the flow of information from the entorhinal cortex to the hippocampus via the perforant pathway.

Changes in the memory domain may also strongly relate to the notion of cognitive reserve. Education primarily affects memory performance in tasks with high strategic demands. High levels of education may be a proxy indicator of cognitive reserve and higher cognitive reserve implies more resources (in terms of resilience to neuropathological damage, and responding to challenges and pathology) and therefore ageing individuals take longer to reach a critical threshold where deficits start to appear. (Drag & Bieliauskas 2010). Changes in memory performance may also relate to affective changes: Ballesteros et al. (2009) highlight that age-related changes in emotional processing influence the types of information that are remembered best.

1.3.1.5 Language

Failure to produce a word is often reported as a cognitive problem in older adults (Burke & Shafto, 2004). Many language abilities are maintained in normal ageing, therefore it is thought that the difficulties that arise in some from problems with retrieval, and that these failures become more likely with age (Burke & Shafto, 2004; Mortensen, Meyer & Humphreys, 2006). Meijer, de Groot, van Gerven, van Boxtel and Jolles (2009) suggested

that when it comes to deep processing tasks, age-related cognitive decline already exists in middle age. Therefore, decline in language abilities may be a good indicator of wider cognitive problems.

Recall for words is worse in older than younger adults, with tip-of the-tongue (TOT) experiences, in which a word is known but cannot immediately be retrieved from memory, often reported more frequently with increasing age (Salthouse & Mandell, 2013; Burke, MacKay, Worthley, & Wade, 1991). This experience is possibly as a result of age-related weakening of connections between lexical and phonological nodes (Burke, MacKay, Worthley & Wade, 1991). Atrophy of the left insula, important for phonological production, has been implied as a potential cause for some of these retrieval difficulties (Shafto, Burke, Stamatakis, Tam, & Tyler (2007). However, it is suggested that changes in frontal or sensory processes may account for other language difficulties (Drag & Bueliauskas, 2010). This is supported by the view that the age-related decrement in strategic organisation is due to a decrease in cognitive flexibility (Ballesteros et al., 2009). Taken together, these findings suggest that more general declines in cognitive ageing are accountable for the resulting langue difficulties seen in older age, rather than difficulties with language itself.

1.3.1.6 Visuospatial Functioning

While visuospatial functioning declines with age, it is unclear whether this is because this type of information is sensitive to the ageing process, or rather as a result of the information being complex and therefore more susceptible to ageing affects, perhaps as a result of changes in frontal functions such as working memory (Drag & Bueliauskas, 2010). However, Greenwood (2000) reports that frontal activation during visuospatial attention tasks may occur in conjunction with eye movements (the prefrontal motor cortex activation seen in imaging studies may relate to saccadic eye movements), with visuospatial attention largely mediated by non-frontal areas, in particular the posterior parietal cortex and pulvinar. As a result, it can be concluded that visuospatial functioning may again represent a complex cognitive function, where the frontal ageing hypothesis is not sufficient to explain the age related difficulties experienced. Instead, a failure of the connections between the various parts of the brain required to execute this function efficiently, could provide a plausible explanation for the deficit.

1.4 Domain Specific Ageing: Motor Function

Wu, Zang, Wang, Long, Li and Chan (2007) suggested that the ageing process may disrupt the function of motor areas in the resting state, which may contribute to the declined motor ability in an aged population. Regional homogeneity of blood oxygen level dependent (BOLD) signals was found to be significantly decreased in motor regions, including in the cerebellum in aged subjects. In relation to this, Mattay et al. (2002) found that additional cortical and subcortical areas were recruited for the performance of simple motor tasks in elderly, relative to younger subjects. The authors suggest that this indicate the involvement of compensatory mechanisms associated with ageing, specifically reorganization and redistribution of functional networks in response to altered brain structure and neurochemistry. There is also evidence of microstructural damage (likely axonal, in afferent and efferent connections of the cerebellum) in ageing (Cavellari et al., 2013) and age-related atrophy of motor cortical and cerebellar structures (Koppelmans, Hirsiger, Mérillat, Jäncke, & Seidler, 2015), which may contribute to declined motor function that can be seen across a range of tasks. The following subsections consider changes in function in specific motor task domains.

1.4.1 Manual Dexterity

Manual dexterity can be defined as the ability to accurately and rapidly control finger movements, in a coordinated and adaptive manner (Carment et al., 2018); a function that declines with age. While this is recognised as part of normal ageing, it is important to examine when this goes beyond the physical difficulties of loss of hand/ finger strength, and instead reflects a cognitive problem over and above the general decline in attention expected (Rodrigues-Aranda, Mittner & Vasylenko, 2016; Kluger et al., 1997). It has been suggested that older adults rely on cognitive processes to control skilled hand movement more than their younger counterparts, and therefore that motor tests are actually able to distinguish between normal ageing, mild cognitive impairment and mild Alzheimer's disease (Vasylenko et al., 2018b; Kluger et al., 1997). Curreri et al. (2018) suggested that difficulties with fine motor skills were more than just able to distinguish between healthy and pathological ageing, but actually predictive of cognitive impairment. The authors stated that straightforward methods such as pegboard tasks could be used to evaluate visuomotor coordination and processing speed, as well as fine motor coordination, demonstrating the ease with which motor tests could be incorporated into current testing batteries (Curreri et al., 2018). Moreover, these

tests are likely to be independent of level of education, so may have a particular benefit in detecting potential decline in poorly educated adults (Kluger et al., 1997).

The leading suggestion as to why fine motor control is not only a good indicator of cognitive decline, but also a good predictor, cites cerebellar function as the crucial component. Koppelmans, Hirsiger, Mérillat, Jäncke and Seidler (2015) report significant positive relationships between performance on pegboard tasks and cerebellar volume, suggesting that less white matter cerebellar volume could represent lower qualitative connections with other brain regions, which in turn results in worse performance. This is not overly surprising given the cerebellum's well established role in motor function. However the idea that testing the cerebellum in order to investigate more widespread relationships to function in other domains, is of interest in predicting cognitive decline across a wide range of domains.

1.4.2 Postural Stability

Older adults have been shown to have diminished postural control, and again it is the neural mechanisms underlying this that are of importance. While physical factors such as musculoskeletal and joint weakening are associated with normal ageing, postural control also relies on visual, vestibular, haptic, proprioceptive and cerebellar systems (Sullivan, Rose, Rohlfing & Pfefferbaum, 2009; Du Pasquier et al., 2003). Teasdale, Stelmach & Breunig (1991) reported that older adults used compensatory sensory mechanisms to correct for disruption of just one sensory output, but that disruption across this complex network seriously degraded balance control in older adults, in comparison to their younger counterparts. Seidler et al. (2010) suggest describe postural control as representing a complex interplay between the sensory and motor system, while putting forward the hypothesis that motor control becomes more reliant on central mechanisms with age. Cerebellar contributions to the motor system are already well established, with Hogan (2004) suggesting that the aging of this structure leads to the decoupling of previously automatic functions, as is seen in the case of postural stability, where a complex network fails to execute efficiently. Together, the evidence suggests that there is no singular mechanism underlying the decline in postural stability seen in older adults, but it is instead the failure in the ability to integrate multiple systems in a way that was previously automatic that leads to difficulty in maintaining balance. As automaticity of skill is widely accepted as being a

cerebellar function (Nicolson & Fawcett, 2005) it logically suggests that the cerebellar deficits seen in ageing would contribute to declines in postural stability.

1.5 Domain Specific Ageing: Sensorimotor

In comparison to the considerable attention paid to frontal- and prefrontal executive functioning, sensorimotor function has been relatively under investigated in relation to cognitive function in older adults. Yet there is an abundance of evidence to suggest not only that sensorimotor function declines with increasing age (Anstey, Lord & Williams, 1997; Rodriguez-Aranda, Mittner, & Vasylenko, 2016; Curreri et al., 2018), but also that this decline is associated with intelligence and cognition (Anstey, Stankov, & Lord, 1993; Lindenberger & Baltes, 1997; Anstey, Luszcz, & Sanchez, 2001). While it is likely that the motor cortex retains its plasticity in ageing (Morales, 2008), older adults possess declining ability to learn new manual motor skills (Seidler et al., 2013).

1.5.1 Sensorimotor Deficits and Cognitive Function

Various sensorimotor tasks have been connected with normal ageing. While this area is of utmost importance for ageing, it was not included in great detail because of practical reasons. Visual acuity and visual contrast sensitivity are both associated with biological and cognitive ageing (Anstey et al., 1993), and are thought to represent an overall reduction in the functioning of the nervous system as we age (Greenwood, 2000), although it is acknowledged that cataracts may be responsible for a large part of this. But more than this, their predictive power has been noted. Difficulties with fine motor coordination, loss of visuomotor processing speed and limb apraxia have been strongly associated with a risk of cognitive impairment in community-dwelling older adults (Curreri et al., 2018). Lindenberger and Baltes (1997) found that 59% of the total reliable variance in general intelligence was predicted by sensorimotor variables in the old and very old (age 70-103 years). This is supported by Anstey et al. (1997) who found that sensorimotor variables explained age-related variance in measures of reasoning after education, health, mood, and physical activity were controlled for, concluding therefore that these measures are an important predictor of performance on cognitive tests. Lower limb strength has also been found to be an important predictor of performance on cognitive tests (Anstey et al., 1997). Moreover, Baltes and Lindenberger (1997) concluded that vision and hearing were excellent predictors of age differences in intellectual functioning across the life span, but that the expression of the

mechanisms underlying the connection between sensory and cognitive functions are amplified in older age, suggesting that these mechanisms also drive age differences in complex cognition. However, Anstey et al. (2001) reported that while cognitive performance, visual acuity and auditory thresholds are strongly correlated in cross-sectional studies, longitudinal studies reveal a disassociation. They reported that memory performance may be more closely related to visual function than measures of processing speed or verbal ability (Anstey et al., 2001). Moreover, Anstey et al. (1993) found that despite the inclusion of both health and sensorimotor variables in their model, education was still the most important individual predictor of fluid intelligence. Therefore, it could be suggested that sensori-motor measure contribute less, but still significant amounts, of the variance seen in cognitive performance.

1.5.2 Explanatory Mechanisms of the Relationship between Sensorimotor and Cognitive Decline

There are numerous explanations offered as to how and why sensorimotor measures relate to cognitive functioning. Mauk and Buonomano (2004) argue that all sensory and motor processing ultimately relies on spatial-temporal patterns of action potentials, and that most sensory stimuli are not purely spatial or temporal. It is important to remember that part of the reason sensorimotor tasks are likely to be predictive of cognitive performance, is that like cognition, these tasks rely on complex mechanisms, evoking connections between multiple brain regions. With this in mind, while Anstey et al. (2001) report that decline in visual performance had a significant effect on decline on memory, it is possible that this is due to visual encoding of memory test stimuli, so represent changes in vision rather than higher cognitive processing.

The implication from the literature is that the cerebellum plays a large role in sensorimotor network, providing an interface between sensory and motor events (Manni & Petrosini, 2004). The cerebellum has been shown to receive sensory projections from the cerebral hemispheres, as well as auditory and visual input (Schmahmann, 1998), while the dentate nuclei along with other deep cerebellar nuclei and lateral vestibular nucleus have all been implicated in playing a role in sensorimotor functioning (Habas et al., 2009). Seidler et al. (2015) investigated resting state sensorimotor network connectivity in older adults, concluding that cerebellar seed regions displayed both positive and negative associations between network strength and age, with better motor performance being linked to stronger

connectivity within these networks. Taken together, the evidence suggests that sensorimotor tasks are not only related to, but predictive of cognitive decline, and that the cerebellum plays a key role in maintaining the networks that support sensorimotor functioning.

1.6 Cerebellar Contributions to Cognition

Early influential models of the cerebellum focussed exclusively on motor function, widely believed to be essential for smoothness and effectiveness of movement (Bellenbaum & Daum, 2007; Manni & Petrosini, 2004). Yet the shift towards its role in cognition has gained substantial support in recent years, largely due to the advancement of neuroimaging techniques (see Buckner, 2013 for a good review). Furthermore, there is emerging evidence in support of a cerebellar role in sensory and affective processing too (Schmahmann, 1998; Stoodley & Schmahmann, 2009; Allen et al., 2005). It is suggested that the cerebellum forms an internal model for motor control through a learning process, which then allows the brain to precisely control movement without the need for sensory feedback; and that this system is paralleled in cognition (Ito, 2008). As a result, the cerebellum keeps functions steady around a homeostatic baseline, smoothing out performance in both motor and cognitive domains (Leggio, Silveri, Petrosini & Molinari, 2000). Schmahmann (1998) posits,

> In the same way as the cerebellum regulates the rate, force, rhythm, and accuracy of movements, so might it regulate the speed, capacity, consistency, and appropriateness of mental or cognitive processes. In this model, the cerebellar contribution to cognition is one of modulation rather than generation. (p.367)

This suggests that the cerebellum facilitates the efficiency of all other brain structures to which it is connected (Schmahmann, 1998), solidifying its importance in a wide range of functions. Moreover, the role of the cerebellum in cognition is supported by the characterisation of cerebellar cognitive affective syndrome, in which patients experience disturbances of executive function, impaired spatial cognition and linguistic difficulties (Schmahmann & Sherman 1998).

1.6.1 Cerebellar Structure and Cognition

It is thought that as one of the most rapidly evolving brain regions to develop, the human cerebellum has developed to play a large role in cognitive function, particularly the neocerebellum, which contains the most phylogenetically more recent cerebellar regions (Ramnani et al., 2006; Hogan et al., 2011). For example, it is thought that the older part of the dentate nucleus ensures the skilled manipulation of muscles though its connections to the

motor cortex, while the newer part of the dentate nucleus connects to the association cortex, ensuring the skilled manipulation of information instead (Botez, Botez, Elie & Attig, 1989). The cerebellum has been found to play a role in emotion, executive function, language, music, timing, planning, attention, non-motor learning, conflict resolution, visuospatial tasks, long- term memory, working memory and in particular verbal working memory (E, Chen, Ho & Desmond, 2014; Ramnani, 2006; Botez et al., 1989; Schmahmann & Sherman, 1998; Schmahmann, 1998; Timmann & Daum, 2007; Bellebaum & Daum, 2007; Schweizer et al., 2007; Gordon, 2007; Hayter, Langdon & Ramnani, 2007; Stoodley, 2012). A summary of these studies is presented in Table 1. Gordon (2007) summarises the literature in terms of cerebellar location for many of these deficits, finding a dominant role for the posterior cerebellar regions in cognitive and affective processing. E et al. (2014) provide a good summary of the cerebellar regions associated with each of these functions in Table 2 below, with Stoodley (2012) confirming that different cortico-cerebellar circuits are stimulated dependent upon the task at hand, with activation patterns confirming this regional functional topography. And there are differences between younger and older adults. Variations in cerebellar structure are associated with cognitive ability in older adults, while executive functioning and fine motor control correlate significantly for older, but not younger adults (Miller et al., 2013; Corti et al., 2017). Bernard, Leopold, Calhoun and Mittal (2015) found that volumetric patterns with age varied regionally, and that regional cerebellar volume was associated with cognitive performance, particularly processing speed and spatial working memory. The authors concluded that these structural changes may result in the decline of internal behavioural models, which then manifest as the motor and cognitive difficulties seen in advancing age (Bernard et al., 2015).

Study	Method	Sample	Findings/ Conclusions
Bellebaum & Duam (2007)	Original article, focussing on the role of the cerebellum in executive processing. Special emphasis on working memory, multitasking or inhibition.	Review of neuroimaging studies or from studies investigating deficits related to cerebellar dysfunction.	Widely accepted that the cerebellum contributes to cognitive processing, but nature is not well understood. Suggested that the cerebellum contributes to motor and non-motor function in a similar way; region of interest withing the cerebellum dependent on the executive subprocess being explored. Differences in definition of executive subcomponants likely to contribute to discrepancies in empirical findings. Moreover, there is the potential for "contamination" or effect of motor deficits on cognitive variable outcomes.
Bernard et al. (2015)	Structural MRI to measure cerebellar volume. Cognitive assessment: symbol coding, Trails A, spatial span, letter-number span, verbal learning and spatial learning. The Wide Range Achievement Test (Boulder sample) and Wecshler test of Adult Reading (Albuquerque sample) were used as measures of general intelligence.	Cross-sectional sample of 123 (age 12-65)	Volumetric patters with age vary regionally within the cerebellum. Regional cerebellar volume was significantly associted with several cognitive variables, particularly processing speed and spatial working memory. May be gender differences with respect to the relationships between age, regional volume and cognitive performance. Found several associations between cognitive function and regional cerebellar volume, irrespective of age.

			Structural changes in advanced age may result in performance declines seen in motor and cognitive domains in ageing.
Botez et al. (1989)	Between-subjects experimental design using a neuropshycological test battery, comprising the following tests: the Ottawa-Wechsler scale, the immediate and delayed recall subtests from the Wechsler memory scale, Stroop test forms I and II, the B-M dexterity test, and visual and auditory reaction and movement time.	Thirty-three outpatient epileptics with normal CT scans, 31patients with cerebellar and brian stem atrophy. (No statistical differences in age, education and number of seizures between groups).	Analysis of composite score of neuropsychological performace showed that the cerebellum interferes with the following complex behavioural functions: visuo-spatial organisation for a concrete task, planning and programming of daily activities and the speed of information processing.
Corti et al. (2017)	Purdue Pegboard tested fine motor control; the Cambridge Neuropsychological Test Automated Battery tested Spatial working memory; The Stockings of Cambridge was used to assess planning, and the Intra-Dimensional Extra-Dimensional Set-Shift task was used to assess set-shifting.	Thirty young adults aged 18-23 (m=21.03, SD=1.67, 18 female, 12 male) and 32 older adults aged 60-80 (m=72.38, SD=6.69, 20 female, 12 male). Groups did not differ significantly for years of education.	For older adults only, executive functioning correlated significantly with all measures of fine motor control. Preservation of planning ability may support fine motor control in older adults.

E et al. (2014)	Meta-analysis of studies demonstrating cerebellar activations in higher cognitive domains involving emotion, executive function, language, music, timing and working memory.	88 Neuroimaging studies	Largely consistent with Stoodly and Schmahmann (2009), a 54 imaging study meta-analysis, which found cerebellar role in motor, somatosensory, spatial, language, executive function, emotion and working memory. Consistent cerebellar presence in the timing domain, which is important for the complex activity of music processing.
Gordon (2007)	Original article	Cerebellar cognitive affective sydrome is described and discussed, in particular using neuroimaging studies.	Timing has been proposed as the basic function of the cerebellum, underlying its contribution to both motor control and cognitive functions. Cognitive deficits found in children with cerebellar ataxia supports its role in learning.
Heyter et al. (2007)	Between subjects experimental fMRI study. Experimental group took part in a varient of the Paced Auditory Serial Addition Test in combination with a sparse sampling method to avoid artefact casued by speech-related head movements on the BOLD timecourse. Control group took part in a task that was identically matched in terms of	15 Right-handed volunteers (aged 18-29, 9 females). No known neurological or psychiatric history.	Activity in the experimental condition was evoked in medial portions of cerebellar cortical lobule VII which is interconnected with the prefrontal cortex in non-human primates. “We suggest that the cerebellar activation reflects the automated simulation of cognitive operations that are initially reliant on interactions between prefrontal areas, and that interaction

	sensory and motor requirements, but lacked the sepcific cognitive demands of the experimental condition.		between prefrontal areas and its targets is simulated within the circuitry of cerebellar cortical lobule VII." (p950).
Hogan et al. (2011)	Voxel based morphometry and structural equation modelling to analyse relations between general cognitive ability (G) ands volume of grey (GM) and white matter (WM) in frontal areas and the cerebellum.	228 older adults (121 males, 107 females)	Cerebellar GM volume predicts G, even when total intercranial volume and GM and WM volumes in frontal lobes are statistically controlled for. Results differ by gender; males show a stronger relationship beween cerebellar volume and G.
Miller et al. (2013)	Measured cross-sectional area of four areas of the cerebellar vermis correlated with individual cognitive test scores and two cognitice factors derived from principle components analysis.	45 community dwelling men aged 71-76 (m=73, SD=1.3). Subjects using psychoactive medicaton were excluded.	Atrophy of certain areas of the cerebellar vermis are associated with worse cognitive function in the sample. Two out of the four areas showed positive correlations, with a general cognitive factor accounting for almost half the cognitive test variance.
Ramnani et al. (2006)	In vivo diffusion imaging and probabilistic tractography.	Nine healthy adults (six males, aged 26-33), two adult male macaque monkeys (Macaca fascicularis).	Dominant contribution of the cortical motor areas to the macaque monkey cereral peduncle. Relatively large prefrontal contribution to the human cortico-ponto-cerebellar system in the cerebral peduncle. Results reveal substantial growth of prefrontal projections that complement

			the evolutionary expansion seen in the human prefrontal cortex and ventral dentate nucleus in the human cerebellum. This suggests that the human cerebllum may play specialised roles in processing cognitive information.
Schmahmann & Sherman (1998)	Neurological examinations, bedside mental state tests, neuropsychological studies and anatomical neuroimaging.	20 patients with diseases ocnfined to the cerebellum.	Impairment of executive functions such as planning, set-shifting, verbal fluency, abstract reasoning and working memory were found as well as difficulties with spatial cognition including visuo-spatial organisation and memory; blunting of affect or disinhibited and innapropriate behaviour; and language deficits including agrammatism and dysprosodia.
Schwizer et al. (2007)	Task-switching paradigm	Eleven patients with chronic, focal lesions to the cerebellum, and eleven healthy controls.	Patients were slower and less accurate in conditions involving conflict resolution, in the presence of an intact pre-frontal cortex. The cerebellum may play an important role in coordinating with other areas of the cortex to modulate active response states.
Stoodley (2012)	Review	Functional neuroimaging studies	Cerebellar activation is revealed during a variety of tasks including language, visual-spatial, executive and working memory proceses. The cerebellum is engaged during conditions which

			either control for motor output, or do not involve motor responses. Resting-state functional connectivity data reveal that, in addition to networks underlying motor control, the cerebellum is part of "cognitive" networks with prefrontal and parietal association cortices.
Timmann & Daum (2007)	Editorial	n/a	"Convincing evidence for a cerebellar involvement in some aspects of cognitive processing, most notably verbal working memory" (p161).

Table 1: A summary of the studies reviewed contributing to the knowledge about cerebellar involvement in cognitive processes.

Table 2: E et al. (2014)

Summary of results from the current and Stoodley and Schmahmann's [2009] meta-analysis

Task type	Location
Emotion	**Left Crus I; Right lobule VI**; *Left VIIAt*; Right lobules VIIIA; IV/V; IX; Left lobules VI; VIIIB; Right Crus I; Left Crus II
Executive function	**Bilateral Crus I**; *Left lobule VI; Left VIIB*; Left Crus II; Midline lobule VIIAt; Right lobule VI
Language	**Bilateral lobule VI; Right Crus II**; *Right Crus I; Right lobule VIIAt*; Midline lobule VIII; Left Crus I
Music	Right lobule V; Bilateral lobule VI; Bilateral lobule VIIIA
Timing	Right lobule VIIIA; Right lobule VIIIB; Right Crus I; Midline lobule IX
Working memory	**Bilateral Crus I; Right lobule VIIIA**; *Bilateral lobule VI; Left lobule VI/Crus I*; Left lobule IV/V

Locations identified in both meta-analysis are highlighted in bold; locations found only in Stoodley and Schmahmann's [2009] study are italicized; locations found only in this study have been placed last in regular style.

1.6.2 Cortico-cerebellar Loops

Recent advances in neuroimaging have allowed for detailed understanding not only cerebellar structure, but of cortico-cerebellar loops, though there is still a general lack of attention to the cerebellum in intrinsic connectivity networks (Habas et al., 2009). The cerebellum receives input from most cortical areas, and forms closed output loops with their respective cortical targets (Timmann & Daum, 2007). The simple and homogenous micro circuitry of the cerebellum suggests that proposed theories for understanding its role in motor function can be extended to the cognitive functions in which it plays a role (Timmann & Daum, 2007). The proposal is that the cerebro-cerebellar system consists of discretely organised anatomical systems, which act in parallel to serve organised functional neural circuits (Schmahmann, 1998). Present findings already describe the differences in function seen across the cerebellum. The anterior lobe is implied in motor and somatosensory processing, while cognitive processing activates the posterior lobe, and emotional processing is likely to be associated with the posterior vermis (Stoodley & Schmahmann, 2009).

Multiple closed-loop circuits are proposed, with the cerebellum receiving input from the basal ganglia, thalamus, hypothalamus, parahippocampal gyrus, cingulate gyrus, superior temporal cortex, posterior parietal cortex, motor cortex and prefrontal cortex (Leiner, Leiner & Dow, 1986; Kelly & Strick, 2003; Allen et al., 2005; Hayter et al., 2007; Balsters & Ramnani, 2008; Stoodley & Schmahmann, 2009), and projecting back to the various cortical regions via the thalamus as well (Leiner et al., 1986; Ramnani et al., 2006). Schmahmann and Sherman (1998) described the circuitry as having a feed-forward limb via the corticopontine and pontocerebellar pathways, as well as a feedback limb via the cerebellothalamic and thalamocortical systems. Cerebello-parietal loops have been implied in visuospatial organisation; cerebello-frontal loops have been implied in planning, speed of information processing, and the cerebello-limbic loop has been implied in spatial processing and the modulation of emotion (Botez et al., 1989; Stoodley & Schmahmann, 2009). Disruption of these loops puts the entire network at risk, with Charlton et al (2006) reporting that where integration of information is needed, disconnection of these loops due to white matter tract disruption is what leads to cognitive disruption.

1.6.3 The Cerebellum and Automaticity

The evidence indicates that the cerebellum moderates cognitive function in the same way as it does for motor function, so a failure in automaticity may be responsible for the difficulties

seen in both domains. As previously suggested, the cerebellum helps us to learn programmes for executing motor actions seamlessly, and without conscious effort (Ito, 2008; Leggio et al., 2000; Hayter et al., 2007). Therefore it is likely that cerebellar programmes in association rather than motor cortex account for mental rather than manual dexterity (Leiner et al., 1986). Bellebaum and Daum (2007) reported that performing more than one task at a time requires at least one of them to be performed automatically, so that more attention can be directed toward the other. Schweizer et al. (2007) suggest that the cerebellum mimics the information processing carried out in cortical structures, but that it is done more rapidly via an established, automatic circuit. However, the speed advantage comes at the expense of flexibility, thus serving to reduce processing demands on the prefrontal cortex, allowing it the necessary capacity to complete more complex cognitive operations (Schweizer et al., 2007). Findings from lesion studies appear to confirm these conclusions. Schmahmann and Sherman (1998) suggest that disruption of the cerebro-cerebellar circuitry is likely to result in the neuropsychological and affective disorders patients with cerebellar lesions experience. Right hemispheric lesions are associated with linguistic impairments, while damage to the left cerebellar hemisphere has been found to result in visuospatial difficulties (Stoodley & Schmahmann, 2009).

1.6.4 Cerebellar Contributions to Cognition: Conclusions

Although many questions over the precise mechanisms underlying cognitive function still remain, the functions of the cerebellum appear to offer some explanation to close previously existing gaps in the literature. Impairments in functions that are often ascribed to the prefrontal cortex are seen following cerebellar lesions when the prefrontal cortex is intact, and the relationship between gait speed and cerebellar grey matter volume has been found to be influenced by information-processing ability (Schweizer et al., 2007; Nadkarni et al., 2014). It is concluded that different parts of the human cerebellum are utilised for the specific cognitive or motor functions with which it is associated, with highly uniform but specialised regions apparent, and that cortico-cerebellar loops provide an explanation as to how the cerebellum works in conjunction with the rest of the cortex to allow for cognitive and motor functions to be carried out with accuracy and precision. However, the function of these clearly defined anatomical loops still requires further research, as a potential weakness is that functional neuroimaging contributes correlational rather than causal evidence (Balsters & Ramnani, 2008). While it is generally accepted that the cerebellum serves a broader role in

the nervous system than previously believed (Allen et al., 2005), Strick, Dum and Fiez (2009) conclude that "the neuroimaging and neuropsychological literatures provide compelling, although not conclusive, evidence that the human cerebellum has important nonmotor functions" (p.425).

1.7 Cerebellar Contributions to the Affective State

As previously stated, the cerebellum has been implied in emotional functions, as well as sensory, cognitive, and motor function (Schmahmann, 1998; Allen et al., 2005; Gordon, 2007; Habas, 2009). Schmahmann and Sherman (1998) noted that personality changes, in particular a blunting of affect, are one of the aspects that characterise cerebellar cognitive affective syndrome. In much the same way that it is thought the cerebellum controls the effective and smooth running of motor and cognitive skills through closed-loop circuits, and disruption of these circuits' leads to difficulties in performance, Schmahmann (1996) suggests a similar dysmetria of thoughts and emotions as a result of cerebellar deficits. This view is supported by Gordon (2007) who concludes that the cerebellum forms an essential component of the brain mechanisms responsible for personality and mood, as well as intellect. Snider (1950, cited in Schmahmann, 1998) refers to the cerebellum as a modulator of neurological function, important not only in the field of neurology, but in psychiatry too.

1.8 The Cerebellum as a Time Keeper

One of the leading theories for explaining why the cerebellum has such wide ranging involvement in such a variety of domains, is that it acts as a time keeper for each of them, underlying its contribution to them all (Gordon, 2007). If precise timing of information is lost, and messages are not received in their entirety, an individual may become less co-ordinated, both motorically and cognitively (Strick et al, 2009). There are two leading suggestion for precisely how this happens. The first proposal is that the cerebellum serves as an internal timing mechanism, while the second suggests that it acts as an error corrector, acting as a general modulator to the brain (E et al., 2014). Each proposal will be considered in turn.

As an internal timer, the cerebellum tracks the temporal order in which a sequence is performed to execute a motor or cognitive 'movement,' with waves of activity being propagated along parallel fibres, reaching Purkinje cells at incremental delays after onset (Ben-Yehudah, Guediche & Fiez, 2007). Koch et al. (2007) found that the cerebellum is

essential for timing in the order of milliseconds, not seconds, which are important for motor control and speech. So while much of the literature suggests the basal ganglia is involved in the timing of sensory and motor events, this is usually to the order of seconds, which is important for decision making processes that concern time processing (Mauk & Buonomano, 2004; Koch et al., 2007).

As an error corrector, the cerebellum helps us learn sequences and makes error driven adjustments that crucially occur preceding the execution of an inaccurate command (Ben-Yehudah et al., 2007). It is likely that this occurs as a result of feed-forward prediction. As we age, if cerebellar connections to the cerebral cortex degrade, performance updates and behaviour monitoring cannot be transmitted effectively, which could account for the motor, cognitive, and affective difficulties previously described (Bernard & Seidler, 2014). Kawato and Gomi (1992) proposed a model for cerebellar motor learning that assumed that climbing fibre responses possess magnitude and direction of information that is conveyed through motor error messages, and based on the long-term depression in Purkinje cells, each microcomplex of the cerebellum learns to execute predictive and coordinative control of movements. Given what is now known about the way in which the structure of the cerebellum allows for multiple separate but structurally similar cortical loops, it is possible to see how this theory can be extended beyond the motor domain. However the two systems may not be mutually exclusive (Ben-Yehudah et al., 2007), though Mauk & Buonomano (2004) suggest that the error corrector hypothesis is more likely as it explains the involvement of the cerebellum in both interval timing tasks (in terms of predicting when the next occurrence of an action should happen), and in the timing of learned responses.

Lesion studies again offer support for the time keeping hypotheses. Cerebellar lesions are linked with increased variability in motor timing, mediating conditioned eyelid responses, and oscillating-like tremors, (Gordon, 2007; Mauk & Buonomano, 2004). This is possibly as a result of a failure to accurately predict and correct movements before an error occurs, instead producing a series of overshoots (Mauk & Buonomano, 2004). Taken together, with substantial evidence arguing for a role for the cerebellum in precise timing of motor control, along with the advances in structural imaging determining the uniformity of the cerebellar cortical circuitry (Stoodley, 2012), it is possible to extend the theory beyond the motor domain, to also suggest an underlying role of the cerebellum in cognition and affect.

1.9 The Cerebellum and Ageing

While traditionally there has been a focus on executive function decline in ageing, with much research looking at the frontal cortex, more recently there has been growing interest in subcortical involvement in cognitive processes. Typically, the cerebellum is thought of as a primarily motor structure, coordinating fine motor movements. However, a growing body of evidence suggests that it may also be involved in coordinating cognitive processes, while extending the motor theory to demonstrate a somewhat vital role in controlling balance. Hulst et al. (2015) found considerable overlap in regions with the strongest cerebellar loss when comparing the cerebellar degeneration of a healthy ageing population to cerebellar patients, suggesting its involvement in both motor and cognitive systems.

As previously described, the cerebellum is not spared from the global neuronal loss seen in ageing; global cerebellar white matter has been found to reduce by as much as 26% with age (Andersen, Gundersen, & Pakkenberg, 2003). While many structural differences are described, it is generally agreed that the cerebellum plays a complex cognitive role in ageing (Ramanoel et al., 2018) that is not yet fully understood. Hoogendam et al. (2014) found that although cerebellar volume has an influence on cognition in ageing, it is not the leading structure. Yet this region is hugely under-investigated in ageing, especially in comparison to frontal regions. While frontal lobe atrophy is much more widely studied in the literature, it is important to recognise the role the cerebellum plays in supporting the frontal lobe, and how this circuit is sensitive to the effects of ageing (Hogan et al., 2011). Buckner (2004) provides a good overview of the effect of age on regional brain volume, yet the cerebellum is omitted entirely.

At the macro level, smaller grey matter volume in the right cerebellum has been found when comparing older adults to a middle aged group (Ramanoel et al., 2018); on a micro scale, Purkinje cells (the sole output neurons in the cerebellar cortex) appear to be particularly sensitive to ageing, in both morphology and function (Zhang, Zhu and Hua (2010). However, Andersen et al. (2003) reported that most regions in the cerebellum show only minor morphological change with ageing, with the exception of the anterior lobe, which is functionally concerned with motor function. Here, they found a 40% reduction in granule and Purkinje cells, and a 28% loss of cortex, mainly in the granule cell layer (Andersen et al., 2003). Hulst et al. (2015) found similar results, suggesting that the lack of apparent ageing in the posterior parts of the cerebellum are likely to protect against pronounced cognitive deficits, yet conclude that their findings show a pattern of cerebellar degeneration in healthy older adults that is partly equivalent to cerebellar degenerative disease. As well as structural

changes, neurochemical differences have been reported. Decline in motor coordination and learning is associated with a decline in cerebellar beta-adrenergic receptor function (Bickford, Shukitt-Hale & Joseph, 1998; Gould, 1999). Cerebellar cholinergic input has also been implied in the modulation of cerebellar functions (Zhang, Zhou, & Yuan, 2016) highlighting the role this system could play in ageing. It is evident that structural and chemical differences between younger and older adults exist, yet what is not yet clear is how these changes manifest behaviourally, and relate to the cognitive deficits previously described. Further research to establish the link between the cerebellum and cognition, and particularly the role this structure plays in ageing is needed, and something this thesis seeks to address.

1.10 A Causal Role for the Cerebellum?

Much of the evidence that describes the change in cognition as we age is simply correlational in terms of cerebellar degeneration. What is still yet to be established is a causal link. The question here is whether or not the changes in cerebellar structure and circuitry with age are in some way responsible for the behavioural and cognitive difficulties experienced. There is a distinct possibility that it does, given the role the cerebellum is now known to play in precise timing, both in motor and cognitive domains. If the cerebellum is in fact responsible for maintaining the efficient running of neural circuits, it stands to reason that current function should also be predictive of future decline. Hulst et al. (2015) report that the cerebellum is important in prediction of both motor and cognitive function in older adults, with the cerebellum showing earlier senescence than the hippocampus in trials done with mice (Woodruff-Pak et al., 2010). This paves the way for research using cerebellar function, in particular motor function, as a predictor of future cognitive function in older adults.

While the cerebellum looks likely to play a large role in cognitive decline as we age, it must be remembered that other factors such as an inactive lifestyle, may contribute to the decline of cognitive-motor functions (Yan & Zhou, 2009). However, Voelcker-Rehage, Godde and Staudinger (2010) report that physical and motor fitness are differentially related to cognitive processes. The benefits of cardiovascular exercise to healthy living across the lifespan are well documented, as well as in enabling the body to age well. Physical fitness has been associated with faster reaction times, better cognitive performance, lower rates of cognitive decline over time, and a lower risk of cognitive impairment or dementia (Drag & Bueliauskas, 2010). Colcombe et al. (2006) found significant increases in brain volume for older adults who took part in aerobic exercise, with no significant changes reported in those

taking part in nonaerobic exercise, or in the group of younger participants. More specifically, Erikson et al. (2011) reported that aerobic exercise increased the size of the hippocampus, therefore protecting against, or even reversing hippocampal volume loss, and in turn improved memory function in a trial with older adults. With regards to the cerebellum, exercised aged rats had significantly more Purkinje cells, larger Purkinje cell soma volumes and an equal number of Purkinje cells to younger animals, than were found in sedentary aged rats (Larsen, Skalicky & Viidik, 2000). In addition to cardiovascular training, coordinative training has been found to differentially improve cognitive performance and neural processing in older adults (Voelcker-Rehage, Godde & Staudinger, 2011). So while the benefits of cardiovascular exercise are well documented, the benefits of coordinative exercise in the ageing process are less well established, and require further investigation. With the cerebellum arguably controlling the coordination of cognitive, as well as motor networks, exercises that target this structure seem to be a logical place to start.

1.11 Conclusion

Through all the research that has been presented, two things clearly emerge from the literature. Firstly, that there are structural and neurochemical cerebellar differences between younger and older adults that are manifested as deficits in both motor and cognitive function as we age. And secondly, that there is no clear consensus on the activation patterns, precise anatomical locations of structural change, or relationship between biology and behaviour to explain exactly how this happens. The cerebellum has been largely overlooked in favour of frontal lobe theories of ageing, and with recent developments in the understanding of its contributions to cognition via timing mechanisms and neural networks, demands more investigation to help further unlock this complex pattern. Not only have strong links between cognitive ageing and the cerebellum been established, but there is evidence to suggest that cerebellar function may in fact be predictive of cognitive decline. This line of reasoning forms the basis of this thesis, in addition to the question: if we are indeed able to predict cognitive decline, what can we do to prevent it?

1.12 Prevention over Treatment: Evidence from Intervention Studies

What is of more importance than how we, more accurately, describe cognitive ageing; is what we do with this new understanding. If we are able to establish a more reliable pattern of early cognitive deficits, what is of significance is what we do with this knowledge to improve the

lives of older adults. Balcombe and Sinclair (2001) suggested that this was possible through preventative healthcare strategies, which will in turn have financial benefits for Western economies, struggling to cope with the financial reality of an ageing population. This view was echoed by Ball et al. (2002) who stated that "interventions designed to delay or prevent the need for nursing homes, home care, and hospital stays can save health care costs, while also ensuring the independence and dignity of the aging population" (p.2271). The present thesis seeks not only to provide a step towards a single unifying theory of ageing, but also to help devise an easy to administer, cost effective, yet highly accurate battery of tests to predict cognitive decline. And once we have established who is likely to decline, it would be morally irresponsible not to suggest targeted interventions to alleviate the symptoms. As previously discussed, the decline in motor function often predates the decline in cognitive function. Evidence suggests that the cerebellum plays a role not only in motor but cognitive function. Therefore, testing the suitability of a motor test provides the next logical step in aiming to devise a predictive test battery. Recently, Curreri et al. (2018) found that assessing fine motor skills in older adults may help to identify subjects at high risk to develop cognitive decline. So finding further evidence to support this is crucial.

As mentioned beforehand, if we identify people who are likely to cognitively decline, we need to offer those people support. Interventions to improve cognition have so far struggled to provide the effective relief required. Ball et al. (2002) provided participants with memory, reasoning, speed of processing or no training at all. They found that cognitive training improved targeted cognitive abilities, but that in the initial two year follow up, there was no generalisation of such interventions to everyday performance. Raz et al. (2013) found that age-related brain shrinkage is detectable in less than 6 months, but in the cerebellum, intense cognitive training was associated with slower shrinkage, though the improvement was not necessarily in the cognitive skills targeted. Motor practice or skill learning has been found to improve speed, smoothness and accuracy of motor tasks (Yan & Zhou, 2009), and so taken together with the evidence to suggest that the cerebellum plays a similar role in cognition as it does in motor function, it is likely that motor practice can improve the speed, smoothness and accuracy of cognitive function too. Moreover, McDermott et al. (2019) report in a synthesis of systematic reviews, that multi-component exercise improves global physical and cognitive function in those with dementia. They reported that stretching, walking and other strength exercises appeared to be beneficial for cognitive functions and activities of daily living, while reduction in physical activities such as these have also been found to be associated with accelerated cognitive decline in this population (McDermott et al., 2019; Soni et al., 2019).

This highlights the need to target coordinative rather than cardiovascular exercises as part of an intervention.

With evidence to suggest the cerebellum provides an underlying system coordinating many of these functions, it seems reasonable to assume that an intervention specifically targeting cerebellar function would show marked improvement across many cognitive domains. Yan & Zhou (2009) suggest that computer assisted techniques that provide a combination of both physical and mental activities may be the most effective way of enhancing older adults' motor and cognitive function. The present study aims to provide a simple at home intervention that will fill precisely that gap.

1.13 The Benefits of Coordinative Exercise

While the general health benefits of physical exercise are well established (National Health Service, 2018; Penedo & Dahn, 2005) the effects of coordinated movement are less well researched. Physical exercise that leads to an increased heart rate keeps blood pressure and LDL cholesterol low (Swain and Franklin, 2006; Williams, 2008) and helps protect from a number of diseases, such as cancer and heart disease, where age is a major risk factor (Cancer Research UK, 2016; Dhingra & Ramachandran, 2012). Activities that feature slow, coordinated movement offer a different kind of protection against ageing. Li, Hong and Chan (2001) report that Tai Chi is beneficial to cardiorespiratory function, immune capacity, mental control, flexibility, and balance control, functions of the human body that are all particularly vital to maintain as we age. Furthermore, research suggests that Tai Chi can slow grey matter atrophy (Liu, Li, Liu & Guo, 2019), and prevent cognitive decline in older adults (Tsang et al., 2019). Ageing well, cognitively, is of as much importance as ageing well physically, if not more so given recent advances in modern medicine. Stents allow those with blocked arteries to have them opened again, those who break a bone can have metal pins inserted to help them grow strong again, but the human brain is far too complicated for comparable 'quick fix' treatments to be available. Effective treatments for age-related degenerative diseases of the brain remain lacking, and so an emphasis must remain on prevention. We must stop people cognitively declining in the first place, as the prognosis once it begins is poor in comparison to other diseases in the general population (van de Vorst, Vaartjes, Geerlins, Bots, & Koek, 2015).

While Tai Chi offers excellent benefits to those who engage with it, participation in classes is often based on a number of factors. Finding a qualified instructor, the time to attend

classes, access due to reduced mobility and having the money to take part all come in to play. There is a pressing need to promote this style of exercise amongst the ageing community. Therefore, it is of utmost importance to society, that such preventative measures are available and accessible to all. An at-home intervention, which people could fit into their own lives, would be of great benefit to all.

1.14 Aims of Research

There is currently no consensus as to the underlying mechanisms of ageing (Drag & Bueliauskas, 2010) and 'normal' ageing must be fully understood before we can understand pathological problems. Following from this, there is the applied problem that no suitable testing battery is currently available to identify those at risk, *before* clinical symptoms are a noticeable problem. Therefore this thesis aims to not only gather evidence to help clarify the picture, but contribute to formulating a test battery that is quick and easy to administer, while being highly predictive of future cognitive decline. We then have the moral responsibility to help those identified as at risk, to prevent the potential decline. These issues will be tackled from the point of view of cerebellar contributions to ageing and cognition. The research therefore has three main aims;

1) To establish the potential role of tests sensitive to the cerebellum in general cognitive ageing, and how this could motivate specific approaches to screening and intervention.
2) To be able to accurately determine who is most at risk of cognitive decline. This should be done through a short, easy to administer, but highly predictive screening test, which would act as the first step before further testing.
3) Once we are able to reliably predict who is most likely to decline, to then be able to offer a suitable intervention to prevent it.

These questions are addressed through the three studies in this thesis, by investigating lifespan changes in a range of cognitive and motor functions; refining the test battery to become more predictive and succinct at each stage; and finally by testing an intervention designed to stimulate the cerebellum. This is done from the perspective of cerebellar contributions to cognition as well as motor function.

A schematic overview of the overall aims is provided in figure 1 below. Once a more accurate ageing theory is used to develop a more accurate testing battery, it can be used to identify whether or not someone is at risk of later developing cognitive decline. Should one present with sensorimotor deficits, working with the hypothesis that these appear before cognitive deficits, an intervention to target motor skill would be highly beneficial to preventing cognitive decline. This thesis will therefore test an at home cerebellar challenge intervention to support this.

If one was found not to present with sensorimotor difficulties, they are potentially less at risk of future cognitive decline, and therefore an intervention to support stabilising their cognitive reserve would perhaps be more effective.

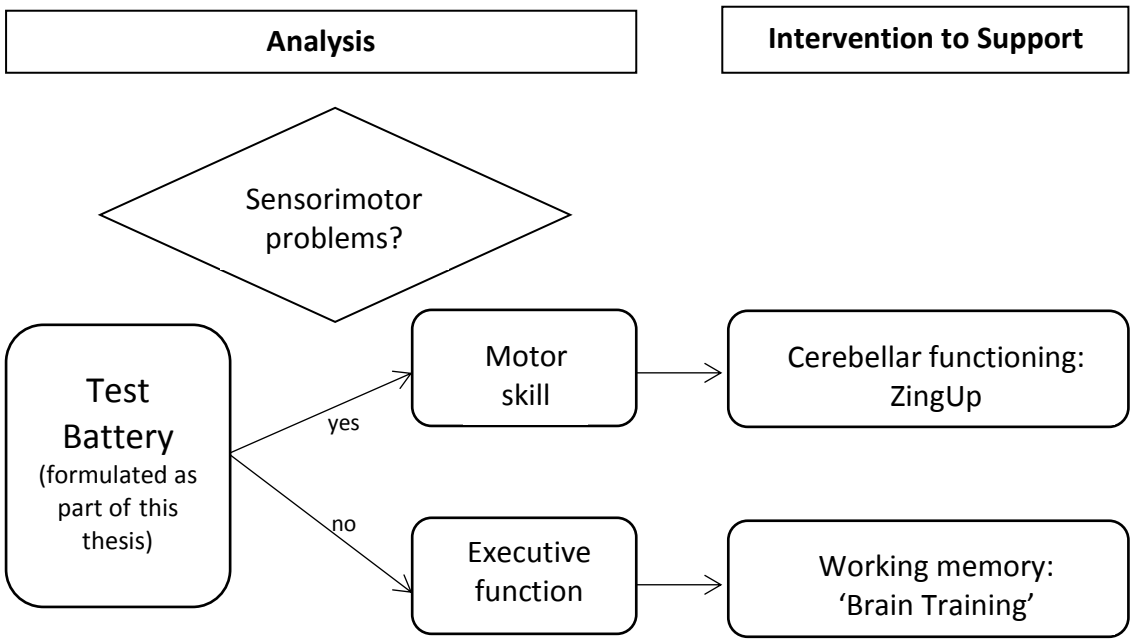


Figure 1. Schematic overview of thesis aims

1.15 Dementia and Diagnosis

One of the main aims of this thesis is not only to identify factors that might be predictive of cognitive decline, but to also design a suitable test battery as a means of putting these findings into practice. Current test batteries for cognitive decline unsurprisingly follow the trend in the literature, to focus heavily on memory and frontal executive function. However, with current research highlighting cerebellar input to cognitive function, there is a pressing need for the assessment tools to follow in the same direction.

Clinically, the Mini Mental State Examination (Psychological Assessment Resources Inc.) is used to measure global cognitive function, but memory is one of the functions that is not well assessed. This screening test is often used in research settings to determine whether or not someone is cognitively normal. However, one can start experiencing cognitive difficulties long before these are picked up by this over simplified test, which is affected by education and IQ (Drag & Bueliauskas, 2010). Moreover, this test is easily available online, and can therefore be practiced at home before a patient/participant is seen. As a result, it can be difficult to assess what 'normal' ageing is. There is no clear distinction between normal ageing and mild cognitive impairment (MCI), as there is also difficulty in describing the difference between late stage MCI and early stage dementia. Therefore, it is important not only that we understand more about the ageing process, but look towards potential alternatives for assessment and diagnosis. The aim was to identify tests sensitive to normal ageing.

The need to describe ageing not by chronological age, but instead by the underlying process and mechanisms has been highlighted (Li & Schmiedek, 2002). Gely-Nargeot, Mure, Guerin-Langlois, Martin and Descours (2000) describe ageing as a process that involves psychological, biological and social dimensions. In describing ageing using all of these distinctions, more accurate diagnoses and interventions would be possible. This thesis attempts to tackle this issue from the point of view of cerebellar deficits. Known to be involved in motor function, but now also associated with cognition, this leads to a potentially fruitful path for intervention development. With the cerebellum being reciprocally connected to all major cognitive brain structures, a targeted intervention to improve cerebellar functioning, should in theory improve overall cognition.

Engagement with cognitively stimulating activities has been associated with lower risk of dementia, but improvements are limited to the trained task, there is no transfer, and general cognition is not improved (Drag & Bueliauskas, 2010; Ball et al., 2002). Therefore, an intervention that targets the underlying mechanism behind general cognition is of extreme importance. Curreri et al. (2018) found that baseline performance on fine motor tasks (as assessed by participants buttoning up a shirt, and a speeded pegboard insertion task) predicted the onset of cognitive impairment, concluding that motor function is important in the preclinical phase of dementia. By targeting the cerebellum and improving processing speed, general cognition is likely to be improved through the cortio-cerebellar loops already described.

1.15.1 Thesis Overview

With the aim being to create a quick and easy to administer, yet highly predictive test battery, first evidence was needed to support the idea that motor function, as a test of cerebellar function, was an avenue worth pursuing. This was done (Chapter 2) by analysing the normative data of the Dyslexia Adult Screening Test (Fawcett & Nicolson, 1998). While not originally designed to test for signs of ageing, the 11 sub tasks cover a wide range of cognitive domains. Additionally, the tests were all speeded, which was identified in the ageing literature as a crucial factor and was also found to be sensitive to cerebellar decline (see table). Cattell (1943) stated that speed had so far been the most clear cut factor for distinguishing between declining and non- declining tests. Therefore, by using this data set, we could explore the way in which distinct cognitive tasks change with age.

If, as expected, motor skill and speeded tests was shown to decline greatly with increasing age, focussing on this factor would be the logical next step (Chapter 3). As a result, more robust measures of motor function and sensitive to cerebellar function were introduced in the form of the Purdue Pegboard (Tiffin & Asher, 1948) subtasks. It can be used to evaluate visuomotor coordination, processing speed and fine motor control (Curreri et al., 2018) and again keeps that speeded element that is so important as a distinguishing factor. A further test of sensory skill was also added in the form of the Contrast Sensitivity task (Vector Vision Inc.) in a bid to explore sensorimotor skills in more depth. Finally, tests devised as part of the South Yorkshire Ageing Study (Tarmey, 2012), further explored memory, each testing differential pathways. Altogether, this aimed to provide a clearer picture of the deficits experienced in ageing, but more accurately targeting the domains of interest.

For the final study (Chapter 4), a large test battery was narrowed down, aiming to work towards creating that highly predictive, yet quick to administer battery, as we seek to bridge the gap in clinical diagnosis for early markers of age-related cognitive decline. There is the need to provide a battery that is simple and practical, replicating movements used in everyday life, which assess the efficiency of these movements, and are suitable for rapid quantification (Carament et al., 2018; Yan & Zhou, 2009). Testing the function of the cerebellum meets all of these criteria, and is therefore the foundation of developing this battery.

2 Chapter 2: Identifying the Changes in Ageing (Study One)

2.1 Introduction

The effects of cognitive decline are well documented, though psychologists differ in their attempts to characterise the changes in mental functioning that occur after middle age. An accurate characterisation should illuminate not only theoretical issues of developmental/degenerative cognitive change, but should also be of applied value in job design, retirement support, and prediction of catastrophic changes such as Parkinson's or Alzheimer's Disease.

Physical changes including the loss of muscular flexibility (such as accommodation in the eye muscles), potential loss of muscular strength, reduced agility, postural changes, sensory loss in hearing, vision, and olfaction, and perhaps decreasing physical confidence linked to increasing balance difficulties occur with increasing age (Rosano et al., 2005; Shkuratova, Morris, & Huxham, 2004; Kalina, 1997; Walling & Dickson, 2012; Invitto et al., 2018). Although deficits in certain aspects of memory (Drag and Bueliauskas, 2010) and executive functioning (Buckner, 2004; Drag & Bueliauskas, 2010; Troller & Valenzuela, 2001; Greenwood, 2000) are reported, crystallised mental abilities appear to be somewhat more resilient. The classic work on cognitive ageing goes back to the dawn of the communication theory approach, where theorists (Crossman & Szafran, 1956; Welford, 1962) characterised the differences in terms of increasing neural noise. This led to reduced signal to noise ratio, and hence longer signal processing times, and hence reduced processing speed. With the advent of the information processing approach, Welford (1958) highlighted processing speed as a key component for effective cognitive functioning. Rabinowitz, Craik, and Ackerman (1982) suggested reduced attentional resources may be responsible in some cases of age deficits in memory , and the fact that elderly people's difficulties were most marked on externally paced tasks, whereas they functioned well working at their own pace has been highlighted (Broadbent, 1971).

Chapter 1 discusses the leading brain ageing theories, and the attempt made by the fronto-cerebellar theory of ageing (Hogan, 2004) to bring them together. The cerebellum has been found to play a role in language, working memory, processing speed, learning, attention and probably even emotion, (Leiner et al., 1993; Ramnani, 2006; Eckert, 2011; Raz, 2000; Strick, Dum & Fiez, 2009; Ito, 2006), with its role in cognition being discussed more fully in Chapter 1. Moreover, a dynamic set of gains and losses are described by many theories and theoretical approaches. These can be broadly organised into four main domains: processing

speed and executive functioning; implicit learning and (implicit) memory; cognitive flexibility and episodic memory; and emotional information processing (Ballesteros, Nilsson & Lemaire, 2009). The theoretical challenge remaining is to link these cognitive level theories to the increasing knowledge of the ageing brain and especially to the rapidly expanding knowledge of the contribution of the neuroscience of skilled action. The applied challenge is to develop a cost-effective screening test that may provide information relevant to the need for early identification and proactive support for incipient mental and physical difficulties. The present study is a preliminary step towards addressing these challenges.

The physical changes that manifest in the ageing brain are characterised behaviourally. As previously mentioned, problems with sensory and motor function start to appear, as well as difficulties with cognition. While in comparison to the volume of work investigating each domain separately, there is little looking at all three domains together, there is evidence to suggest that this avenue is worth pursuing. Anstey et al. (2001) reported that decline in visual acuity (as measures using a well-illuminated Snellen chart at a distance of 3m in their study) had a significant effect on memory decline, but not on verbal ability or processing speed. Kikkert et al. (2018) describe the use of gait dynamics as a predictor of future cognitive decline. 3D trunk accelerations were recorded while participants walked for three minutes, and it was found that future cognitive decline was correlated with a more regular and predictable gait pattern, but not with gait speed (Kikkert et al., 2018). Yamada et al. (2016) report that dual sensory impairment (concurrent vision and hearing impairment) was associated with greater cognitive decline among socially disengaged residents at a nursing home, highlighting the interplay between social activity and sensory impairment in resulting cognitive decline. The cerebellum has been found to be involved with non-motor functions such as working memory, language, and spatial processing (Ramnani, 2012; Stoodley, 2012; Hayter et al., 2007; Strick et al., 2009; details presented in Chapter 1) as well as the motor functions it is traditionally known to control, so a link between sensory, motor and cognitive decline is entirely possible.

Though these studies lend support for the idea that these faculties all decline simultaneously, there is still a gap in the knowledge about how or why this occurs. An interesting avenue for investigation is put forward by Bernard and Seidler (2014) who suggested that in several cases, cerebellar morphology is as good a predictor of behavioural performance decline in older adults as is the prefrontal cortex, if not better. This finding was based following a review of studies investigating morphological differences in the cerebellum between young and older adults. Shrinkage in the cerebellum has been found to accelerate

with age (Luft et al., 1999), and training of multi-sensory processes such as sensorimotor control and balance control can affect structural changes in the older brain (O'Callaghan et al., 2018). The relationship between sensory impairments and postural control is likely to depend on complex, integrative processing from a variety of inputs (Teasdale, Stelmach & Brunig, 1991), with DuPaquier, Blanc, Sinnreich, Landis, Burkhard and Vingerhoets (2003) suggesting that maintaining balance in an upright position is the result of the interplay of cognitive (such as attention), motor, cerebellar, vestibular and proprioceptive systems. Strong evidence for a link between the cerebellum and an overall role in cognitive function mostly comes from neuroimaging studies, suggesting that it is part of a complex network that contributes to higher cognitive function (Stoodley, 2012; Gordon, 2007, Ramnani, 2006, 2012; Bernard & Seidler, 2014; Leiner, et al., 1986). Additionally, the use of cerebellar tasks to foster neural growth in the elderly has been proposed as a potential tool to combat cognitive decline. Yan and Zhou (2009) state that exercises physical practice and skill learning prompt the creation of new connections among brain cells and the formation of neurons, and that this slows down the progress of aging and cognitive deteriorations. The authors conclude this after critically reviewing recent studies from both theoretical and practical perspectives. With evidence to support cerebellar contributions to sensory, motor and cognitive functioning, the interplay between these domains is poorly understood and it is therefore important that they are investigated simultaneously.

One of the greatest challenges to investigating cerebellar function is finding a specific cerebellar only task. Many tasks used to test cerebellar function would involve other brain regions such as the primary motor cortex, pre-frontal cortex and basal ganglia, as is the case with many motor tasks. This must be considered when interpreting the results of any such test. Balance and coordination tasks are often used as well as gait analysis to diagnose cerebellar complaints clinically, and distinguish cerebellar from sensory ataxias (Medistudents, 2018). The Luria-Nebraska Neuropsychological Battery (LNNB) is a standardised test battery that provides useful information in the diagnosis of brain damage or dysfunction (Purisch & Sbordone, 1986). Unfortunately, given the cost and time needed to conduct this battery (269 items) this test was not appropriate for the present study, and therefore alternative tests were sought after.

A similar issue arises at the other end of the developmental spectrum when attempting to diagnose developmental disabilities such as dyslexia (Nicolson & Fawcett, 1990), in which it is possible to achieve high accuracy but low fluency of reading or other skills by means of extensive 'controlled processing' (Shiffrin & Schneider, 1977). In response to these

difficulties Nicolson and Fawcett designed a variety of screening tests for children and adults (Fawcett & Nicolson, 1996, 1998; Nicolson & Fawcett, 1996) that were intended to assess the range of cognitive and motor skills – speed, literacy, phonology, memory, coordination, verbal and semantic fluency, and nonverbal reasoning. The tests were intended to be quick, fun, and to test 'primitive' skills, which are not amenable to conscious compensation. Although developed for a different purpose, these tests are directly relevant to assessing changes of skill in ageing, while being sensitive to the changes given that many of the tasks are speeded. They address the issues of fluid vs crystallised intelligence, motor vs cognitive skill, speed and working memory that remain at the forefront of cognitive ageing theory while being simple, quick and usable by a range of professionals without training in psychological testing (Fawcett & Nicolson, 1998). Consequently, they could address the above theoretical and applied challenges.

This study re-analyses the data from the validation and norming study for the Dyslexia Adult Screening Test. Using this dataset allows us to work with an established set of existing normative data, and examine a large cohort as a cross section. The nature the study is exploratory: we want to better understand the patterns of cognitive functioning within an aging population, as a first step towards creating a sensorimotor test battery for predicting cognitive decline. It is hypothesised that motor function will show a significant negative correlation with age, in addition to the confirmation that older participants will perform worse than their younger counterparts in tests of processing speed and fluid skills as well.

2.2 Method

2.2.1 Design

This was an exploratory correlational study, designed to investigate behavioural changes in cognition with increasing age.

2.2.2 Participants

This dataset is taken from the normative testing data obtained during the development of the Dyslexia Adult Screening Test (DAST, Fawcett & Nicolson, 1998). For the earlier Dyslexia Screening Test (Fawcett & Nicolson, 1996) whole classes in schools were tested using Ofsted performance data to select representative schools selected to fit a range of demographic variables. For the DAST, a 'whole cohort' approach was used wherever possible - testing everyone in the group in question and trying to select groups with little academic selection

component, using schools information to select the regions for testing. Data was carefully checked for continuity between the data of 16-17 year olds in the DST and 17-18 year olds in the DAST. No medical data was collected as this would not be standard for a screening test, but occupation was checked against demographic requirements for a stratified sample.

A standardisation sample of 600 was derived from over 1,100 UK adults, as the non-verbal reasoning test was added to the battery at a later stage, with an extra cohort who did not necessarily complete the full test. The authors have provided a subset of 441 participants for analysis here, who provided 'across the board' data. This however includes large amounts of missing data for the postural stability test, as many testers were reluctant to engage with it. Participants were volunteers tested in London and Sheffield at job centres (with the unemployed), churches, banks, supermarkets, lunch spaces, homeless, police, the army, working men's clubs, probus men's groups and youth clubs. The distribution of socio-economic status groups was also loosely based on that of the WAIS-R (Wechsler, 1986) sample. The sample here are aged 15 to 75 (M= 39.74, SD= 15.25), with a gender split of 45% male, and 55% female. The average school leaving age was 16.9 (SD= 2.35), with 68% having left school by age 17. Only 4% of the sample left further or higher education aged 21 or above. It should be noted that this data was collected in 1997, when only 15.9% of the UK population was aged 65 or over (Office for National Statistics, 2018c), and was not intended for the purpose of analysing age related changes or differences in cognition

2.2.3 Materials

While never intended for the purpose of analysing age-related changes in cognition, the DAST (Fawcett & Nicolson, 1998) comprises of 11 subtests, designed to test the spectrum of cognition. This includes literacy, sensori-motor skills, executive functioning and speed of processing. Although originally intended to screen for dyslexia, it is quick and simple to administer, and provides rapid assessments of cognitive domains which are relevant to the study of ageing. Currently, there is no quick and easy test of cerebellar functioning, nor any test with normative data. There are major difficulties in assessing cerebellar function, partly because the cerebellum is never working alone; it works in tandem with other brain regions. The entire battery takes just 30 minutes to complete using pen and paper, and all subtests have clear discontinuation instructions.

2.2.3.1 Rapid Automated Naming (RAN)

This test measures the crystallised ability of the naming process, and is a good measure of processing speed. Participants are required to name 40 common outline drawings (two blocks of repeated stimuli) as quickly as possible. Example items include hand and bird. The dependent variable is the time taken (in seconds) to complete the task. An adjustment is made for any errors. It should be noted that a higher score represents worse performance.

2.2.3.2 One-minute Reading (OMR)

Participants are asked to read a list of 120 words, increasing in reading difficulty, as quickly as possible. They are arranged on the card in columns, with participants having one minute to complete the task. The dependent variable is the number of words read. Adjustments are made for errors, as well as any time remaining if the list is completed. This test combines fluency and accuracy.

2.2.3.3 Postural Stability (PSt)

Postural stability difficulties are generally accepted to be representative of cerebellar abnormalities. The DAST test pack comes with a balance tester, which must be calibrated to provide 4kg of force. Participants are asked to stand straight while wearing a blindfold, and the force is applied to their lower back several times, full details of which are provided in the manual (Fawcett & Nicolson, 1998). The degree of sway is assessed by the experimenter, with higher scores indicating more sway. This test is not suitable for those over 70 or those with physical difficulties with standing; however this would only be expected to account for a very small proportion of the data missing from this dataset.

2.2.3.4 Phonemic Segmentation (PSeg)

Participants must perform 12 phonemic manipulations, and three spoonerisms, where the first sound of two words must be swapped. For example, car park becomes par cark. The phonemic manipulations require participants to segment a whole word, and deliver only the required portion. An example would be to ‘say /glow/ without the /l/’. The dependent variable was the number of correct responses. This task is likely to test both phonological skill and working memory.

2.2.3.5 Two-minute Spelling (TMS)

The experimenter is required to read a list of 32 graded spellings, with the participant required to write as many of them correctly as possible within two minutes. The dependent variable is the number of words correctly spelled. The maximum score is 40, as eight points

are added if the participant does not need the additional (more simple) words. It is an index of spelling fluency.

2.2.3.6 Backwards Digit Span (BDS)

Participants were given a string of numbers, and asked to repeat them back to the experimenter in reverse order. Strings started at two digits long, but increased in length every two trials, until a maximum string of eight digits. Presentation stops following two consecutive errors, with the dependent variable being the total number of correct responses. The strings were played via a tape recording at a spoken rate of one per second, with a beep before and a beep afterwards. This is a test of working memory with a strong executive component.

2.2.3.7 Nonsense Passage Reading (NPR)

Participants were required to read a passage in the format of a meaningful short story, containing 59 normal English words, and 15 nonsense words. The nonsense words follow the normal rules of English spelling and pronunciation, but are novel. An example of such a word used is 'frumbunctious.' The participant therefore has to break down and interpret each word, before attempting to articulate the word, a test of both crystallised and fluid skills. The dependent variable is a score comprised of both speed and accuracy measures.

2.2.3.8 Non-verbal Reasoning (NVR)

This sub test was designed to measure fluid intelligence/ frontal executive function. There are three sets of questions. Questions 1-3 ask participants to find the last piece in a sequence. Questions 4-6 follow the pattern 'if A is to B, then C is to ?' with the participant needing to select the appropriate pattern for D. There are two questions in the third section, which ask the participant to group patterns together looking for similarities and differences between the five patterns presented. The participant has 90 seconds to complete each of part one and two, and 60 seconds for part three. The dependent variable is the number of correct responses provided.

2.2.3.9 One-minute Writing (OMW)

Participants were provided with a short, written passage of 50 words to copy within one minute. Scoring was a combination of number of correct words copied, followed by adjustments for speed, errors, poor handwriting, or poor punctuation. This tested writing speed; a motor task.

2.2.3.10 Verbal Fluency (VF)

Participants were asked to name as many words as they could beginning with 'S' whilst being timed for one minute. The dependent variable was the number of valid words named within the time. There was no penalty, but no score, for repetition.

2.2.3.11 Semantic Fluency (SF)

This test is very similar to the verbal fluency task, but instead asked participants to name as many animals as they could within a minute. The dependent variable was measured in the same way as for the verbal fluency task.

2.2.4 Procedure

Tests were run according to the DAST Manual (Fawcett & Nicolson, 1998).

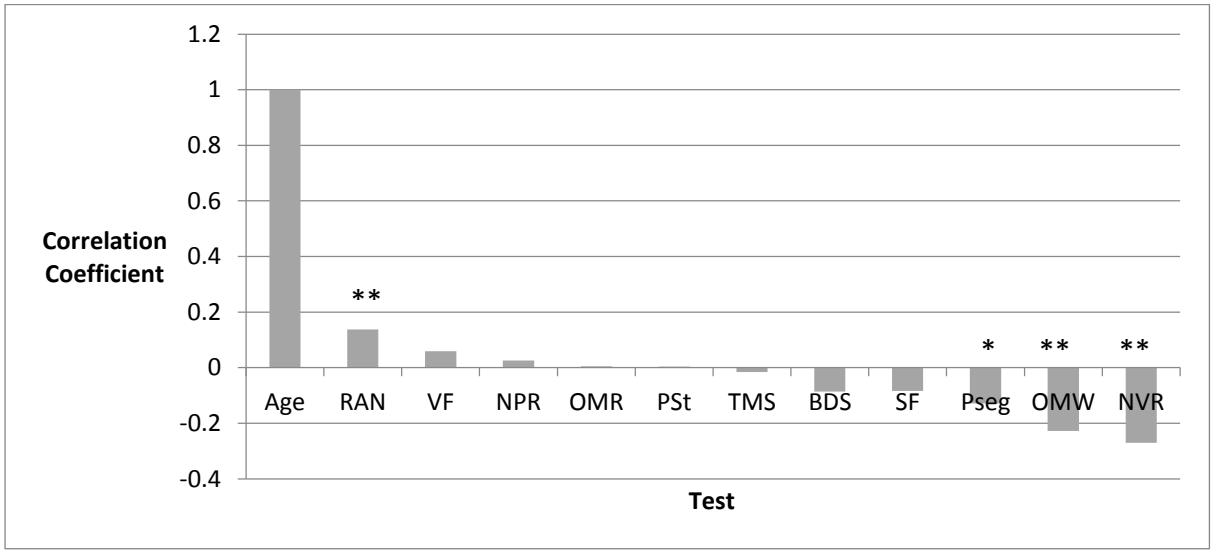
2.3 Results

2.3.1 Whole Sample

Firstly, analysis was run on the whole sample to look at differences across the lifespan. The distribution of each variable was inspected using the Shapiro Wilk test, which revealed that none were normally distributed. As this test can be overly sensitive, histograms, Q-Q plots and box plots were visually assessed, as well as measures of skew and kurtosis. Together they confirmed a mix of outliers, and problems with and kurtosis amongst the variables. Therefore, median and interquartile range are reported in Table 3 as descriptors of the data distributions, alongside mean and S.D. Spearman's correlations with age are presented (Figure 2) to describe the change in all cognitive domains in relation to age, followed by correlations between the cognitive domains themselves (Table 4).

Variable	N	Mean	SD	Median	IQR
RAN	440	28.12	7.13	27	9
VF	436	18.47	6.15	18	8
NPR	439	91.39	11.16	94	12
OMR	438	106.36	15.74	108	23
PSt	236	1.59	2.76	0	2
TMS	436	33.08	5.17	34	7
BDS	438	6.77	2.40	6	3
SF	437	20.57	7.67	20	10
Pseg	438	13.15	2.22	14	3
OMW	437	31.26	6.65	32	7
NVR	437	4.48	1.64	5	3

Table 3: Descriptive Statistics for the 11 DAST sub tests



Note: *sig at p=.01, ** p=.005, *** p<.001

Figure 2: Spearman's Rho Correlations with Age

It should be noted that higher scores for rapid naming and postural stability are indicative of lower performance in this test. For all other tasks, lower scores indicate lower performance.

Significant negative correlations with increasing age were seen for Rapid Automated Naming (r_s=.138, n=440, p=.004), Phonemic Segmentation (r_s=-.129, n=438, p=.007), One Minute Writing (r_s=-.228, n=437, p<.001) and Non Verbal Reasoning (r_s=-.270, n=437, p<.001). This suggests that the strongest associations with age are with complex tests that require

speeded or complex controlled information processing, loading on working memory, with executive function performance is also being affected. It is of note that postural stability, a test that is expected to be particularly sensitive to cerebellar dysfunction, did not correlate with age.

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. RAN										
2. VF	-.230**									
3. NPR	-.270**	.344**								
4. OMR	-.365**	.374**	.561**							
5. PSt	.047	-.195*	-.030	-.189*						
6. TMS	-.293**	.299**	.596**	.462**	.006					
7. BDS	-.241**	.275**	.327**	.315**	-.084	.294**				
8. SF	-.169**	.598**	.341**	.289**	-.013	.263**	.267**			
9. PSeg	-.183**	.287**	.510**	.342**	-.050	.450**	.391**	.286**		
10. OMW	-.288**	.306**	.415**	.384**	-.064	.597**	.269**	.338**	.280**	
11. NVR	-.172**	.253**	.205**	.172**	-.049	.392**	.360**	.293**	.292**	.344**

Note: ** sig at p<.005, *** p<.001

Table 4: Correlations between the 10 sub- tests

Correlational analysis reveals that across the whole age group, with the exception of postural stability, all measures of cognition correlate significantly with each other (the negative correlation seen with Rapid Automated Naming is seen as a result of reverse scoring on this sub test). This is suggestive of a general pattern of reduction in complex cognitive functions as age increases, which is common across all cognitive domains. It should be noted that there were fewer participants completing the postural stability task (N ranged from 234-236, whereas N for all other correlations ranged from 433 to 440) and that it correlated negatively with verbal fluency and one minute reading, again reflective of higher scores implying worse performance for postural stability.

2.3.2 Age Group Comparisons

Participants were then categorised into decades, so that comparisons could be made between younger and older adults. Group 1 represented everyone 19 and under (10.9%); group 2 represented ages 20-29 (21.6%); group 3 represented ages 30-39 (17.5%); group 4

represented ages 40-49 (20.9%); group 5 represented those aged 50-59 (17.5%); group 6 represented ages 60+ (11.6%). Demographic data, and sub test means and SD are presented for each age group in Table 5. Postural stability was eliminated from analysis at this point due to low group numbers, particularly in the older groups; there were only 21 participants in total aged 50 or over for this variable.

	Group 1 (n=48)	Group 2 (n=95)	Group 3 (n=92)	Group 4 (n=92)	Group 5 (n=77)	Group 6 (n=50)
F/M ratio	29/19 M(SD)	49/46 M(SD)	30/47 M(SD)	56/36 M(SD)	39/38 M(SD)	37/13 M(SD)
Age	17.96 (.87)	24.59 (2.90)	34.98 (2.52)	44.88 (3.05)	52.85 (2.97)	67.13 (5.92)
School leaving age	16.92 (1.09)	17.63 (1.87)	17.48 (2.28)	16.65 (1.81)	16.08 (1.80)	15.88 (1.25)
Rapid Automated Naming	25.50 (4.95)	26.61 (5.99)	25.09 (4.41)	26.69 (4.55)	26.69 (4.29)	27.75 (6.69)
One Minute Reading	102.54 (19.06)	106.25 (17.15)	110.14 (13.96)	106.62 (15.39)	107.85 (11.86)	108.50 (12.48)
Phonemic Segmentation	13.50 (1.48)	13.62 (1.77)	12.14 (2.16)	13.62 (1.63)	12.62 (2.93)	13.25 (1.67)
Two Minute Spelling	32.35 (3.63)	33.58 (5.27)	34.10 (4.71)	32.35 (6.33)	33.38 (6.35)	33.25 (5.18)
Backwards Digit Span	8.00 (2.35)	7.11 (2.69)	6.76 (2.68)	7.00 (2.06)	6.92 (1.55)	6.50 (2.67)
Non-Verbal Reasoning	5.08 (1.41)	4.88 (1.72)	4.79 (1.41)	4.50 (1.81)	4.54 (1.27)	2.00 (1.41)
Nonsense Passage Reading	89.88 (8.49)	92.17 (9.44)	92.19 (9.75)	92.92 (7.42)	90.46 (8.89)	95.00 (7.82)
One Minute Writing	32.04 (4.34)	33.41(6.41)	31.95 (5.54)	29.96 (6.17)	29.38 (5.94)	29.00 (6.91)
Verbal Fluency	16.62 (5.49)	18.04 (6.12)	19.36 (6.50)	19.50 (5.53)	18.54 (5.44)	14.88 (2.80)
Semantic Fluency	19.19 (7.36)	21.25 (8.57)	23.05 (7.71)	20.46 (7.34)	20.62 (7.63)	16.75 (5.68)

Table 5: Demographics and results of neuropsychological tests by age group

Data were converted into z scores before the mean of each age group was plotted to explore the change of each cognitive test with age (Figure 3). It should again be noted that a higher score in the Rapid Naming test indicated lower performance, for all other tests, lower scores indicate lower performance.

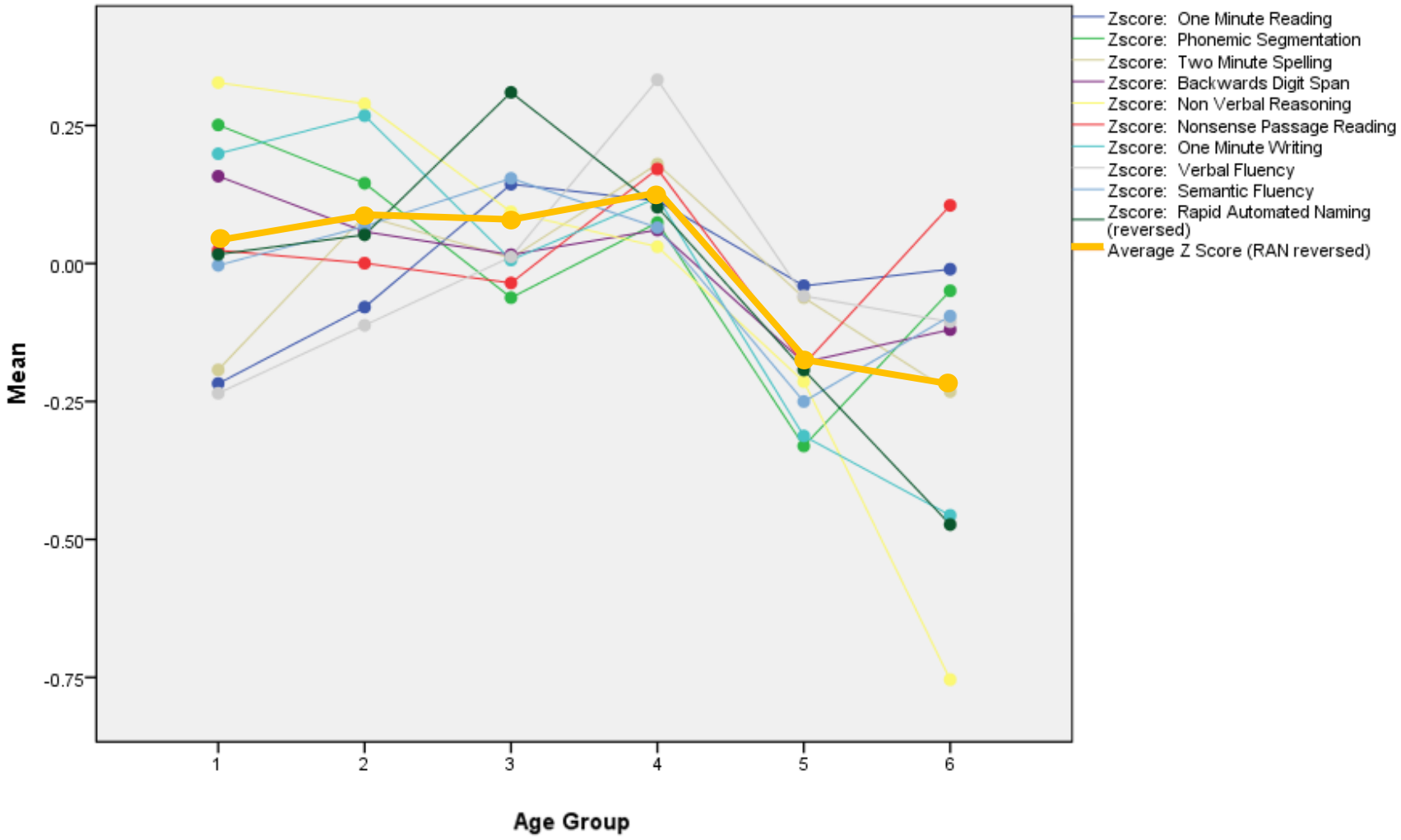


Figure 3: Mean Z score of the 10 subtests by age group

Figure 3 reveals two clear results; a constant reduction in function between age groups across the lifespan in Non Verbal Reasoning; and a sharp reduction between younger and older age groups in Rapid Automated Naming from age 30 onwards. There is also a marked difference between age groups in One Minute Writing, with lower scores being associated with increasing age group. The average Z score shows a slight increase in cognitive abilities up until the age of 40, after which a sharp drop between age groups occurs, emphasising the general pattern of reduction between age groups across all domains. The individual test scores reveal that there are some improvements between ages 30 and 49 (One Minute Reading, Semantic Fluency, Verbal Fluency, and Two Minute Spelling), as well as some improvements after age 50 (Phonemic Segmentation and Nonsense Passage Reading). Together, this suggests a differential pattern of age-related differences underlies each domain.

Comparisons were then made between those aged 20-29, and those aged 50-59 and those over 60. The decision was taken to use the group aged 20-29, as those younger are arguably still developing, and therefore represent a less stable cross-sectional picture of cognition. Effect sizes were calculated using the following formula; Cohen's $d=2*t/\sqrt{df}$ (Cohen, 1988) which is applied to between groups change analysis. No change would result in an effect size of 0, whereas a score of +1.0 indicates a change of one standard deviation unit. Cohen (1988) suggests that effect sizes of 0.8, 0.5, and 0.2 be labelled large, medium and small respectively. Results are presented in Figure 4.

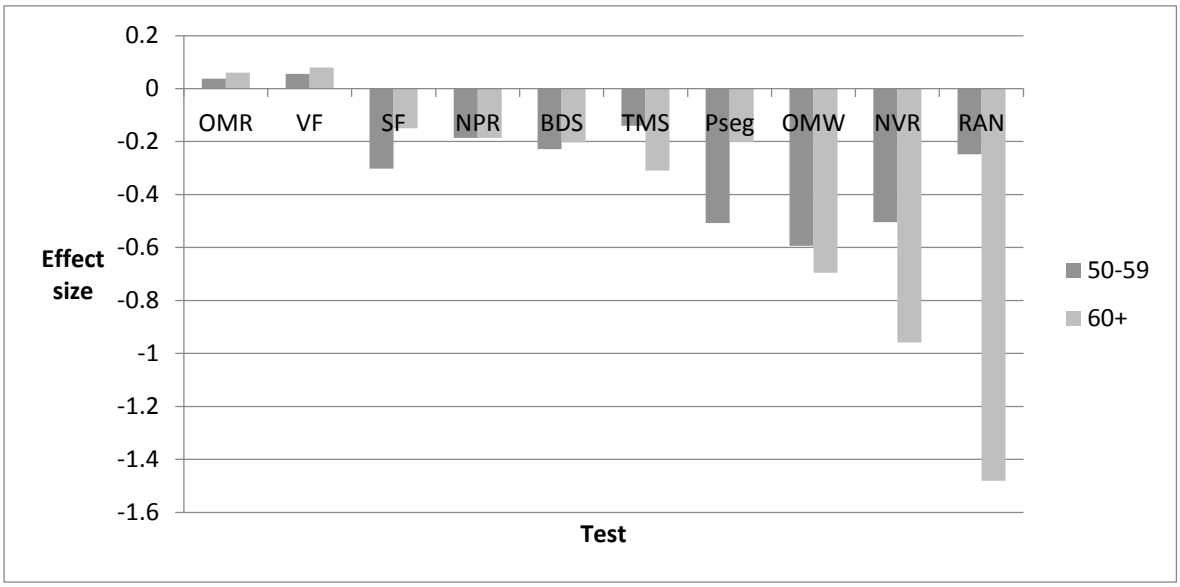


Figure 4: Effect size compared with mean and SD of 20-29 year old sample

Effect size analysis reveals that One Minute Reading and Verbal Fluency performance both increase in older age, in comparison to younger counterparts. All other tests show a reverse of this difference. Large effect sizes are seen for Non Verbal Reasoning and Rapid Automated Naming, as well as a medium effect size for One Minute Writing. In the 50-59 group, OMW shows a larger effect size than Non Verbal Reasoning and Rapid Automated Naming, perhaps suggesting that this domain is first to show a noticeable difference. A medium effect size is also found for Phonemic Segmentation in this age group. In order to test whether these group differences were significant, a MANOVA was performed. There was a significant difference between groups (age group 2 mean=4.96, SD=1.73; group 5 mean=4.54, SD=1.27; group 6 mean=1.25, SD= .96) for Non Verbal Reasoning (F(2,95)=9.70, p<.001, pn2= .17,. There was a non-significant difference between groups (age group 2 mean=33.65, SD=6.62; group 5 mean= 29.38, SD= 5.94, group 6 mean= 29.50, SD= 5.45) for One Minute Writing however this was approaching significance, F(2,95)= 2.99, p=.055, pn2= .06. All other variable showed no significant differences between age groups. As there were specific hypotheses about where the differences between groups would lie, a series of t tests were selected in favour of using planned contrasts, and Bonferroni corrected results are presented in Table 6. The critical alpha used is therefore *p*=.005. Despite the non-normal distributions of the variables, it was decided that given the large sample size, t-tests were robust enough to cope with the violation of the normality assumption (Lumley, Diehr, Emersen and Chen, 2002). Additionally, Bonferroni is arguably rather conservative, and therefore any significant findings can be interpreted with some confidence.

Test / Age	OMR	VF	SF	NPR	BDS	TMS	PSeg	OMW	NVR	RAN
50-59	*t*=-.25	*t*=-.36	*t*=1.97	*t*=1.22	*t*=1.49	*t*=.907	*t*=2.83	*t*=3.84	*t*=3.27	*t*=-1.62
	NS	NS	NS	NS	NS	NS	*p*=.005	*p*<.001	*p*=.001	NS
60+	*t*=-.36	*t*=-.04	*t*=.89	*t*=-.61	*t*=1.16	*t*=1.85	*t*=1.20	*t*=4.09	*t*=5.71	*t*=-2.77
	NS	NS	NS	NS	NS	NS	NS	*p*<.001	*p*<.001	NS

Table 6: Independent t-tests comparing age 20-29 (n=94 or 95) to both 50-59 (n=75-77) and 60+ (n=49-51) across the ten DAST sub tests.

After Bonferroni correction, t tests revealed significant differences in One Minute Writing, Non Verbal Reasoning, and Phonemic Segmentation only. There was a significant difference between 20-29 (*M*= 33.41, *SD*=6.41) and 50-59 (*M*=29.39, *SD*=5.94) for One Minute Writing Score (*t*(170)=3.34, *p*<.001), as well as between age 20-29 and age 60+ (*M*=29.00, *SD*=6.91),

t(142)=4.09, p<.001. There were also significant differences between age 20-29 (*M*= 4.88, *SD*= 1.72) and age 50-59 (*M*= 4.54, *SD*= 1.27) for Non Verbal Reasoning (*t*(169)=3.27, *p*=.001 50-59) and between age 20-29 and age 60+ (*M*= 2.00, *SD*=1.41), *t*(142)=5.71, *p*<.001. Phonemic segmentation is significantly different between age 20-29 (*M*= 13.62, *SD*= 1.77) and 50-59 (*M*= 12.62, *SD*= 2.93), *t*(133)=2.83, *p*=.005). Levene's test indicated unequal variances (*F*=8.10, *p*=.005), so degrees of freedom were adjusted from 170 to 133. It should be noted that Rapid Automated Naming for those aged 60+ was approaching significance at *p*= .006. Together, these results suggest significant age related differences in executive functioning and motor skill.

2.4 Discussion

This study was exploratory in nature, and thus a series of investigative analyses were run. RAN, PSeg, OMW and NVR, all revealed a significant negative correlation with age. All 11 subtests correlated significantly with each other, with the exception of postural stability, which only correlated with VF and OMR. Comparison of Z scores between age groups revealed large age-related differences in RAN and NVR, as well as a moderate difference in OMW for the over 60's compared to younger counterparts. NPR shows a sharp drop in the 50's age group, but a marked increase between this group and those in their 60's. Effect size analysis revealed that in comparison to those in their 20's, those in their 50's and the over 60's show improvement in OMR and VF (both fluency tasks) but perform worse in all other tests. T-tests revealed that these differences were significant in the 50's age group for and PSeg; for both the 50's and over 60's for OMW and NRV.

Support was therefore found for the hypothesis that motor function shows a significant negative correlation with age, and was confirmed by all analyses as deficits in OMW were found. Partial support was also found for the confirmatory hypothesis of frontal executive functioning/ fluid skills also showing reduced performance with increasing age. This was measured by NVR and PSeg. However, Bonferroni corrected t-tests revealed that there was no significant difference between age groups for BDS, a test of working memory. There was mixed support for the hypothesis that processing speed shows reduced performance with increasing age. While there was a significant correlation with age, and the line graph showed a sharp increase in score (therefore indicating slower performance), and t-tests failed to reveal a significant difference between those aged 20-29 and those aged 50 and above. Possible explanations for this are discussed.

Correlations with age reveal a significant negative relationship with processing speed (as measured by RAN), motor skill (as measured by OMW) and frontal executive functioning/ fluid skills (as measured by PSeg and NVR). No significant relationships between age and fluency tasks (VF, OMR, TMS AND SF), the BDS or PSt were found.. Difficulties with executive functioning and motor skill are often noticeable as we age, and results here confirm that these are significant changes, that are measurable using existing tests. The negative correlation between age and processing speed can be attributed to the failure of the cerebellum to act as a precise time keeper (Strick et al., 2009); cerebellar control of fine motor movement is well established; and a network involving the cerebellum and frontal lobe has been implied in executive functioning (Stoodley, 2012; Gordon, 2007, Ramnani, 2006, 2012; Bernard & Seidler, 2014; Leiner et al., 1986). The fact that BDS didn't show significant relationship with age suggests that further work is needed to establish the precise nature of the cortico-cereballar loops that are most involved in cognition, and are most susceptible to the effects of ageing. Evidence to suggest that fluid intelligence declines, while crystallised skills are maintained (Horn, 1982) is demonstrated by the fact that VF, NPR and OMR actually improved with age in the current sample. However, these findings were not significant. The fact that PSt showed an increase, albeit non- significant, is somewhat surprising given that the cerebellum is likely to also be involved in the complex mechanism behind postural control (DuPaquier et al., 2003). Yet close inspection of the data analysed in this study reveals a great imbalance. As previously mentioned, there is a large amount of missing data, due to the late addition of the NVR test, and not all participants then being asked to complete all tasks, and experimenters being uncomfortable with administering the PSt test. There are 205 missing data points for PSt, and the majority of the missing data is within the older age groups; the average missing percentage for age groups 1-3 (up to age 39) is 13.83%, while for those 40 and over is 76.85%.

Given that the spread of the data by age was uneven, it would seem reasonable to assume that a more complete sample may have in fact revealed the differences that would have been expected. In summary, the reduction of executive functioning and processing speed with increasing age is well documented and confirmed by this study, while the finding that tasks involving motor function also show significantly reduced performance with age is a noteworthy discovery, given that this can be attributed directly to cerebellar functioning, and the role of the cerebellum in cognitive ageing is far less well established. The fact that all variables correlate significantly with each other (with some exception for PSt which may be

explained by methodological issues) adds further weight to the argument of cortico-cerebellar loops being at play in cognitive ageing.

These results are further confirmed once the data is divided into age groups. Line graph analysis of the z scores reveals a dramatic drop in executive functioning (as measured by NVR) and speed of processing (as measured by RAN) between age groups, further confirming what is well established in the literature (Buckner, 2004; Drag & Bueliauskas, 2010; Troller & Valenzuela, 2001; Greenwood, 2000; Deary et al., 2010; Albinet et al., 2012; Ren et al., 2013). In line with what was found through correlational analysis, motor function (as measured by OMW) also shows a marked drop between age groups. The important difference between this analysis and the correlations, is that it demonstrates the pattern of the age-related differences. Executive functioning continuously drops between age groups as age increases, with the sharpest drop coming after the age of 50. Processing speed improves into our 30's, but then sharply drops after this. Motor functioning shows a mixed pattern increases and decreases in function between age groups up until our 40's, showing a substantial negative difference after that. What is of great importance here, is that problems with executive functioning are often first to be reported as we age, yet processing speed and motor functioning could potentially start declining earlier, a possibility suggested by Vasylenko et al. (2018b) after assessing the relationship between cognitive function and dexterity in young and older adults The authors used a battery of cognitive tests (including executive function, working memory and attention)_and dexterity assessment was based on the Purdue Pegboard. Regression analysis revealed significant involvement of cognitive abilities in dexterity, particularly for older adults, leading the authors to conclude that it is the cognitive component of dexterity rather than peripheral changes that these tests are detecting (Vasylenko et al., 2018b). It should be noted that the present study had relatively small numbers in each group (n ranged from 48 to 95) and that what is noticeably low is the number or participants that are at the top end of the age scale. The present sample only included 50 people aged 60 or above, accounting for less than 12% of the total sample, with the oldest participant at 75. In today's society, 60 isn't even pensionable age anymore, with 18.2% of UK adults presently over 65 (compared to 6.8% in the current sample; Office of National Statistics, 2018c). This data was collected in 1997, when only 15.9% of the UK population was aged 65 or over (Office for National Statistics, 2018c), and not intended for the purpose of analysing age related changes in cognition, so this must be kept in mind when interpreting the results. It is likely that a more representative sample including more participants at the higher end of the age scale would

have helped to clarify the pattern of age related changes seen here, but the plausible conclusion of cerebellar involvement driving age related deficits cannot be ignored.

Effect size analysis compared older adults (aged 50-59 and 60+) to those aged 20-29, and revealed a similar pattern of results. For the 50-59 group, moderate negative effect sizes were found for PSeg, OMW and NVR. For the over 60 group, there were large effect sizes for OMW, NVR and RAN, with OMW and NVR showing significant differences between young and old after Bonferroni corrected t-tests were run. What is interesting here is that processing speed did not show a substantial difference between young and old until 60 years of age, and that motor functioning showed the largest difference between young and old for the 50-59 group. This again highlights the potential use of motor tasks (in this case OMW) to predict future cognitive decline, given that frontal executive and processing speed tasks do not show large effect sizes until 60 years old, and that the motor deficit is present earlier in life.

The other tests revealed no significant changes, although the trends reveal an interesting pattern for discussion. One minute reading and verbal fluency (fluency tasks) may improve, while semantic fluency (fluency task), nonsense passage reading (fluid and crystallised abilities), backwards digit span (working memory) and two minute spelling (crystallised ability) could be potentially more subject to age-related differences. Crystallised abilities are often spared, or even show some improvement across the lifespan (Park et al., 2002) which would explain why no significant differences were found in the verbal fluency tasks. It is possible that the neural networks involved in fluency tasks are differentially affected by age. It is beyond the scope of this thesis to investigate this further, but an interesting future direction to be pursued, using neuroimaging techniques to better understand this relationship. Understanding the neural correlates of behavioural age-related change will allow targeted treatments and interventions to be utilised effectively, preserving quality of life in old age. The retrieval deficit proposed by Drag & Bieliauskas (2010), in which they suggest that semantic tasks are likely to represent a problem in retrieval, rather than a semantic deficit itself, could also explain why TMS showed a non-significant negative relationship, and the similar pattern seen in NPR and BDS was expected given that it is well established that fluid abilities decline with age (Horn, 1982). However, it should be noted that for all of these sub tests, the effect sizes were small at best, with t tests revealing that none of these differences were significant. Given that the test battery and sample collected were never intended for the purpose used in the present study, it is worth considering how these tests may be better utilised in future study designs.

Phonemic Segmentation was significantly different between those aged 20-29 and 50-59, while significant differences were found between the young and both older age groups for motor function and frontal executive functioning. Remarkably, after Bonferroni correction, RAN was no longer significantly different between the over 60s and younger groups. This lends support for the fronto-cerebellar theory of ageing over that purely based on processing speed, given that only differences in motor and frontal executive functioning persist in the oldest age group. This theory therefore could accurately account for the significant deficits found in tasks largely controlled by the frontal lobes (executive functioning) and cerebellum (motor function).It is worth remembering that this theory argues the need for fully functioning cortico-cerebellar loops, rather than the dominance of a particular brain region per say. Treitz et al. (2007) noted that executive functioning does not decline unilaterally, as normal ageing differentially affects executive subcomponents, which could also offer further explanation as to why RAN was not found to be significant in this sample.

2.4.1 Summary of Main Findings

The results of study one overall are consistent with the literature. As expected there are strong effects of age on fluid intelligence (NVR) and processing speed (RAN). The crystallised skill (of reading) remains intact, as (perhaps more surprisingly) do tasks measuring fluency. There is some evidence of increasing difficulties with working memory and segmentation, and strong evidence of reduced speed of writing. Correlations with age were significant for nonverbal reasoning, writing, rapid naming and segmentation. The norm analyses suggest that nonverbal reasoning shows a pattern of reduced performance for participants between the age groups, but substantially over 50 years, whereas the difficulties with rapid automatic naming and with writing appeared primarily before this age. The effect size analyses suggest that the effects for the latter three scales occur for both of the oldest groups, with accelerating problems for the oldest group.

2.4.2 Limitations and Future Directions

Some of the limitations for this study have already been discussed, particularly in relation to postural stability and missing data. It has also previously been mentioned that this data set was not originally designed to test older adults, and this is reflected in the lack of participants in the oldest category. While younger adults are important to understand changes across the lifespan, this needs to be balanced with people at the other end of the scale This is something

that will be addressed by the next study, which will focus more heavily on older adults, and attempt to recruit participants in the later stages of life.

As a test battery that is quick and easy to administer, the DAST is perfectly suited to assess a wide range of cognitive and motor abilities. However, the findings suggest an important role for motor function as part of a test battery, it would be sensible to use a task that is more specifically designed to test this skill in an ageing context. Additionally, further measures of executive functioning, memory, and sensory functioning could be added, to gain a wider perspective of age related changes. It is possible that the tests that were sensitive to age were non overlearned tests requiring controlled processing, while automated tests were not affected. It is important to ensure that visual issues (such as cataracts) are taken into account when testing older adults, so this should also be recorded in future studies. The present study has made an important start on addressing the uncertainties in this area, but more accurate testing of these domains, and establishing causal links will be important next steps in understanding cognitive ageing.

The first aim of this thesis was to establish the potential role of the cerebellum in cognitive ageing, and how this could motivate specific approaches to screening and intervention, while the second was to be able to accurately determine who is at risk of cognitive decline. This study has contributed to both of these aims, as there is evidence to suggest motor tasks show a negative difference between age groups before a similar pattern is seen in cognitive tasks as demonstrated by the fact that OMW shows a significant difference between young and old before a NVR. However, it is unfortunate that there were such large amounts of missing data for PSt, which may have contributed to defining this relationship more clearly. Steps to refine the test battery are outlined. The next step (addressed in Chapter 3) is to test whether motor function is actually predictive of performance in these domains.

2.4.3 Conclusion

Decline in sensorimotor and cognitive function is well established as a factor of ageing, yet there is little consensus as to how the mechanisms underlying these deficits work. The present study found significant negative relationships between executive functioning, processing speed and motor function with age, and particularly that speeded motor function is potentially the first of these domains to show behavioural signs of a deficit. This adds extra weight to the fronto-cerebellar ageing hypothesis, and provides evidence of a causal role for the cerebellum in ageing, as its functioning has been linked not only to motor control, a fact

that is well recognised, but to cognition as well. In the attempt to create a highly predictive battery for assessing cognitive decline, as well as to provide suitable interventions to prevent said decline, evidence points to targeting the cerebellum as a means to helping an ageing population age well.

3 Chapter 3: Motor Function as a Predictor of Cognitive Function (Study Two)

3.1 Introduction

From a physiological perspective, changes occur in all organ systems (Boss & Seemiller, 1981).This has implications for muscles, cartilage, bone and tissue, as a failure to repair leads to further physical weakening. While an absence of disease is no longer used to define healthy ageing, emphasis on the ability to learn and make decisions, therefore preserving a high quality of life and independence, is stressed instead (World Health Organization, 2019). Therefore, maintaining cognitive health is central to the successful ageing process. There is a pressing need to consider the needs of older adults, as distinctly different to those younger. They face additional challenges, but may have developed strategies to counteract them.

While these patterns describe a compensatory mechanism in the brain, it can be argued that none of these models fully account for the series of cognitive difficulties experienced in ageing. Cognitive decline is well established in the elderly, yet questions remained as to how this is characterised, as variability in testing mechanisms have led to variability in the results. Historically, these changes have been linked to cerebral cortex impairments (West, 1996), but strong evidence of subcortical contributions to cognition are emerging. Not only is this evidence particularly strong for cerebellar involvement (Hayder et al., 2004) through examination of cortio-cerebellar loops, there is also evidence of neuronal loss in subcortical structures in ageing (Gordon, 2007). Hogan's (2004) frontal-cerebellar aging hypothesis attempts to bring several theories together by describing the full range of difficulties experienced.

The processing speed theory of ageing has gathered wide support, with the decline in processing speed well established in the elderly. Hogan (2004) argues that it is not just frontal degeneration, but the combination of this with cerebellar degeneration, and therefore the disruption of fronto-cerebellar feedback and feed-forward control loops that are of central importance, based on a review of current literature. Furthermore, the cerebellum is more than just a motor structure: a functional role is implied in language (as ascertained by a review of neuroanatomical, neuroimaging and behavioural reports of cerebellar involvement in cognitive and language functions (Leiner et al., 1993) and cognition (as described using in vivo diffusion imaging and probabilistic tractography to contrast cerebellar organisation in macaque monkeys and humans (Ramnani, 2006)), although precisely how it is involved is not well defined with further work to clarify this relationship being essential. Leiner, et al. (1986)

suggest (based on a review of the neuroimaging literature on humans and primates) that the parts of the human cerebellum that have developed most recently are responsible for cognition, while the earliest evolutionary substructures are responsible for motor function. Since the cerebellum also has a strong role in motor coordination, yet its involvement in cognition is less well established, therefore leading to the important and unanswered question of whether motor skills might be associated with – or even predict - cognitive performance. Although it is difficult to find a purely cerebellar task, it is assumed that the motor skills being tested here are mediated by the cerebellum, so this will be examined by the present study.

3.1.1 The Cerebellum: More than just a Motor Structure

The role of the cerebellum in motor function is extremely well established. However, there is a growing body of evidence to suggest cerebellar involvement across the spectrum of cognitive function. Cerebellar contributions to language, working memory, processing speed, learning, attention and probably even emotion, have all been determined (Leiner et al., 1993; Ramnani, 2006; Eckert, 2011; Raz, 2000; Strick, Dum & Fiez, 2009; Ito, 2006). A summary of these papers is provided in table 7 below. A series of feedback and feedforward control loops between the cerebellum and the frontal lobes are the key to understanding the vital role of this sub-cortical structure across so many cognitive domains (Hogan, 2004). As stated by Leiner at al. (1993): "the cerebellum can improve the performance of any other parts of the brain to which it is reciprocally connected" (p.446). It has global connectivity with other areas of the brain, in particular with the cerebral cortex (Ramnani, 2006), and given that the structure holds 50% of the neurons in the human brain, it can be proposed that the cerebellum may play a substantial role in all domains of human brain function.

Study	Method	Sample	Findings/ Conclusions
Eckert, 2011	Review paper	Evidence for neurobiological predictors of age-related changes in processing speed. Used source based morphometry findings that show unique patterns of frontal and cerebellar grey matter predict age-related variation in processing speed.	The degree to which cerebellar declines reflect impairments in specific cerebellar systems and/or reflect changes in a dorsal attention system is still unclear.
Ito, 2006	Original paper discussing cerebellar circuitary as a neuronal machine, with the aim of bridging behavioural/cognitive and molecular/cellular knowledge.	Various papers detailing the micro circuitary of the cerebellum and cognitive functions of the cerebellum using anotomical, brain imaging, clinical and modelling techniques.	Evidence of cerebellar contributions to cognition are described, while acknowledging the remaining challenges in continuing to integrate experimental and computational approaches.

Leiner et al., 1993	Examining papers that describe the evolutionarily enlarged dentate nucleus in humans to debate whether the cerebellum is involved in higher functions	Various papers that address the debate topic using neuroanatomical, neuroimaging and behavioural data.	Cerebellum being involved in just motor function is too narrow a description, should be expanded to include mental functions.
Ramnani et al. (2006)	In vivo diffusion imaging and probabilistic tractography.	Nine healthy adults (six males, aged 26-33), two adult male macaque monkeys (Macaca fascicularis).	Dominant contribution of the cortical motor areas to the macaque moneky cereral peduncle. Relatively large prefrontal contribution to the human cortico-ponto-cerebellar system in the cerebral peduncle. Results reveal substantial growth of prefrontal projections tht complement the evolutionary expansion seen in the human prefrontal cortex and ventral dentate nucleus i nthe human cerebellum. This suggests that the human cerebllum may play specialised roles in processinf cognitive information.
Raz, 2000	Participants performed a pursuit rotor task, and verbal and non verabl memory tests. Volumes of the cerebellar	Sixty-eight healthy volunteers (age 22-80). Screened for various medical conditions and	Age related declines in procedural learning are assocuated with reduced volume of the cerebellar hemispheres and lower non-verbal working memory scores.

	hemispheres, neostriatum, prefrontal cortex and hippocampus were measured using MRI.	assessed for dementia and depression. All were right handed.	
Strick, Dum & Fiez, 2009	Review paper	Various papers, largely using neuroimaging techniques	"Anatomical evidence that the cereballum exerts an influence over nonmotor regions of the cerebral cortex is complimented by data from neuroimaging and neurophysiology." p429

Table 7: Summary of studies presented

Hogan (2004) champions the cerebellum as a modulator in sensory and motor behaviour, as well as playing a basic modulatory role in cognitive processing at the level of information-processing efficiency. By asking participants to press a button as an olfactory stimulant was detected and then extinct while having an fMRI scan, Ferdon and Murphy (2003) found cerebellar age differences between young and elderly participants. They argue that their findings provide additional support for the role of the cerebellum in attentional processing and sensory integration, as age-related sensory perceptual loss places greater attentional demands on the elderly for such tasks, resulting in the greater activation of the cerebellum in the ageing brain (Ferdon & Murphy, 2003). While this demonstrates that there is evidence to suggest cerebellar involvement in sensory processing, it is still an area that needs further research. The inclusion of sensory perception tasks alongside cognitive and motor tasks is an important addition for the investigation of age-related changes in function and one that will be implemented in the present study.

The cerebellum has also been implicated in the precision of timing, a function of the brain that is critical for sensorimotor processing and learning. While it is well accepted that neural timing involves a wide range of brain regions, Paton and Buonomano's 2018 review concludes that there is now a large amount of cumulative data supporting the population clock hypothesis, wherein the nervous system encodes time in the dynamically changing activity of populations of neurons, ranging from sequential chains of activity, to complex patterns, and that this hypothesis, which was first proposed by Buonomano and Mauk (1994),

is based on cerebellar circuitry. With evidence now in place to describe the contributions of the cerebellum to such a wide range of neural and behavioural functions, it is now left to investigate these contributions within the framework of human ageing.

3.1.2 Cerebellar Contributions to Ageing

Decline in some aspects of executive function as we age has led to extensive investigation of frontal lobe contributions to cognitive ageing. However, it is argued that these models alone do not fully account for the difficulties experienced in later life, and therefore theories of ageing that may describe the picture more accurately, may include cerebellar contributions to cognitive decline. Structurally, there are differences with age. The volume of the cerebellum is smaller in older adults, and its white matter integrity is reduced (Bernard & Seidler, 2014). The role of the cerebellum in cognition has been described above, but the role played by the cerebellum in cognitive ageing is not well established, and is somewhat unclear. Here, two leading theories of ageing are presented, highlighting the essentiality of cerebellar contributions.

Processing speed refers to the efficiency with which a series of tasks with simple cognitive content can be completed (Deary et al., 2010). The processing speed theory of ageing suggests that a deficit in a global mechanism, due in large part to diffuse global deterioration of white matter throughout the brain, accounts for the age-related changes in cognition (Albinet et al., 2012). Furthermore, such a theory can also account for ageing related changes in memory and verbal and spatial ability (Finkel, Reynolds, McArdle & Pederson, 2007). The authors applied two growth curve models (quadratic and two linear slopes) to longitudinal data from the Swedish Adoption/Twin study. Eight hundred and six participants (aged 50-88 at the first round of testing, including both twins who were separated before age 11 and reared apart and twins reared together) were tested on five occasions over a 16 year period, on a wide range of cognitive tests (see paper for further details; Finkel et al., 2007). It is argued that given the contributions of the cerebellum to cognition, that the deterioration of white matter in this structure is perhaps more significant that previously considered. Moreover, one of the strongest criticisms of frontal lobe theories of ageing, is that it fails to include the deficits accounted for by the widely supported processing speed theory. A more holistic approach is presented in the form of the fronto-cerebellar theory of ageing.

The fronto-cerebellar theory of ageing suggests that it is disruption of subcortical-cortical loops that lead to the difficulties experienced with advancing age. Eckert et al. (2010)

suggested that it is the disruption of the coordination of cerebellar and frontal/parietal regions with ageing that leads to slowed motor and perceptual processing speed. After a review of the literature, Hogan (2004) suggests that ageing of the cerebellum and/or disconnection between the cerebellum and the pre-frontal areas will reduce the efficiency of working memory and executive control by reducing the base capacity by the key functions of timing, processing speed, and automaticity. Bernard et al. (2013) find further support for disrupted cortico-cerebellar connectivity in older adults, specifically in cerebellar connections with the striatum and medial temporal lobes. They reported that associations between connectivity strength and both sensorimotor and cognitive task performance indicates that cerebellar engagement with the default mode network and striatal pathways is associated with better performance in older adults (Bernard et al., 2013). Despite such evidence to support the fronto-cerebellar theory of ageing, this area of research remains sparsely investigated, with a need for further empirical studies to better understand and more accurately describe the changes that occur with advancing age of the human brain.

3.1.3 Motor Function as a Predictor of Cognitive Function

Executive functioning and fine motor control correlate significantly for older, but not younger adults (Corti et al., 2017) and it is likely that motor function (as assessed using nine manual motor tasks including finger, tapping, foot tapping, grip strength, and Purdue Pegboard tasks among others - see paper for further details) declines earlier than cognitive function (Kluger et al., 1997). Some of this can be attributed to physical components of ageing, such as progressive loss of skeletal muscle mass, strength and power (Clegg, Young, Iliffe, Rikkert & Rockwood, 2013). But global decline in white matter would affect motor cortex structures, and fine movement is controlled by the cerebellum, so therefore neuronal loss in this region could be a key contributor. At the micro level, Sullivan, Rohlfing and Pfefferbaum (2010) found that greater transverse diffusivity, an index of myelin integrity, in cerebellar hemisphere fibre bundles contributed to slower finger movement, perhaps as a result of interhemispheric transfer of information not being necessary for good performance on this task. A stereological study of mice revealed that the processes of ageing impact brain structures and associated behaviours differently, with the cerebellum showing earlier age-related decline than the hippocampus (Woodruff-Pak et al., 2010). Together, these studies show not only that there are structural changes in the cerebellum with age, but that these manifest into tangible deficits in some aspects of motor function that may actually precede

the memory deficits that are often reported in ageing. Furthermore, Bernard and Seidler (2014) suggested that older adults may show increased reliance on cognitive resources during motor performance, as dual-task motor and cognitive paradigms have shown greater declines in motor performance. Based on this evidence, there may be an opportunity to predict changes in cognitive functioning, using motor performance. Importantly, this could be done well before clinical symptoms are present, and without expensive and time-consuming neuroimaging studies.

The fronto-cerebellar theory, supported by multiple models for cortico-cerebellar loops, implies a causal role for the cerebellum in ageing, and thus a clear link between the cognitive domains.

"In order to propose that the age-related changes in the cerebellum have implications for observed reductions in information processing efficiency, it needs to be demonstrated that components of information processing which are known to be under the control of the cerebellum show age-related declines." Hogan (2004, p.109)

This uncertainty is indeed highlighted by Gottwald, Wilde, Mihajlovic and Mehdorn (2004) who concluded that a general motor impact on cognitive performance did not exist when comparing 21 cerebellar patients to age and education matched healthy controls. Using a wide battery of cognitive tests including memory and working memory tasks, Stroop and attention, and using the Purdue Pegboard (peg moving tasks only), the authors concluded that cognitive impairment could not be explained by motor disabilities (Gottwald et al, 2004). This study attempts to resolve some of the ambiguity, as evidence within an ageing sample is needed to link these domains, and pave the way for using cerebellar function, or performance on tasks that index this, as a predictor of cognitive decline. Bernard and Seidler (2014) reported that in several cases (following a review of the literature), cerebellar morphology is as good a predictor of behavioural performance decline in older adults as is the prefrontal cortex, if not better. It has been suggested that differential losses in cerebellum and motor cortical regions lead to increased cognitive demand of motor tasks, and that this coupled with losses in pre frontal cortex and corpus callosum lead to reduced availability of cognitive resources (Seidler et al. 2010). This then manifests as the deficits seen in sensorimotor control and functioning in ageing, in everyday tasks that involve fine motor control, gait and balance (Seidler et al. 2010). It is acknowledged that smooth execution of these tasks is not only dependent on cerebellar function, but also on the supplementary motor area, prefrontal

cortex, and basal ganglia. Yet while the field is under-investigated and somewhat unclear, it remains essential to continue gathering data to test the relationship between sensorimotor and cognitive function in ageing, as well as better understanding the constructs underlying the behavioural outcomes.

3.1.4 Development from Previous Study

The first study described changes in cognition between cohorts of younger and older adults. Having revealed a marked negative relationship between age and motor function, as well as the well-established age-related deficit in frontal executive function and processing speed; it is important to update the methodology to more effectively test these domains. The present study introduces a direct measure of sensory functioning, as well as a more complex motor skill task. Sensory functioning has been suggested as a strong late-life predictor of individual differences in intellectual functioning (Lindenberger & Baltes, 1994), while the Purdue Pegboard (Tiffin and Asher, 1948) has been found to predict the presence of brain damage (Costa et al., 1963). The authors of the latter paper intended only to assess the use of this test as a screening device in detecting the presence and laterality of cerebral lesions, and therefore no further details on the location of the lesion were provided (Costa et al., 1963). Participants with brain lesions were compared to a control group who had lesions either in the peripheral nervous system or below the level of the thoracic spine (Costa et al, 1963). While it may not be argued that this is a purely cerebellar task, such a task is rather difficult to find, and the sensori-motor nature of the task makes it appropriate for the present study. There is an abundance of literature to support the use of motor function as a predictor of cognitive function, with the added benefit that such tests are independent of education (Kluger et al., 1997). These tests are introduced in order to further establish tasks that are both highly predictive, as well as easy to administer, in the pursuit of a test battery that can be used to screen older adults. The decision to only include older adults in this study was taken as testing younger adults would not have addressed the aims of the study.

3.1.5 Aim

In summary, there is currently a lack of understanding of the relationship between changes in motor and cognitive function in the context of ageing and with regards to the differing theoretical perspectives on the main neuroanatomical drivers of these changes. This represents a missed opportunity to better understand and predict age-related cognitive

function, which is likely to represent a reduction in performance compared to younger-aged counterparts. The overarching aim of this study is therefore to investigate the relationship between the various cognitive domains, within an aging sample.

3.1.6 Hypotheses

1. There will be a significant negative correlation between age and performance across all cognitive domains
2. There will be a correlation between processing speed (a measure of mental coordination, as assessed by the rapid naming task) and motor function (as measured by the pegboard tasks)
3. Motor function will be predictive of cognitive function (as measured by the memory subtasks presented in this study).

It should be noted that memory was selected as the dependent variable for the regression analyses due to the practical implications the results might have. Memory loss is one of the most common early symptoms of dementia (National Health Service, 2017), therefore finding a test to precede a noticeable difference is highly beneficial to the population as a whole. While not directly testing the population at risk, the implications of these findings demonstrate clear benefits in terms of our understanding of unsuccessful ageing, which would be directly applicable to that population.

3.2 Method

3.2.1 Design

This study is exploratory in nature. The full data set was used in a correlational design, followed by regression analysis in which performance on the Purdue Pegboard (peg moving and assemblies) were used to predict performance on the memory tasks included in the battery.

3.2.2 Participants

Two hundred and fifty six older adults (69 male, 182 female, 5 preferred not to say) were recruited through local press advertisements, information sent to older peoples' social clubs in the Sheffield and Rotherham area, through low dependency day care centres run by the

national charity Age Concern, or through the University of the Third Age. This process included rolling recruitment for two years. Participants were aged 46 to 97 (mean 72.34, SD 11.66) and were recruited to the South Yorkshire Ageing Study (Tarmey, 2012). Therefore they were participating in a wider set of investigations into ageing than those presented here.

3.2.2.1 Inclusion/Exclusion Criteria

Community dwelling adults without any formal clinical diagnosis of dementia were invited to take part in the study. All participants lived independently in their own home or part of a local authority sheltered housing scheme without the need for 24 hour care. Individuals with stable, chronic medical conditions were included, while anyone with acute medical conditions affecting major organ systems were not. The advert asked for people aged 50 or above, but people 46+ were not excluded if they expressed such a strong desire to take part.

Identifying a 'healthy' sample comes with challenges—pre-clinical symptoms, issues without diagnosis—the term healthy can be seen as somewhat subjective. Although operationalised for this study (and the next) as without any formal diagnosis of dementia or MCI, this of course does not exclude the possibility of there being underlying problems yet to manifest clinically, or there being clinical symptoms that were yet to be formally diagnosed.

3.2.2.2 Consent and Ethical Approval

Ethical approval was provided by the University of Sheffield, Department of Psychology Ethics Committee. All participants were given an information sheet, and given the opportunity to ask questions. Participants provided written informed consent prior to take part in the study prior to the commencement of data collection procedures. Participants were repeatedly reminded that they held the right to withdraw at any time without giving a reason, including once testing had ended. All data were kept anonymously, through the use of ID codes. All raw data/ original test packs were stored in line with the Department of Psychology's confidentiality guidelines. Participants were able to subsequently withdraw their data by providing the research team with their name, which was then matched to their unique ID number.

3.2.3 Development of Test Battery

A battery of sensorimotor and cognitive tests was developed following preliminary work by Drew Tarmey (unpublished tests, Department of Psychology, University of Sheffield) as part of the South Yorkshire Ageing Study, a non-profit making initiative aimed at assessing the abilities, particularly sensori-motor and cerebellar function, of older adults using a range of methods (Tarmey, 2005)These tests were developed to overcome some of the issues with commercially available screening tools, in particular that they are time consuming and expensive in the case of large test batteries. The final battery of tests combined tests from the Dyslexia Adult Screening Test (Fawcett & Nicolson, 1998) with tests of declarative memory, learning and manual dexterity, ensuring a wide range of cognitive domains was covered.

Key factors in the development of the battery included creating a set where equipment could be easily transported, as it was often the case that there were multiple testing rooms being used at once, or that participants requested to be tested at another site (i.e. in Rotherham, rather than in Sheffield where testing was based). Furthermore, the final battery required a substantial compromise in terms of the time needed to test each participant. By testing participants across all domains in a single session, each participant required a minimum of three hours to complete the entire battery. Testing would involve more time should a participant be less physically able, and testing had to adapt around the existing routines of the participants. Therefore, sample size for the individual tests was ultimately limited by the time constraints of this project.

3.2.3.1 Tests Included for Analysis

Purdue Pegboard (PP)

This task was originally intended to test factory workers manual dexterity, for jobs requiring fine motor control. However, dexterity tasks have been found to be sensitive in identifying age-related decline (Carment et al., 2018; Vasylenko et al., 2018b). Participants were presented with the Purdue Pegboard (model 32020, Lafayete Instrument Co.) in which two vertical rows of holes had been drilled. Participants were asked to perform three sub tasks. Each task required different levels of planning and dexterity, and therefore it was deemed necessary to include all tasks. They were conducted and scored in line with the official test manual.

The first task asked participants to place pins in the holes, using one hand, starting at the most distant and working towards the closest. They were timed for 30 seconds, and asked

to do the task with each hand separately. The number of pegs placed in this time was counted for scoring. The second subtest was similar to the first, though participants were required to enter pegs simultaneously with both hands. Again they were timed for 30 seconds, and number of simultaneously placed pairs counted for scoring. Scores for subtests one and two were combined for analysis, as both involve the same task to be performed repeatedly at high speed, relying on precision and speed of manipulation of the same type of peg (Rodrigues-Aranda, Mittner & Vasylenko, 2016). This will be referred to as 'peg moving'.

The third subtest required greater cognitive load, and more precise motor control from the participant. Each participant had one minute in which to complete as many assemblies as possible. An assembly consisted of building a column in the order peg-washer-collar-washer, using alternating hands to do this. The number of completed assemblies was counted for scoring. This task was named 'peg assembly, and analysed separately from the others, as it required manipulating different types of pegs, and relied on planning strategies to coordinate finger and hand movements in the correct order (Rodrigues-Aranda et al., 2016). Lindstrom-Hazel and VanderVlies Veenstra (2015) noted the importance of this task in being most likely to correlate with everyday activities.

While fine motor tasks arguably test both basal ganglia and cerebellar function, the two are closely linked and work together (along with the motor cortex) for such tasks. It is likely that the 'peg moving' tasks rely slightly more on the basal ganglia, while the 'peg assembly' task relies on the cerebellum more, but in reality, it is hard to tell them apart. This is a challenge when it comes to testing cerebellar function, as it is likely that the cerebellum is working in tandem with most other parts of the brain. It is acknowledged that his task is no more a basal ganglia test than one of cerebellar function.

Age-related norms for these tests have not been published. While there are papers that attempt to provide normative data, these are often done with small sample sizes or did not include the full range of ages of interest. Desrosiers, Hérbert, Bravo and Dutil (1995) report norms based on just 35 60-89 year olds. Agnew, Bolla-Wilson, Kawas and Bleecker (1988) use a larger sample (212) of healthy 40-85 year olds, where they report that performance on all subtests slowed significantly with age, and that women were significantly faster than men on all tasks. Though Tiffin and Asher (1948) provide a large sample size (total 7814), many of those included were not of the age of interest at present, and those that were, were all men (1958 veterans). Neither the age range nor an average age was provided.

Desrosiers et al. (1995) report a test-retest reliability of .66-.90 for each of the subtests in people aged in a sample of 35 people aged 60-89. Each participant was evaluated twice by

the same investigator, with an average interval of 8.6 days between measurements. Reddon, Gill, Gauk and Maerz (1988) used more trials (five) but again a small sample size of just 26 participants. They found a test-retest reliability of .63-.83 across all subtests and genders. These finds are summarised in table 8 below. As can be seen, there are difficulties with depending on these findings, and in applying them to the population presently of interest.

Paper	Sample	Findings
Reddon et al. (1988)	26 self-reported right handed subjects (12 men, 14 women)	Average over 5 sessions for men/women Right hand: .63/.76 Left hand: .64/.79 Both hands: .67/.81 Assemblies: .81/.83
Desrosiers et al. (1995)	35 male and female subjects aged 60-89	After 2 sessions: Right hand: .66 Left hand: .83 Both hands: .81 Assemblies: .84 (R+L+both= .90)

Table 8: Test-retest reliability

Contrast Sensitivity (CS)

A CSV-1000 device (Vector Vision Inc.) was used to test visual contrast sensitivity. Participants were required to sit one metre from the box, and were asked to look at a series of illuminated spatial gratings. They were required to identify the gratings as a forced choice between two circles, with the 'false' choice being blank. Scores were reported as the number of correctly identified circles through the forced choice. Lindenburger & Baltes (1994, 1997, cited in Drag & Bieliauskas 2010) found that sensory tasks can account for large amounts of age related variance across many cognitive tests. They listed skills including memory, processing speed, reasoning and fluency as some of those that may be sensitive to these tasks, and MacDonald, Keller, Brewster and Dixon (2018) go further in suggesting that sensory functioning may in fact be used to detect those at risk of cognitive decline and impairment. Therefore the purpose of including the contrast sensitivity measure was to further explore sensorimotor function in older adults.

The Vector Vision website (http://www.vectorvision.com/csv1000-norms/) cites population norms for those aged 50-75, providing a reference to Pomerance and Evans (1994) as the source. However, this paper was interested in the test-retest reliability of the test and its relation to glaucoma therapy. The sample consisted of just 24 participants with an average age of 63.9 (S.D.= 12.17) and the test-retest interval was 2.65 months on average (S.D.= .588). Moreover, these are not easily comparable to younger adults, as the results reported come from another paper, and log averages under photopic and mesopic conditions are presented separately. As such, it is difficult to cite appropriate and reliable data on these measures.

Dyslexic Adult Screening Test (DAST)

Although originally intended to screen for dyslexia, the DAST is quick and simple to administer, and provides rapid assessments of cognitive domains which are relevant to the study of ageing. Such domains include cognitive speed measures and examination of performance on fluid and crystallised language tasks.

The DAST has 11 sub-tests, with seven of these being used in the present study. Each test has a practice round to ensure participants understand the task, and also discontinuation instructions, to avoid unnecessary distress or time wasting. Full description of each of the tests can be found in Chapter 2. All tests were administered and scored in line with the official manual. Insufficient data means that four of the sub tests have not been included here for analysis, those retained are as follows: Rapid Automatic Naming (RAN), One-minute Reading (OMR), Nonsense Passage Reading (NPR), Non-verbal Reasoning (NVR), Backward Digit Span (BDS), Verbal Fluency (VF) and Semantic Fluency (SF). See former chapter for a description of tests

3.2.3.2 Tests of Memory and Learning

A series of computer-based tasks were designed as part of the South Yorkshire Ageing Study (Tarmey, 2005 as cited in Tarmey, 2012, p48) to test memory and declarative learning. No validity or reliability data is available for these tests, which is a clear requirement for future data. However, there was no problem associated with inter-rater or test-retest reliability, and all tests were objectively measured.

Verbal (VM), Visual (picture, PM) and Abstract Memory (AM) tests: Simple verbal and visual memory tests were used, in which participants were presented with a series of on screen stimuli (each item was presented for three seconds). There were 12 words in the verbal condition and 18 photos of household objects in the visual condition. Participants were asked to immediately recall stimuli (in any order), before repeating the recall after a 20-minute delay (without re-presentation of stimuli). Scoring was based on the number of correct words/pictures recalled.

A similar test using a set of 16 abstract patterns was also used. As stimuli are novel it is more difficult for participants to assist recall by assigning verbal labels to the patterns. Participants were presented with the patterns, and then were tested on recall through a forced choice recall between targets and distracter patterns. There was again a 20-minute delay before asking participants to choose between targets and distracters again. Participants were scored for the number of correct yes/no answers given.

Paired Associates Spatial Memory (SM) Task: This test measured declarative learning, by presenting a target stimulus in one of 8 locations on the screen for 50 milliseconds (ms), and they must therefore learn the association between stimulus and spatial location. Target stimuli were abstract patterns, with the same difficulty as mentioned previously associated. A series of test blocks of increasing difficulty (with two, four and six patterns) are presented. After each block, participants are presented with a stimulus, and asked to point to the location in which it was displayed. Each block was repeated until the participant made no errors in recall, or was clearly incapable of progressing further without undue distress. Participants were scored for the number of correct associations they declared on the first trial of each test block. This paradigm is similar to that used in other commercially available neuropsychological test batteries.

3.2.3.3 Test Excluded from Analysis

Participants were taking part as part of the wider SYAS project, and therefore took part in many tests, some of which were not deemed necessary for analysis as part of this investigation. Details of these tests can be found in Tarmey (2012).

3.2.3.4 Suites for Analysis

The final 17 tasks included for analysis were divided into 5 suites based on the findings presented in the previous chapter. The memory suite included eight tasks. These were the

immediate and delayed recall of the picture, abstract and verbal memory tests (declarative memory), as well as the spatial memory task and the backwards digit span (working memory). The verbal dexterity suite comprised of the nonsense passage reading, one minute reading and rapid automatic naming tests. Sensory processing covered just one test; contrast sensitivity. The fluid thinking suite comprised the non-verbal reasoning, verbal fluency and semantic fluency DAST sub tests. The final suite represented physical coordination and included the Purdue Pegboard peg moving tasks and assemblies.

3.2.4 Procedure

Participants were asked to fill in a consent form, and were given the opportunity to ask questions before testing began. The EEG (not analysed here, as it formed part of a different study) took approximately 90 minutes, and the sensorimotor and cognitive testing battery took between 90 and 120 minutes. Therefore, total testing time took around 3- 4 hours, with breaks. Participants were invited to have their EEG first, unless the testing room was unavailable, in which case they began with the test battery. Tests were run in the same order for each participant, unless the participant expressed that they did not want to complete that test, in which case it was omitted.

The picture memory test was presented first, with recall recorded immediately after presentation. There was a 20 minute wait before they were asked to recall the items again (delayed recall condition) in which time participants were asked to fill in their demographic data. This data covered medical and lifestyle factors, as well as a short form of the Geriatric Depression Scale (Yesavage et al., 1982 cited in Tarmey, 2012). Evidence of self-reported medications was sought in the form of a current prescription, and information about dietary choices and disease states were analysed as part of a separate study. The verbal memory test was then run, with immediate recall recorded before being asked again (delayed recall condition) 20 minutes later. During this time, participants had their tremor measured using a Polhemus 3SPACE FASTRAK motion tracker. This test was also excluded from analysis, and therefore the specific sub tasks are not described here. The abstract memory test was then run, again with immediate recall being recorded, followed by the delayed recall condition after a 20 minute break. During this time, participants completed the National Adult Reading Test, (Nelson, 1982; also excluded from analysis here), and contrast sensitivity, and Purdue Pegboard tasks. It should be noted that the 20 minute window was strictly adhered to, and if it was not possible to complete all tasks within this time, participants were given a break, and

the test battery continued after recall had been recorded. Participants then completed the DAST sub tests, before ending on the paired associated spatial memory task. While participants were aware ahead of arriving that they should allow 4 hours for complete testing, some grew tired or simply had to leave before testing was completed.

3.2.5 Analysis Methods

A series of correlations were run to inspect the relationship between age and each test variable, as well as between the test variables themselves. Regression analyses were performed in order to determine whether motor skill was predictive of cognitive functioning, over and above the effect of ageing.

Factor analysis (not shown) confirmed the classification used. However, cross loading and difficulty naming the factors resulted in cutting this from the thesis and using theory driven categories insight.

3.3 Results

3.3.1 Descriptive Statistics

Descriptive statistics for the lifestyle data collected is presented in table 9 below. The large amounts of missing data should be noted.

Measure	**n**	**Mean (SD)**
Average number of hours sleep per night (Disruption: no=42, yes=50)	127 (92)	6.65 (1.44)
Average number of outings per week	59	2.58 (1.22)
School leaving age	51	14.29 (2.37)
Average number of portions of fruit and veg consumed per week	130	3.62 (1.33)
Average number of portions of fish consumed per week	136	1.49 (1.04)
Number of medical conditions	68	3.10 (1.56)
Number of medications	136	1.71 (1.56)

Table 9: Descriptive Statistics by measure

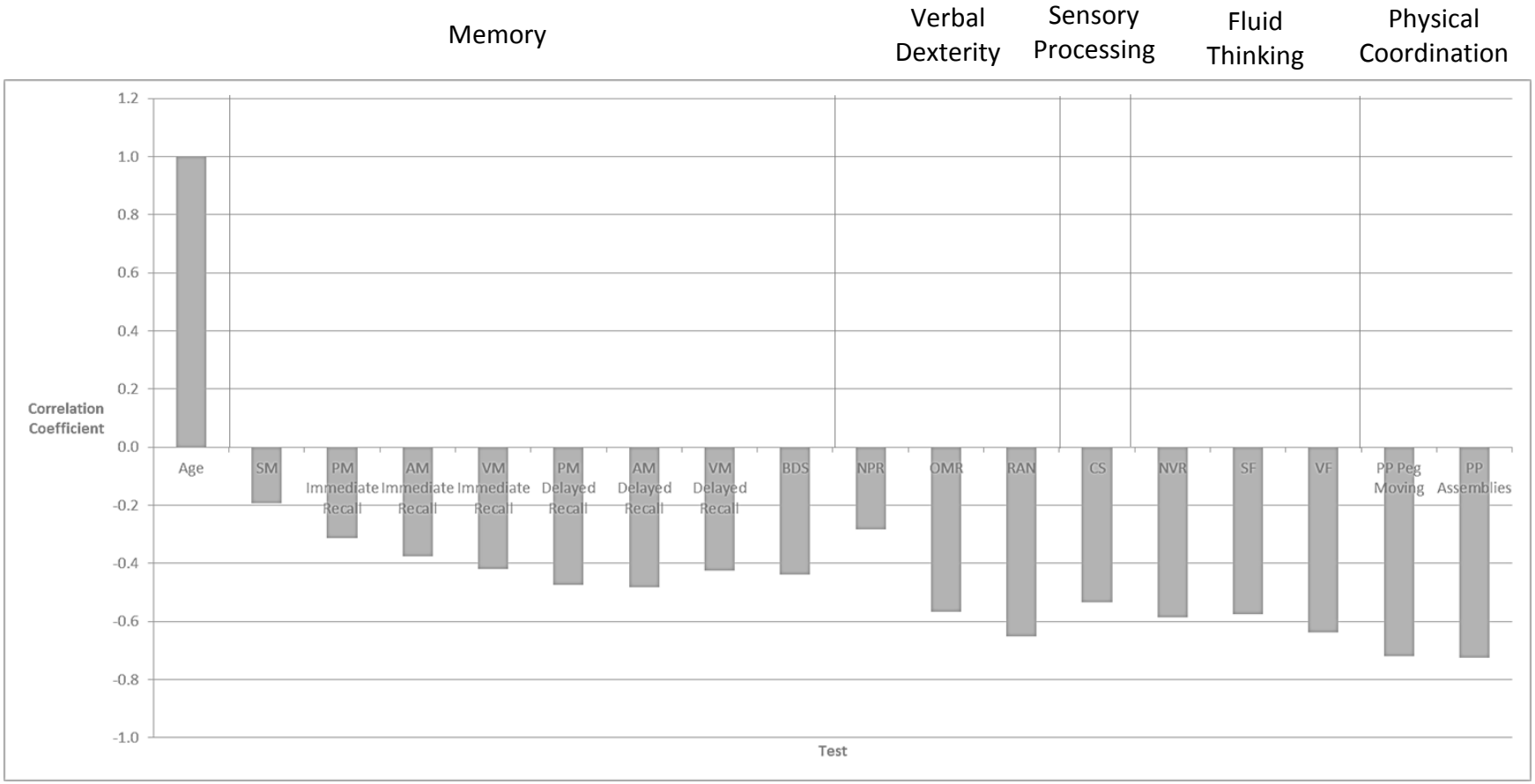
The distribution of each variable was inspected. With the exception of Abstract Memory Delayed Recall, Shapiro Wilk revealed that all variables are not normally distributed. Given that this test can be overly sensitive, histograms, Q-Q plots and box plots were visually assessed, as well as measures of skew and kurtosis. Together, they confirmed a mix of outliers, skewed and bimodal distributions amongst the variables. Therefore, median and interquartile range are reported in Table 10, alongside number for each variable, and non-parametric inferential tests follow.

Variable	N	Median	IQR
RAN	235	35	18.5
SM	112	5	3
NPR	226	84.5	8
PM Immediate Recall	171	7	5
AM Immediate Recall	178	27.5	5
VM Immediate Recall	187	6	3
PM Delayed Recall	139	6	5
AM Delayed Recall	116	24	7
VM Delayed Recall	183	5	5
BDS	42	5	4
CS	218	18	10
OMR	233	98	35.5
VF	26	10	9
SF	26	12	5
NVR	38	3	4
PP Peg Moving	220	34	11
PP Assemblies	221	5	3

Table 10. Descriptive statistics for the 17 variables

3.3.2 Correlations

Correlational analyses were firstly conducted between the seventeen test variables and age (Figure 5), and then between all of the 17 test variables (Table 11).



Note: * sig at =.05, ** sig at .005, *** sig at <.001

Figure 5: Spearman's Rho correlations of the seventeen tasks with age

		Memory								Verbal Dexterity			Sensory Processing		Fluid Thinking		Physical Coordination
		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.
1.SM																	
2. PM Immediate Recall		.268**															
	N	106															
3. AM Immediate Recall		.176	.371***														
	N	101	155														
4. VM Immediate Recall		.348***	.619***	.402***													
	N	105	164	172													
5. PM Delayed Recall		.358***	.804***	.458***	.630***												
	N	102	139	124	134												
6. AM Delayed Recall		.183	.494***	.818***	.449***	.540***											
	N	93	110	116	111	104											
7. VM Delayed Recall		.291**	-.044	.259**	.423***	.478***	.423***										
	N	101	160	168	183	130	107										
8. BDS		.437*	.601**	.699***	.562**	.579**	.678**	.550**									
	N	22	28	23	30	27	19	27									
9. NPR		.143	.296***	.308***	.325***	.382***	.366***	.193*	.664***								
	N	97	155	169	174	123	109	170	40								
10. OMR		.299**	.274***	.373***	.390**	.423***	.448***	.274***	.650***	.549***							
	N	105	163	174	181	132	112	177	40	223							
11. RAN		.326**	.309***	.441***	.505***	.513***	.542***	.407***	.618***	.443***	.744***						
	N	108	165	175	182	134	114	178	41	223	232						
12. CS		.233*	.162*	.314***	.338**	.324***	.404***	.263***	.386*	.360***	.441***	.417***					
	N	106	164	171	179	133	111	175	37	192	198	200					
13. NVR		.111	.570**	.668***	.579**	.530**	.558*	.616**	.686***	.709***	.587***	.477**	.348*				
	N	21	25	23	26	24	19	24	36	37	37	37	34				
14. SF		.171	.526**	.654**	.368	.494*	.532*	.609**	.553**	.556**	.510**	.615**	.579**	.504*			
	N	21	25	20	26	24	17	23	26	26	26	26	24	23			
15. VF		.321	.535**	.623**	.499**	.510*	.692**	.562**	.694***	.649***	.680***	.596**	.473*	.602**	.595**		
	N	21	25	20	26	24	17	23	26	26	26	26	24	23	26		
16. PP Peg Moving		.237*	.213**	.283***	.343***	.406***	.388***	.377***	.584**	.271***	.577***	.649***	.406***	.669***	.440	.646**	
	N	95	146	158	160	115	100	158	30	201	203	204	191	28	20	20	
17. PP Assemblies		.416***	.256**	.272**	.340***	.437***	.350***	.315***	.684***	.321***	.608***	.673***	.457***	.763***	.571*	.814***	.786***
	N	93	145	157	160	116	99	158	31	202	205	205	190	29	19	19	217

Table 11: Spearman's correlations between the 17 sub-tests, presented by suite

Note: * sig at <.05, ** sig at <.01, *** sig at <.001

Correlations with age reveal that all tasks declined significantly with age. The declarative memory suite showed the weakest correlations, while physical coordination showed the strongest. Correlations between the 17 sub- tests showed that the majority of tasks correlated significantly with each other. However, SM only correlated with 10 sub-tests, including none from the fluid thinking suite. PM immediate recall failed to correlate significantly with VM delayed recall, and SF did not correlate significantly with VM immediate recall, or PP peg moving. The strongest cross- suite associations were seen between fluid thinking and declarative memory (excluding SM), between fluid thinking and verbal dexterity, and between fluid thinking and physical coordination. Of particular interest, rapid automatic naming correlated well with both peg moving (r_s= 6.49, p<.001) and peg assemblies (r_s=6.73, p<.001).

3.3.3 Manual Dexterity as a Predictor of Cognition

In order to test whether motor function was predictive of cognition over and above age, a series of regressions were run, and are summarised in Table 12. For each regression, P-P plots, scatterplots of the residuals and VIF values were assessed. All assumptions were met for each regression, although the low number of participants for BDS meant that this pattern was less clear.

Each regression was carried out individually in order to assess the predictive contribution of the peg moving task and peg assemblies separately for each memory task. In all cases, the enter method was used, with age being entered into the first block, and the pegboard measure (either moving or assemblies) being entered in block 2. It is acknowledged that age is likely to account for a significant proportion of the variance seen in each case, therefore it was important to establish what contribution is made by each pegboard measure, over and above that of age.

Dependent Variables	Independent Variables		*F*	R^2	ΔR^2	B	SE B	*β*
VM Immediate Recall	Step 1	Age		.171		-.084	.015	-.414***
	Step 2	Age	F(2,157)=16.817***	.176	.005	-.067	.022	-.332**
		PP Peg Moving				.033	.033	.109
VM Delayed Recall	Step 1	Age		.164		-.125	.023	-.405***
	Step 2	Age	F(2,155)=	.187	.023	-.074	.033	-.238*
		PP Peg Moving	17.780***			**.103**	**.049**	**.225***
PM Immediate Recall	Step 1	Age		.098		-.105	.026	-.313***
	Step 2	Age	F(2,143)=7.780**	.098	.000	-.106	.037	-.318**
		PP Peg Moving				-.003	.056	-.007
PM Delayed Recall	Step 1	Age		.226		-.144	.025	-.475***
	Step 2	Age	F(2,112)=17.559***	.239	.013	-.104	.038	-.345**
		PP Peg Moving				.080	.058	.173
AM Immediate Recall	Step 1	Age		.139		-.126	.025	-.373***
	Step 2	Age	F(2,155)=15.467***	.166	.027	-.072	.034	-.214*
		PP Peg Moving				**.116**	**.051**	**.229***
AM Delayed Recall	Step 1	Age		.191		-.148	.031	-.437***
	Step 2	Age	F(2,97)=14.506***	.230	.039	-.082	.042	-.241
		PP Peg Moving				**.142**	**.064**	**.278***
SM	Step 1	Age		.027		-.031	.019	-.165
	Step 2	Age	F(2,92)=1.536	.032	.005	-.017	.028	-.088
		PP Peg Moving				.030	.043	.105
BDS	Step 1	Age		.381		-.161	.039	-.617***
	Step 2	Age	F(2,27)=9.207***	.405	.025	-.126	.051	-.483*
		PP Peg Moving				.045	.042	.207
VM Immediate Recall	Step 1	Age		.177		-.086	.015	-.421***
	Step 2	Age	F(2,157)=17.742***	.184	.007	-0.71	.019	-.350***
		PP Assemblies				.117	.100	.110
VM Delayed Recall	Step 1	Age		.163		-.124	.023	-.403***
	Step 2	Age	F(2,155)=16.162***	.173	.010	-.099	.029	-.321**
		PP Assemblies				.204	.149	.129
VM Immediate Recall	Step 1	Age		.098		-.104	.026	-.313***
	Step 2	Age	F(2,142)=7.831**	.099	.001	-.094	.035	-.283**
		PP Assemblies				.083	.189	.046
PM Delayed Recall	Step 1	Age		.230		-.144	.025	-.479***
	Step 2	Age	F(2,113)=18.956***	.251	.022	-.102	.034	-.340**
		PP Assemblies				.330	.183	.203
AM Immediate Recall	Step 1	Age		.147		-.130	.025	-.384***
	Step 2	Age	F(2,154)=16.658***	.178	.031	-.087	.031	-.255**
		PP Assemblies				**.385**	**.161**	**.217***
AM Delayed Recall	Step 1	Age		.204		-.152	.031	-.452***
	Step 2	Age	F(2,96)=14.277***	.229	.025	-.111	.038	-.330**
		PP Assemblies				.381	.217	.199
SM	Step 1	Age		.035		-.035	.019	-.187
	Step 2	Age	F(2,90)=6.226**	.122	.087	-.016	.025	.083
		PP Assemblies				**.425**	**.143**	**.399****
BDS	Step 1	Age		.383		-.170	.040	-.619***
	Step 2	Age	F(2,28)-13.145***	.484	.101	-0.91	.050	-.331
		PP Assemblies				**.433**	**.185**	**.429***

Table 12: Summary of Hierarchical Regressions

*Note: * p*>.05, ** *p*>.01, *** *p*>.001. Bold typeface represents significant contributions made by motor tasks

All models were found to be significant. As well as age, peg moving was a significant predictor of performance on verbal memory delayed recall, and abstract memory immediate recall. Peg moving was the only significant predictor of abstract memory delayed recall, when entered alongside age into the model. Again, as well as age, peg assemblies was predictive of abstract memory immediate recall. Peg assemblies was the only significant predictor of spatial memory and the backwards digit span, when entered into the model alongside age.

3.4 Discussion

Correlations confirm that, as expected, performance on all cognitive tasks declined with age in the current sample. Furthermore, there is a strong significant correlation between processing speed (RAN) and the pegboard tasks, as predicted. Hierarchical regressions were used to assess the ability to predict memory function from motor performance. Age was entered into the model first, to show whether motor function accounted for any variance in the data over and above this. When using peg moving as a predictor, seven of the eight models were able to predict memory function. The exception here was Spatial Memory, which was not predicted by the model. Looking more closely at the seven significant models, age was a significant predictor in every case, with the exception of abstract memory delayed. Here, motor function was the only significant predictor. For verbal memory delayed recall, and abstract memory immediate recall, motor function was also a significant predictor. In the latter model, the beta weight for motor function was larger than for age. Age was again entered into the regression model first, and this time followed by peg assemblies. All models were significant. Age was again a significant predictor in all models, with the exception of spatial memory and backwards digit span. In both cases, only peg assemblies was significant. Peg assemblies was only an additional significant predictor for abstract memory immediate recall.

Taken together, it is reasonable to conclude that motor function is predictive of some aspects of cognitive function, partially supporting the hypothesis. However, this must be taken with the caution that this is not universally true and that the underlying constructs of each memory task may in fact play an important role in how predictive motor function might be.

Upon closer inspection of the correlations with age, it is interesting to see that both tasks in the motor coordination suite showed the strongest association with age. Given that

the cerebellum is traditionally thought of as a motor structure, this lends support to cerebellar theories of ageing. Language tasks such as semantic fluency, verbal fluency and one minute reading (from the verbal dexterity and fluid thinking suites) also show strong associations. This is consistent with Leiner et al.'s (1993) hypothesis of a neural loop in which the red nucleus receives projections from language areas in the cerebral cortex. As the red nucleus relays information from the motor cortex to the cerebellum via the inferior olive, it suggests this loop could participate in both the cognitive process of word finding, and in the motor process of expressing the words (Leiner et al., 1993). They further suggest this could act as a language-learning loop (Leiner et al., 1993).

The strong negative correlation of age with the decline of non-verbal reasoning would traditionally be attributed to frontal lobe theories of ageing. However, with clear indication to suggest that fronto-cerebellar loops are directly implied in ageing (Hogan, 2004; Eckert et al., 2010), the findings of this study are plausibly further evidence to support this. Additionally, the strong correlation between age and processing speed (as measured by the rapid automated naming task) when taken with the decline in other cerebellar tasks, further supports the need to include the processing speed hypothesis in current theories of ageing. Deary et al. (2010) argue that processing speed is essential as a biomarker of cognitive ageing, so the significance of these findings is not to be ignored. Contrast sensitivity, a measure of sensory processing, also shows marked decline with age, perhaps as a result of the increased demands on attentional processing and sensory integration described by Ferdon and Murphy (2003). The scope for further investigation here is vast, as without neuroimaging, this relationship is only descriptive of behaviour. Further understanding of the neural network underlying these behavioural declines is essential to understanding cognitive function with advancing age. However, because of low numbers on some of the tests, this was not done here.

Overall, while still significant, the memory suite measures do not show as strong a negative correlation with age as some of the more 'cerebellar' tasks. Delayed recall showed more decline with age than immediate recall. To date, there is little evidence linking the cerebellum and hippocampus, though Woodruff-Pak et al. (2010) found that the two were impacted differently by ageing, with the cerebellum showing earlier signs of decline. This is an area of research that is greatly under-investigated, and the mechanisms underlying these relationships are poorly understood. However, the cerebellum has been implied in working memory tasks (Ramnani, 2006) which lends support to the finding that there was marked decline in the backwards digit span and spatial memory task. Bernard and Seidler (2014) suggested that older adults may show increased reliance on cognitive resources during motor

performance, as dual-task motor and cognitive paradigms have shown greater motor performance declines. The spatial memory task differed from all the others in that it involved a motor component. Participants were asked to point to where they had previously seen the shape, rather than provide a verbal response. Memory performance has many different aspects to it, and the findings of this study suggest that although there is a general decline as expected, the explanation for memory decline in relation to cerebellar performance, is a clear avenue for future research to explore. With memory difficulties acting as one of the first markers for cognitive impairment and subsequently dementia, it is imperative that we are able to recognise signs of impairment that precede it, and more importantly are able to accurately and reliably predict what is likely to be ahead.

While a general decline in all abilities is to be expected with age, the finding that the largest associations are in motor coordination is of great importance. The pegboard tasks correlate significantly with all other cognitive domains, but particularly well with processing speed, non-verbal reasoning, working memory, (as measured by the backwards digit span) reading (as measured by the one minute reading task) and verbal fluency tasks. This is of particular interest following previous research by Gottwald et al. (2004) who found that the Purdue Pegboard failed to correlate with various cognitive tasks including visual and verbal memory, and working memory. However, the authors only recorded the peg moving tasks, and not the peg assemblies, which in the present study correlated more strongly with all cognitive tasks, with the exception of the delayed recall in picture and abstract memory. However, the strength of the correlations were all moderate and highly significant. Processing speed also correlated significantly with all other cognitive domains, particularly reading, working memory and verbal and semantic fluency, in addition to motor coordination tasks. Non-verbal reasoning correlates strongly across the board, with the exception of the spatial memory task, and weaker correlations with processing speed and sensory processing. Together, these findings again offer strong support for the fronto-cerebellar theory of ageing, and the inclusion of cerebellar tasks as a predictor of other cognitive undertakings.

Memory loss is one of the most common early symptoms of dementia (National Health Service, 2017). While not directly testing the population at risk here, memory is a core component of cognition, and it is affected by the ageing process. The findings of the present study might also be of importance in dementia research, but this does not diminish the importance placed on understanding memory process in normal ageing. With this in mind, the decision was taken to attempt to predict memory performance using motor performance, as a classical cerebellar task. Both pegboard tasks were retained for analysis, as they

distinctly different types of task, which involve different aspects of motor coordination. It is widely acknowledged, and supported by the first study of this thesis, that cognition generally shows age-related differences with age, with older adults performing worse across cognitive tasks than their younger counterparts. Therefore, age was included in each of the models to take account of the variance it explains. As previously mentioned, with the exception of spatial memory when peg moving was a predictor, all models are significant. Looking firstly at the models using peg moving as a predictor, motor function uniquely contributed to the prediction of performance, in verbal memory immediate recall, abstract memory immediate recall, and abstract memory delayed recall. In fact, for the delayed measure, only motor performance was a significant predictor. Motor function was again a significant predictor of abstract memory immediate recall when peg assemblies was used in the model, and it was the only significant predictor in the models for spatial memory and the backwards digit span.

Shaw, Helmes and Mitchell (2006) found that verbal, visual and spatial working memory systems may be differentially affected by age. In the present study, it may be argued that both the picture and verbal memory tests required similar networks of activation, as stimuli was presented on screen, either as a picture or as a word, and required verbal rehearsal of the items. The abstract memory task attempted to correct for this in that it was difficult to form associations or create labels for the items, as each image was novel. The same was true for the images shown in the spatial memory task. Shaw et al. (2006) also reported that performance levels were poorer for recall tasks than on a recognition task, and suggested that recall tasks are more effortful for older adults. In the present study, the picture and verbal memory tests were both recall tasks, the abstract memory test was a recognition task. The spatial memory test included aspects of both, the items were novel and needed to be recognised, but additionally, they needed to be placed, so recall of the location was important. This potentially explains why different results were found for each memory test in terms of being predicted by motor function, despite significant correlations between them. Further research into understanding the way in which the different memory systems interact with, and are possibly supported by, cerebellar function as measured by motor function, would be a logical next step in untangling this relationship.

3.4.1 Summary of Main Findings

There is a marked difference between middle-aged and older adults in both cognitive and motor skills with age, with the latter showing the most decline. Broad cognitive skills

correlate strongly with motor skills and processing speed, both of which test the function of the cerebellum. When age is controlled for, motor function is predictive of some aspects of cognitive function. Together, these results imply a causal role for the cerebellum in memory ageing, as well as suggesting that slowed motor function could be used as a predictor for future memory decline.

3.4.2 Limitations

It can be argued that there was a bias in the data in that the majority of the sample were female. This is a risk with research that relies on volunteers, with the literature suggesting that there are gender differences in volunteering. However, the findings are mixed, inconclusive, and often very specific to a particular situation (Helms & McKensie, 2014; Lobato et al., 2014; Vokic, Maric & Horvat, 2013). Furthermore, women in England have a greater life expectancy than men (Office for National Statistics, 2015) so when researching the elderly, there are simply more women to volunteer. There is also evidence to suggest cerebellar differences between men and women. Rhyu et al. (1999) reported that the cerebellar volume of male participants was significantly larger than that of females, although the size of the vermis did not show significant gender difference. Furthermore, they found that the female vermis had the tendency to shrink after age 50, but this was not the case for males (Rhyu et al., 1999). Difference in cerebellar size between genders is a well-supported finding (Escalona et al., 1991), yet the relationship between ageing and the cerebellum is less clear. Studies suggest age-related shrinkage of the cerebellum may be sex- specific, but it remains unclear as to whether this decline is accelerated in men, or women (Hogan, 2004). In reference to the aim of trying to develop a predictive test battery, there is evidence of gender differences in older adults for dexterity. Vasylenko, Gorecka and Rodriguez-Aranda (2018a) found that older men experience more decline than women. While this was unavoidable in this study, future research should look to balance the sample more evenly for gender. As a possible next step for this data, it could be reanalysed separately for each gender, to help clarify the gender debate.

The average school leaving age in this sample was recorded as 14, however, this represented less than 20% of the total sample, with it being likely that many of those in participation were actually highly educated. One of the most fruitful sources of volunteers for the South Yorkshire Ageing Study came though the University of the Third Age, a group of highly active and highly motivated older adults. As previously stated, the brain reorganises its

activation to compensate for age-related cognitive decline (Cabeza, 2002; Davis et al., 2008; Berlingeri et al., 2013). However, the majority of literature in this area has concentrated on using high functioning adults, with arguably larger cognitive reserves. Cabeza et al. (2002) suggested that low performing adults recruited a similar network as younger adults but used it inefficiently, whereas high-performing adults counteracted age-related neural decline through a plastic reorganisation of neurocognitive networks. As a result, it should be expected that had the sample included lower functioning adults, the same pattern of change would be observed, however perhaps to a lesser extent. It would be worth future research looking into the differences seen between these groups, to understand more about the types of interventions that would be successful.

One final issue that did not deter from the significance of the results, but perhaps from the strength, was that of missing data. Participants were taking part in a wider investigation as part of the South Yorkshire Ageing Study, and therefore the data received for analysis here was second hand, and much of the coding was out of the present researcher's control. The full test battery included an EEG task (not discussed within this paper) as participants were taking part in a wider study. The entire session took between three and four hours per participant (with breaks) and therefore the sample size was ultimately limited by the time constraints of the project. For the correlations, N varies from 19 to 223, which could affect regression analyses Future research should build on these findings by refining these tasks into a battery that encompasses all the cognitive domains sufficiently, while being time effective, and suitably predictive.

3.4.3 Test Retention for Future Research

One of the main aims of this thesis is to refine tests into a highly predictive, yet quick and easy to administer battery. The DAST subtests already provide a strong basis (and should thus be retained) but it is important to review the tests introduced in this study. The first domain to tackle is memory. While there are many separate aspects to memory function, it can be argued that many of the tests included here essentially test the same underlying concept. Factor or cluster analysis to identify this would be useful, but the sample size here for the number of variables included did not allow for this to be done. Working memory is a complex cognitive task, and one which is widely used in cognitive batteries. As such, retaining a fully normed standardised test, which is quick and easy to administer should be retained in order for meaningful comparisons to be made across tasks. The memory tests

devised for the South Yorkshire Ageing study are what need to be refined. In total, the three recall and recognition tasks took over an hour, as each task required a 20 minute delay between recall phases, All three correlated significantly with the pegboard tasks (both immediate and delayed recall) and both VM and AM are predicted by the pegboard. Shaw et al. (2006) suggested that recall tasks are more sensitive to age related changes than recognition, which gives reason to exclude the AM task. As it is likely that the PM and VM tasks are cognitively very similar, attention must be drawn to the aims of research; to have real world application. The PM task is more likely to more closely replicate real world scenarios, especially when taken in combination with spatial memory tasks. For example, trying to remember where you last placed an object is a far more common occurrence than memorising a word list. Furthermore, while it is recognised that older adults have worse word recall than younger adults, this is thought to be due deficits in cognitive flexibility leading to poor strategic organisation (Ballesteros et al., 2009), which would underlie both tasks in a similar manner. For these reasons, of the three SYAS recall and recognition tasks, only PM should be retained.

Although it did not significantly correlate with AM, SM correlated with all other memory tasks, and was predicted by peg assemblies. With peg assemblies also predicting working memory, this leads to the possibility that a more complex motor task is predictive of more complex cognitive tasks. Baldauf and Deubel (2010) highlight the importance of spatial attention in motor tasks, thus retaining this task is recommended to further investigate spatio-motor functioning in ageing. As previously discussed, the peg moving require speeded precision, while the assembly task requires a higher degree of cognitive functioning (Rodrigues-Aranda et al., 2016). As such, both tasks should be retained to again investigate this relationship further.

While statistically significant correlations were found with all other tasks for the CS task, these were low to moderate at best. The current equipment (a CSV-1000 device, Vector Vision Inc.) is large and cumbersome. So while easy to administer, it is not suitable for a portable test battery. For this reason, the current measure should not be retained for the next study. However, sensorimotor functioning is a potentially fruitful avenue to pursue, with evidence to suggest sensory functioning may be a strong later-life predictor of intelligence (Lindenberger & Baltes, 1994), and that it can be used to identify those at risk of cognitive decline or impairment (MacDonald, Keller, Brewster & Dixon, 2018). There are two potential explanations for the sensory deficits seen in older age; first one of sensory deprivation, reflecting accumulated effects of reduced sensory deprivations, and secondly one

of deficits in the underlying physiological architecture of the brain (Lindenberger & Baltes, 1994). While not within the scope of this thesis, this is an important avenue for further investigation. An argument can be made for either a 'use it or lose it' scenario, or there may be a common pathway leading to difficulties in all sensory functioning. It also needs to be taken into account how these difficulties might affect task performance in the current context, where sensory deprivation might mask underlying abilities, but a common pathway might represent more widespread difficulties. Therefore, it is recommended that more suitable tests of sensory functioning are investigated further within the ageing domain.

3.4.4. Future Directions

If we are indeed able to predict who is going to decline cognitively, morally, we should do something to help. It is not enough to make people aware that they are likely to decline cognitively or physically, and not offer support for prevention. Future research should be directed towards providing suitable intervention to slow down, or even stop the process. Bernard and Seidler (2014) suggest that interventions focusing on the cerebellum might be able to mitigate some of the cognitive decline seen. A view supported by Eckert et al. (2010) who stated that interventions designed to improve perceptual-motor integration through cerebellar plasticity may limit the global declines in cognition that are often attributed to declines in processing speed. The next study in this thesis aims to fill this gap, by testing the effectiveness of a cerebellar-based training intervention, in preventing further cognitive decline in older adults.

3.4.5 Conclusion

The findings provide mixed results, and some of this may be explained by the partial incompleteness of the large secondary data set that was utilised. However, a clear link between motor function and cognition has been established, suggesting a potential role for the cerebellum in supervising many cognitive systems, through a series of cortical networks and connections that have previously remained under investigated. As it seems likely that the cerebellum is involved in core processing, a link between sensorimotor function and cognition may be presumed, but requires further investigation. The addition of these findings suggests a potentially fruitful series of research questions. A particularly exciting possibility is that motor skill decline may prove diagnostic of subsequent cognitive impairment. As link has been established, it is important that the next steps in research work towards reinforcing

healthy ageing of the cerebellum, in order to support all of these vital systems, and slow down the effects of aging.

4 Chapter 4: Intervention Study (Study Three)

4.1 Preview

This chapter is adapted from:

Gallant, Z. & Nicolson, R.I. (2017*)* "Cerebellar Challenge" for Older Adults: Evaluation of a Home-Based Internet Intervention. *Frontiers in Aging Neuroscience. 9:332*. doi:10.3389/fnagi.2017.00332.

Following on from the previous study, the test battery is further refined to best replicate everyday tasks, while still covering a wide range of motor and cognitive tasks. Measures of affect are included here as the cerebellum has also been implied in emotional functioning (Schmahmann, 1998; Allen et al., 2005; Gordon, 2007; Habas, 2009). Having already established the role of the cerebellum in cognition, attention now turns to testing whether it is possible to train the cerebellum to perform more efficiently, as measured by improved motor and likely cognitive function.

4.2 Introduction

The brain and body form a complex, self-regulating system capable of coping with a range of environmental and cognitive challenges, together with the pervasive, age-related progressive impairment in function of many system components. In this study a brief overview of the many facets of impairment in ageing is provided, attempting to maintain focus on the underlying systems involved. This study develops the perspective that the functional networks involving the cerebellum represent a significant part of the degradation in ageing. It then briefly review the many interventions that have proved efficacious with older adults, noting the current consensus that multi-component systems designed to maintain a progressive challenge appear to have greater effect than single component systems. On theoretical grounds we argue that interventions designed around 'cerebellar challenge', combining coordinative exercise with cerebellar stimulation should prove particularly

effective. It ends by presenting an evaluation of an internet-based cerebellar challenge system, Zingup, in terms of its effectiveness compared with a life-as-usual control group.

4.2.1 Physical, Structural and Functional changes with ageing

Traditional approaches to the causes of cognitive decline with ageing considered primarily the frontal lobes (Dempster, 1992; Greenwood, 2000; Jackson, 1958). Over the past three decades there has been an explosion of research on all aspects of ageing. Early this century extensive research was undertaken on changes in brain structure with ageing (Raz et al., 2005), genetics (Deary, Wright, Harris, Whalley and Starr, 2004; Erraji-Benchekroun et al., 2005), together with risk factors including increased white matter (Bartzokis, 2004; Head et al., 2004; Sexton et al., 2014; Westlye et al., 2010); excess homocysteine (Schafer et al., 2005) and reductions in dopamine and acetylcholine neurotransmitters (Castner & Goldman-Rakic, 2004; Erixon-Lindroth et al., 2005; Sarter & Bruno, 2004).

Following these discoveries, arguably the greatest recent development has been the change of emphasis from these individual components and processes of the ageing brain to consideration of the brain as a whole system. A major recent development in cognitive neuroscience has been the development of techniques for determining functional connectivity (Buckner, Andrew-Hanna & Schacter, 2008; Fox et al., 2005; Greicius, Krasnow, Reiss & Menon, 2003), and the consequent identification of a range of intrinsic networks (Yeo et al., 2011). The approach has great potential for characterizing the connectivity problems that affect brain function. A recent study (Douaud et al., 2014) identified two major correlates of ageing, a global loss throughout the brain in grey matter, and a specific 'inverted U' degradation of a late-developing neural circuit involving a spatially specific network of mainly transmodal regions encompassing heteromodal cortex (a region that receives input from multiple sensory areas), and limbic and paralimbic regions, together with the cerebellar crus, motor cortex and frontal eye fields (the area in dorsolateral prefrontal cortex involved in cognitive aspects of eye movement control). A recent review (Bamidis et al., 2014) highlights the key role of connectivity changes in brain ageing, and its implications for assessment and intervention.

It is notable that the cerebellum is also involved in seven of the major intrinsic networks (Bernard et al., 2012; Buckner, Krienen, Castellanos, Diaz & Yeo, 2011; Kipping et al., 2013). It is therefore particularly interesting that circuits involving the cerebellum are strongly affected by age (Balsters, Whelan, Robertson & Ramnani, 2013; Bernard et al.,

2013; Bernard & Seidler, 2014; Humes, Busey, Craig & Kewley-Port, 2013; Koppelmans et al., 2015; Seidler et al., 2010). Furthermore, it appears that the pattern of cerebellar degeneration with age in healthy adults is analogous to that shown by cerebellar patients (Hulst et al., 2015). In particular, degeneration in the anterior lobe and lobule VI is found in both groups, but further analysis revealed that cerebellar regions comprising networks which are linked to not only motor behaviours, but also to the frontopariatal network (associated with cognitive control), degenerated in both groups (Hulst et al, 2015).

It is long established that there are major declines with age in sensory function (Humes et al., 2013; Roberts & Allen, 2016; Wayne & Johnsrude, 2015), in motor function (Seidler et al., 2010) and proprioceptive function (Goble, Coxon, Wenderoth, Van Impe, & Swinnen, 2009). The cerebellum is centrally involved in sensorimotor processing (Chadderton, Margrie & Hausser, 2004; Chadderton, Schaefer, Williams & Margrie, 2014; Ramakrishnan, Voges, De Propisl, De Zeeuw, & D'Angelo, 2016) and the involvement of the cerebellum in cognitive function is now established (Balsters et al., 2013; Marien et al., 2014), as are direct, two-way links between the cerebellum and not only motor cortex, but also with prefrontal and posterior parietal cortex and the basal ganglia (Bostan et al., 2013; Strick et al., 2009).

Interestingly, there is extensive evidence that healthy older adults tend to have a larger spread of activation when undertaking a task (Fabiani, 2012; Gordon, Tse, Gratton & Fabiani, 2014). This has been attributed to cognitive 'scaffolding', that is, compensating for performance impairment through additional processing under attentional control (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). This compensation strategy is directly consistent with the perspective that impaired cerebellar function leads to the need for cognitive compensation in learning difficulties (Nicolson & Fawcett, 1990; Nicolson et al., 2001).

Taken together, these results converge on the hypothesis (Bernard & Seidler, 2014) that the cerebellum - given its pervasive connectivity, its involvement in multiple sensory, cognitive and motor circuits; and its central role in adapting to internal changes - may be a critical component in the system degradation with age. This new conceptualization offers the promise that interventions designed to maintain or enhance cerebellar function may alleviate the effects of ageing on sensori-motor-cognitive performance.

4.2.2 Interventions for Ageing

There are many successful interventions for alleviating age-related decline. A recent review (Ballesteros, Kraft, Santana & Tziraki, 2015) focused on three modes of intervention: physical activity, computerized cognitive training and social enhancement and concluded that although single domain interventions were effective the simultaneous training of both cognitive and physical domains offers a greater potential on daily life functioning. One of the key problems identified by the authors was the issue of how to combine different interventions and how to evaluate their effectiveness. The systems approach to healthy ageing provides a theoretical perspective on this issue, suggesting that if a major cause if impairment is functional loss in the intrinsic connectivity networks, the optimal intervention should target function in the network as a whole, rather than individual components thereof.

4.2.2.1 Computerised Cognitive Training Interventions

Computerised cognitive training (CCT) approaches, using computer programs to boost core cognitive capabilities such as working memory, speed of processing, and visual attention have proved highly effective in some studies, but less so in others. Systematic reviews of brain training programmes with older adults (Gross et al., 2012; Kueider, Parisi, Gross, & Rebok, 2012) concluded that computerized training is an effective, less labour intensive alternative to cognitive training. In contrast, a recent analysis (Lampit et al., 2014) concluded that the overall effect size computerised cognitive training versus control was small and statistically significant for nonverbal memory, verbal memory, working memory, processing speed, and visuospatial skills but not for executive functions and attention. A meta-analysis for younger groups (Melby-Lervag & Hulme, 2013) concluded that WM programs produced reliable short-term improvements in WM skills but that the effects were "*short-term, specific training effects that do not generalize"* (p.270).

It would appear, therefore, that although CCT approaches are both effective and cost-effective for the activities targeted, considerable care needs to be taken in the design to maximise the transfer of these effects to functions relevant to everyday life. These insights further highlight the need for a combined, holistic approach.

4.2.2.2 Brain stimulation

One of the most intriguing approaches derived from the systems framework is that of direct brain stimulation. If an intrinsic connectivity network is showing impaired function and

structure, then direct stimulation of the network should lead to increased firing rates in that network which will, via the Hebb rule, lead to the circuits rewiring together again. Indeed, there is evidence that direct brain stimulation is effective in improving function in old age. A recent review (Summers et al., 2016) concludes that transcranial direct current stimulation (tDCS) led to "beneficial effects (a) on both cognitive and motor task performances, (b) across a wide-range of cognitive tasks, (c) on specific brain areas, (d) stimulation offline (before) or online (during) the cognitive and motor tasks." (p. 42).

Surprisingly, the above review found little effect of the locus of stimulation on its effectiveness. Clearly one might expect that tDCS targeted on particular intrinsic connectivity networks should lead to optimal results. Given the role of the cerebellum in multiple intrinsic networks, direct cerebellar stimulation might therefore prove effective. There is indeed extensive information supporting the use of transcranial magnetic stimulation (TMS; single pulse or repetitive (rTMS)) or transcranial direct current stimulation (tDCS; anodal or cathodal). A recent 'consensus' paper (Grimaldi et al., 2014) stresses the need for large scale rigorous studies but concludes:

> There is a consensus amongst the panel of experts that both TMS and tDCS can effectively influence cerebellar functions, not only in the motor domain, with effects on visually guided tracking tasks, motor surround inhibition, motor adaptation and learning, but also for the cognitive and affective operations handled by the cerebrocerebellar circuits. Verbal working memory, semantic associations and predictive language processing are amongst these operations. Both TMS and tDCS modulate the connectivity between the cerebellum and the primary motor cortex, tuning cerebellar excitability. (p.121)

Recent papers highlight the role also in emotions (Ferre Bottini, Ianneti & Haggard, 2013; Ferre, Haggard, Bottini & Ianneti, 2015) and in body schemas (Lopez, Schreyer, Preuss & Mast, 2012). There is also evidence that cerebellar stimulation influences the default mode network (Halko, Farzan, Eldaief, Schmahmann & Pascual-Leone, 2014).

One well-established method (Fitzpatrick & Day, 2004) of stimulating the cerebellum is by direct vestibular stimulation, either caloric (applying heat to the inner ear) or 'galvanic' (direct current stimulation of the ear). Caloric stimulation has revealed the vestibular system's role in body image and sensorimotor processing, and even pain perception (Deroualle, Borel, Deveze & Lopez, 2015; Ferre et al., 2013; Ferre, et al., 2015; Ferre, Walther, & Haggard,

2015; Lopez et al., 2012). These studies have led to the realisation that the vestibular system is widely represented, and at different timescales throughout the brain, with regions comprising the posterior insula and retroinsular regions, the anterior insula and the inferior/middle frontal gyrus, the superior temporal gyrus, the temporoparietal cortex, the pre- and postcentral gyrus, the basal ganglia, the anterior cingulate gyrus, the precuneus, the parahippocampal gyrus and hippocampus, the occipital lobe, the supplementary motor area (SMA) and the cerebellum (Della-Justina et al., 2015; Klingner et al., 2013).

4.2.2.3 Exercise-based interventions

One of the clear limitations, from a systems view, both of computerised cognitive training and of direct brain stimulation, is that the intervention is artificial, and isolated from the physical or mental activities involved in normal system functionality. There is evidence that natural activities, such as exercise, can improve not only physical fitness but also mental fitness, and even stimulate the growth of new brain neurons and connections (Hillman, Chodzko-Zajko, Kamijo, Schott & Schwingel, 2008; Hoetting & Roeder, 2013; Kirk-Sanchez & McGough, 2014). An innovative approach combining both exercise and CCT approaches ('exergaming') was shown to have beneficial effects for healthy older adults and for those with mild cognitive impairment (Gonzalez-Palau et al., 2014)

A recent discovery has been the differential effects of cardiovascular, high intensity, exercise and 'co-coordinative exercise' such as balance training or Tai-Chi. There is evidence that exercise can potentiate the brain for new learning, with coordinative balance exercises possibly leading to neural growth in the hippocampus - a core structure for explicit learning and memory (Niemann et al., 2014) - and also in the cerebellar-cortical loop (Burciu et al., 2013) - a core network for implicit learning and coordination. A further study (Nascimento et al., 2014) concluded that multimodal physical exercise was effective to reduce pro-inflammatory cytokines and to improve brain-derived neurotrophic factor (BDNF) peripheral levels, with positive reflexes on cognition in elderly individuals with mild cognitive impairment.

Recent studies of the effects of exercise on rat brains (Abel & Rissman, 2013; Kellermann et al., 2012) reveal effects on epigenetic changes and in changes in the cerebellar Purkinje cells following a rat vestibular training exercise (Lee, Huang, Tsai, & Yen, 2015). There is also evidence that BDNF is expressed in the cerebellum following environmental enrichment for rats (Angelucci et al., 2009; Vazquez-Sanroman et al., 2013). Of particular

interest, there is evidence (though sparse) that Quadrato exercise (like Tai Chi) led to increased creativity and changes in grey matter and white matter in the cerebellum of human adult females (Ben-Soussan, Berkovich-Ohana, Piervincenzi, Gliksohn & Carucci, 2015).

There have also been detailed neuroimaging studies of interventions for special groups. Daily clinic-based balance training for 2 weeks in cerebellar patients and age-matched healthy controls (Burciu et al., 2013) led to enhanced balance performance in the patients, with associated increased grey matter volume in the dorsal premotor cortex and within the cerebellum for both groups. A six week balance-training study with Parkinson's patients and healthy controls (Sehm et al., 2014) led to improved balance which was maintained for the following year, together with increased grey matter in the hippocampus for the controls and in several brain regions for the patients.

In summary, current neuroimaging and behavioural research appears to be converging to a view that: (i) a systems approach to ageing is the most promising framework for understanding the degradation in multiple functions with age; (ii) there is extensive evidence that the cerebellum is one of the key structures affected, and the multiple intrinsic connectivity networks linking the cerebellum with other brain and body structures may well mediate many of the actual deficits shown; (iii) 'single system' interventions can be effective, but generally it is better to have multiple domain interventions; (iv) a range of interventions, from coordinative exercise to direct vestibular stimulation are likely to have beneficial effects on cerebellar function.

4.3 Study Design

The above considerations informed the design of the current study. We wished to evaluate the effectiveness of a novel internet-based 'vestibular stimulation' intervention, the ZingUp intervention (www.ZingUp.com). This intervention was originally developed to tune up the coordination abilities of top sporting performers, using a series of graded exercises designed specifically to improve three performance dimensions: sensorimotor coordination, eye movement control, and dual tasking. However, extensive feedback had suggested that the programme was valuable for many average performers. Consequently the system was embedded in an internet-based 'game' format designed to challenge and stimulate the user to keep improving their performance. ZingUp offer a number of courses specifically tailored to each individual user, with applications in sporting areas, organisational development, in education.

The ZingUp system involves a series of graded activities on three dimensions – dynamic activity (patterned movement sequences), focus activity (developing the ability both to concentrate and to 'dual task'), and stability activity (coordinative balance). Underpinning the approach is the technique of vestibular stimulation. Rather than cardiovascular exercise, which is designed to have energetic use of highly practised routines, or even coordinative balance such as Tai-Chi, which does involve learning new actions, vestibular activities are designed to cause abnormal input for the vestibular system, for example by requiring the user to put their head on one side while undertaking tasks. This presents the vestibular system, and the cerebellum, with an immediate challenge, requiring activation of many circuits to cope with the ensuing proprioceptive feedback.

A typical course lasts six months and is composed of daily physical activities and digital video games. An example of a screen from the focus strand, at a low level and aimed at developing dual tasking ability is given in Figure 6. A video is also available for each activity.

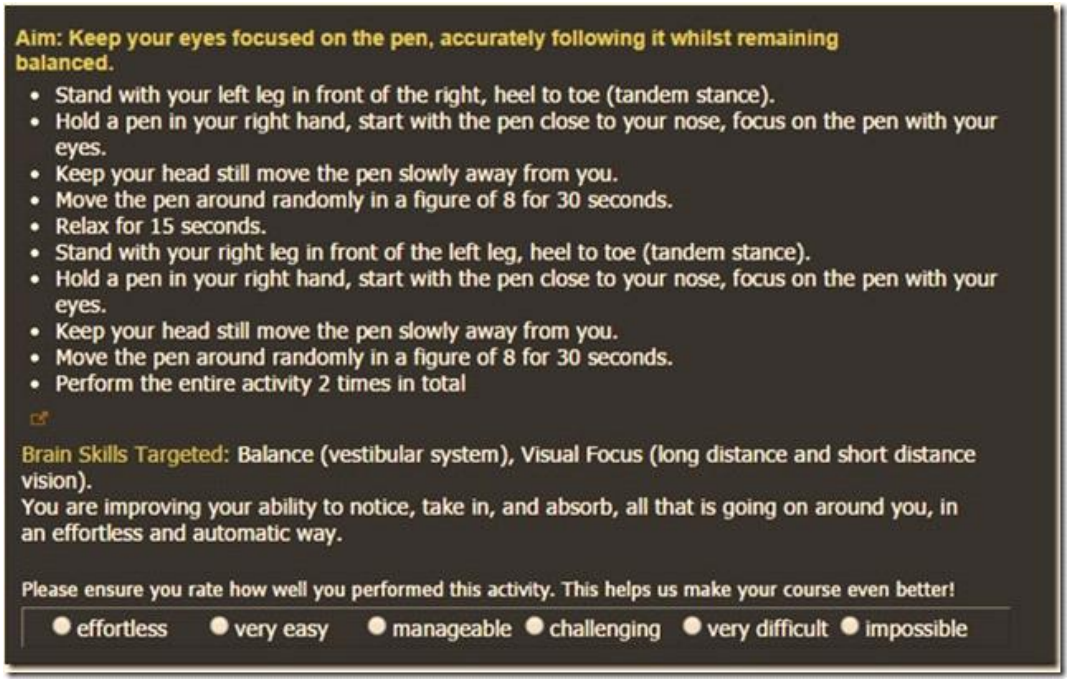


Figure 6: Sample Screen from the ZingUp intervention

The ZingUp platform therefore provides a user-orientated, motivating framework for delivering a cost-effective cerebellar challenge intervention that satisfies the criteria that have emerged for multimodal, challenging interventions in older adults.

We undertook the study to investigate whether internet-based approaches can indeed be an effective and popular method for older adults, and designed an 8 week intervention. It

is important to highlight that although this is a Randomised Control Trial (RCT) study, in that there was a control condition and allocation to condition was random, it is not a full RCT, for which an active intervention condition, matched in time and form to the ZingUp intervention, would need to be used to counter placebo-type effects. Our view is that this non-equivalent–control RCT (NEC-RCT) design is appropriate for a user-centred trial that has the underlying question "If participants undertake the intervention, will it help them, and, if so, in what ways?" We are not investigating the theoretical issue – is intervention A more effective than intervention B, and if so, why? Each design has its strengths and weaknesses. For the purpose of evaluating whether a low-cost, home-based intervention might be beneficial (as opposed to life-as-usual), the NEC-RCT design is the appropriate one. The design allows the following hypotheses to be evaluated:

Hypothesis 1. Improvements in balance and sensorimotor coordination

This is the primary applied hypothesis, directly related to attempting to boost balance performance and thus decrease the danger of falling. One in three people of 65 fall at least once per year, with the incidence rising to one half of those over 80 years old (Todd & Skelton, 2004). Falls are a major cost to elderly people and to national health services, estimated to account for 21% of the Dutch health service costs for injuries (Hartholt et al., 2011). Hypothesis 1 states that ZingUp training will lead to significant improvements in sensori-motor coordination especially balance: (a) for each individual compared with their pre-training; (b) that the intervention group will improve significantly more than a control, no intervention, group.

Hypothesis 2. 'Hippocampal' improvements.

This hypothesis is derived from the research showing the benefits of coordinative balance training for hippocampal function. Hypothesis 2 states that ZingUp training will lead to significant improvements in 'declarative memory' performance: (a) for each individual compared with their pre-training; (b) that the intervention group will improve significantly more than a control, no intervention, group.

Hypothesis 3. Improvement Specificity

Although ZingUp training may lead to significant 'transfer' to other areas, including language, affect and fluid reasoning, any such effects will be minor compared with the specific improvements in hippocampal and sensorimotor skills.

4.4 Method

4.4.1 Participants

98 volunteers (30 male, 68 female) aged 50 to 85 (Mean 68.2, S.D. 6.6) were recruited through advertisements in local newspapers, churches and social groups. An advert also went out on the University of the Third Age Sheffield website. Participants were all without a known diagnosis of dementia, which was self-reported. All participants were White British (96.70%), Irish or Irish Traveller, with 85.71% retired (the other 14.29% were either in full or part time education or work). 31.58% had HND's or undergraduate degrees, with a further 16.84% having postgraduate degrees. Another 13.16% listed a professional qualification as their highest qualification. Table 13 shows the percentage of the sample who reported medical conditions.

Condition	Percentage of sample who reported a history of it
Depression	27.55
Myocardial Infarction	2.06
Diabetes	4.12
Cerebrovascular Pathology	2.06
High Blood Pressure	27.08
High Cholesterol	23.71
Congestive Heart Failure	4.12
Breathing Difficulties	13.40
Stress	19.59

Table 13: Percentage of sample with medical conditions

Of the participants who noted cerebrovascular pathology, one had had a brain haemorrhage, and the other had suffered a Transient Ischaemic Attack, but in both cases no lasting damage was known, and the precise location was unreported. In all cases, medical conditions were well managed by medication (which was verified by repeat prescriptions), and the average number of medications taken by participants was 2.06 (SD 2.33). Finding older adults with a complete absence of medical conditions would be impractical and unrepresentative of the population. So further details on all medical conditions were taken, and participants with a known diagnosis of a neurological disorder excluded.

4.4.2 Design

The aim of this study was to test the effectiveness of vestibular stimulation on physical and mental function. Therefore, a repeated measures design was used. Participants were asked to complete a baseline set of tests at the University of Sheffield, Department of Psychology before taking part in the 8 week ZingUp intervention at home. They were then asked to return to the department for a repeat of the baseline tests.

4.4.2.1 Test Battery

The same tests were used both pre and post-test. While there may be some practice effects here, it would be expected that this would affect both groups equally, and therefore any relative difference in the intervention group's performance is likely to be attributable to the exercises.

We wished to evaluate changes in all the core physical, mental and affective domains, using simple but normed tests where possible. We based the battery on the Dyslexia Adult Screening Test (Fawcett & Nicolson, 1998), which covers the majority of the necessary tests in a 30 minute package. We constructed a battery of 14 tests, divided into 5 suites. Suite 1 was for Physical Coordination and comprised the DAST balance test, the two Purdue Pegboard (Tiffin & Asher, 1948) Tests (Peg Moving and Peg Assembly), and the DAST writing (copying) test. Suite 2 investigated memory. It included two tests of working memory, the DAST backwards digit span test and the South Yorkshire Ageing Study Spatial Memory test (Tarmey, 2012) which determines spatial memory span for non-verbalisable pictures presented in one of 8 locations. There was one declarative memory test, the South Yorkshire Ageing Study (Tarmey, 2012) Picture Memory test which assesses recall for a set of 18 pictures of common objects, presented sequentially for one second, including both immediate recall and delayed recall after 20 minutes. The Language Suite comprised the DAST Rapid Naming, Phonological Processing, Reading, Nonsense Passage and Spelling tests. The Fluid Thinking suite comprised the DAST Nonverbal Reasoning, Semantic Fluency and Verbal Fluency tests. Finally two tests of affect were administered: the Beck Depression Inventory (Beck et al., 1996) and the Authentic Happiness Inventory (Seligman, 2002) as the cerebellum is known to be involved in affect (Schmahmann, 1998).

4.4.2.2 Intervention Training

Participants were required to undertake a minimum of 8 weeks and maximum of 10 weeks balance and sensorimotor coordination training using an online set of activities. These were provided by Zing Performance Ltd., and were designed specifically to stimulate brain regions involved in coordinative balance. Initially, participants had to undergo an assessment to determine their strengths and weaknesses. After this a 30 day programme was set for them, specifically designed to target their biggest needs. Participants were required to do two exercises a day, before rating how difficult they found that particular activity. A screen shot is shown in figure 7 below.

Figure 7: A screenshot from the daily ZingUp Programme

Each week, three exercises were assigned, with two of the three appearing each day. After 30 days, participants were reassessed before continuing onto unit two. Adherence to the programme was verified by checking participant log-ins. However, it was not possible to see what participants did once logged in, so adherence to the exercises was self-reported. It should be noted that a full ZingUp 360 session programme is designed for six months, with

two sessions per day. Consequently this study is very much shorter than intended by the ZingUp designers. Ethical approval for the study was granted by the Department of Psychology, University of Sheffield Ethics Board.

4.5 Results

Data were converted to standard scores (Mean 100, S.D. 15) to allow direct comparison across tasks. Where possible, population norms and standard deviations were used to normalise test scores. The population norm for age 55+ was used for all participants, irrespective of age, to represent absolute performance rather than age-adjusted performance.

4.5.1 Effect Sizes

In order to facilitate comparison of the improvements (or otherwise) in performance from pre-test to post-test, effect sizes were calculated using the formula ES = (post-test – pre-test) / sd (all groups on pre-test), which is a form of Cohen's d (Cohen, 1988) applied to change analysis. No change would result in an effect size of 0, whereas a score of +1.0 indicates a change of one standard deviation unit. Cohen (1988) suggests that effect sizes of 0.8, 0.5, and 0.2 be labelled large, medium and small respectively.

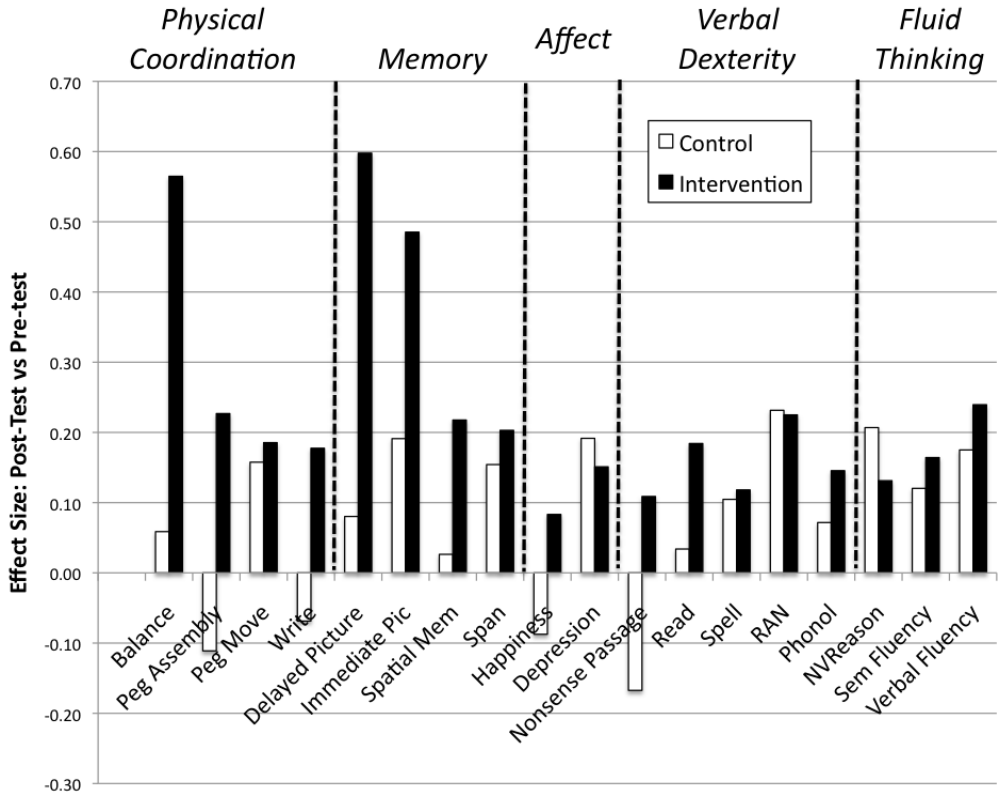


Figure 8: Effect Sizes for the Variables of Interest

Effect sizes for the two groups are shown in Figure 8. Tests have been grouped in order of the hypotheses. The Physical Coordination suite – postural stability, peg moving, peg assembly, and handwriting speed are on the left, then the Memory Suite – immediate picture recall, delayed picture recall, immediate spatial memory and immediate verbal memory. Group 3 include the affect measures – the Beck Depression Inventory (reverse scored such that higher means less depressed) and the Authentic Happiness Index. The remaining tests are the Language Suite and the Fluid Thinking Suite but were not predicted to be affected by the intervention.

4.5.2 Correlations with ZingUp Usage

Next correlational analyses were undertaken utilizing data collected automatically on 'compliance' for the ZingUp group. Of the 53 participants allocated to the ZingUp group, 38 completed at least 40 sessions, as requested, but the differential uptake allowed us to investigate the effects both of frequency of ZingUp use (sessions per week) and the duration (number of weeks). For the frequency of ZingUp use significant correlations one-tailed ($p<.10$) were found for reading ($r=0.262$, $p=0.06$), peg movement ($r=0.31$, $p<.05$), and for

postural stability (r=0.303, p<.05). A significant correlation with number of weeks of the intervention occurred only for nonverbal reasoning (r=0.288, p<.05). A significant correlation with total ZingUp sessions was found only for nonverbal reasoning (r=0.261, p=0.06).

4.5.3 Within-group Statistical Tests

Inferential statistical tests were then undertaken for the 16 tests within the five suites of tests. First repeated measures multivariate analyses of variance were undertaken for each suite separately on the data for pre-test and post-test for each test within the suite. If the multivariate analysis proved significant, no correction was made for multiple comparisons. If the overall MANOVA for the family was not significant, the corresponding Bonferroni correction for multiple comparisons was administered.

For the control group, none of the suite MANOVAs approached significance. In fact the only individual comparison to reach the uncorrected significance level was for Peg Moving [F(1,43)=6.26, p=0.016] but this did not reach the corrected significance level of 0.0125.

For the ZingUp group, the MANOVA analyses of the change from pre-test to post-test were highly significant for the suites for Physical Coordination, for Declarative Memory, for Language, and for Fluid Thinking [F(1,47)=22.95, p<.001; F(1,52)=10.71, p=.002; F(1,52)=15.99, p<.001; F(1,52)=5.72, p=.020 respectively], whereas there was no difference for the Affect suite. The changes for Balance, Peg Assembly and Peg Moving were significant [F(1,50)=14.07, p<.001; F(1,51)=5.53 p=.023; F(1,50)=4.10 p=.048 respectively] with the improvement for writing significant one-tailed [F(1,52)=3.88 p=.054]. The improvements for Delayed Picture Recall, Immediate Picture Recall and Memory Span were also significant [F(1,52)=14.44 p<.001; F(1,52)=15.41 p<.001; F(1,52)=4.20 p=.046 respectively]. The improvements for nonsense passage reading, one minute reading, rapid naming, and spelling were all significant one-tailed [F(1,52)=3.72 p=.059; F(1,52)=6.28 p=.015; F(1,52)=4.73 p=.034; F(1,52)=3.28 p=.076 respectively]. The improvement for verbal fluency was also significant [F(1,52)=5.13 p=.028].

4.5.4 Between-group Statistical Tests

Finally, in the most stringent test of the changes, a series of multivariate 2-factor analyses of variance was undertaken, with the independent groups factor being the group (ZingUp vs

Control) and the repeated measure being time-of-test (pre-test vs post-test. MANOVAs were undertaken separately for each of the five suites. See Table 14. For the MANOVA entry, only the key statistic, the interaction term between time of test (pre vs post) and Group is reported. A significant interaction would typically indicate that the Intervention led to a significant difference between groups at post-test whereas performance at pre-test was equivalent.

(1) Physical coordination	MANOVA: F(1,87)=9.47 p=.003
Postural Stab.	F(1,89)=5.24 p=.024 ^{2}=.056
Peg assembly	F(1,92)=4.36 p=.040 ^{2}=.045
Peg move	F(1,94)=0.03 p=.864 ^{2}=.000
Writing	F(1,92)=0.10 p=.754 ^{2}=.001
(2) Memory	MANOVA: F(1,93)=1.09, p=.300
Delayed Pic Recall	F(1,93)=4.58 p=.035 ^{2}=.047
Immediate Pic Recall	F(1,93)=1.78 p=.185 ^{2}=.019
Spatial Memory	F(1,93)=1.05 p=.308 ^{2}=.011
Verbal memory span	F(1,93)=0.15 p=.703 ^{2}=.002
(3) Language	MANOVA: F(1,93)=2.57, p=.113
Nonsense Passage Reading	F(1,93)=4.20 p=.043 ^{2}=.043
One Minute Reading	F(1,93)=1.72 p=.193 ^{2}=.018
Rapid Naming	F(1,93)=0.01 p=.933 ^{2}=.000
2 minute spelling	F(1,93)=0.01 p=.979 ^{2}=.000
Spoonerisms	F(1,93)=0.13 p=.715 ^{2}=.001
(4) Fluid Thinking	MANOVA: F(1,93)=0.06, p=.813
Nonverbal Reasoning	F(1,93)=0.11 p=.742 ^{2}=.001
Semantic Fluency	F(1,93)=0.06 p=.805 ^{2}=.000
Verbal Fluency	F(1,93)=0.32 p=.571 ^{2}=.003
(5) Affect	MANOVA: F(1,93)=0.99, p=.755
Authentic Happiness Index	F(1,93)=2.38 p=.127 ^{2}=.025
Beck Depression Inventory	F(1,94)=0.02 p=.890 ^{2}=.001

Table 14: Multivariate and Univariate Analyses of Variance for the Variables of Interest

It may be seen that the only suite returning a significant MANOVA result was the Physical Coordination suite. For each of the four tests a univariate two factor mixed measures analysis of variance was undertaken, with the within-group variable being time-of-test (pre-intervention vs post-intervention) and the between-group variable being group (intervention vs control). It may be seen that significant interactions – all reflecting greater improvement for the intervention group than the control group – were obtained for postural stability and for peg assembly. By contrast, there were no differences for peg moving speed or writing speed.

The MANOVA results for the other four suites of tests were not close to significance, and consequently a Bonferroni correction should technically be applied for each of the obtained significance levels – dividing them by the number of tests within the suite. It may be seen that uncorrected significant differences were obtained for Delayed Picture Memory and for Nonsense Passage Reading.

Given the theoretical significance of the Declarative Memory tests in the context of hippocampal function, and the fact that memory span and spatial span reflect working memory function (Baddeley & Hitch, 1974) rather than hippocampal memory retrieval, a further MANOVA was undertaken limited to the two picture memory tests. This did reveal a significant interaction effect (one-tailed) with $F(1,93)=3.81$, $p=0.054$.

4.5.5 Correlations with Age

Finally, correlations with age were calculated. Significant correlations were found for performance on the majority of tests, with correlations between age and each dependent variable in descending order being -0.47 (Nonverbal reasoning), -0.40 (peg assembly), -0.38 (immediate picture memory), -0.35 (immediate picture memory), -0.34 (writing), -0.28 (spatial memory), -0.27 (semantic fluency), -0.26 (postural stability) and -0.26 (spelling). Correlations between age and the amount of improvement for the ZingUp group were also calculated. Few correlations were significant, with only peg assembly (-0.37) being more extreme than -0.25.

4.5.6 Relationship between Cerebellar and Memory Tasks

Regression analyses were run to see whether the change in each of the memory tasks (immediate picture recall, delayed picture recall, spatial memory and verbal memory span)

could be accounted for by the change in either of the pegboard tasks (peg moving and peg assembly) or postural stability in the experimental group. These theoretically-driven regressions used the enter method, but none of the models were significant.

4.6 Discussion

The primary issue addressed by this study was whether a home-based cerebellar challenge internet-administered intervention was feasible for use with older adults and, if used, whether it would result in better balance, and hence reduce danger of falling (Hypothesis 1). A secondary, theoretical issue, was whether the intervention might also improve cognitive functions previously found to be improved by coordinative balance training (Hypothesis 2).

A set of 5 ‘suites’ of tests was applied before and after the intervention, allowing comparison with a ‘life as usual’ control group. Comparing individual performances across the intervention period, the control group performance remained roughly constant, with no significant change for 17 of the 18 tests. By contrast, the intervention participants showed significant improvement in their scores for 12 of the 18 tests administered (9 of the 12 two-tailed), with only the tests of the Affect suite showing no significant multivariate improvement Furthermore, a series of two factor analyses of variance revealed that the intervention group improved significantly more than the control group on two of the four Physical Coordination tests, on one of the memory suite, but not on the two tests of affect, the tests of divergent reasoning, or the tests of written and spoken language fluency.

Hypothesis 1 is therefore clearly supported. Not surprisingly – but crucial for applied purposes – the intervention group did improve significantly on balance compared both with their own pre-intervention performance and with the control group’s change in balance over the period of the study. There was also transfer of this training effect to manual dexterity (as indicated by the ‘peg assembly’ task). More surprisingly, but consistent with the literature on the benefits of balance training on hippocampal function, there was transfer of this benefit to declarative memory in the delayed picture recall condition (Hypothesis 2). The specificity of the differential benefit findings to the hypotheses suggests strongly that the changes are not a practice, placebo or Hawthorne effect (Hypothesis 3).

Of the 52 participants selected for the intervention condition, 38 (73%) completed the requested 40 sessions over 8 weeks. Analyses of the ‘dose effect’ (that is, correlations of performance improvement with number of intervention sessions for the intervention group) revealed significant correlations with intervention frequency for peg movement, reading and

balance, with a significant correlation with intervention duration for non-verbal reasoning. The fact that this was not found for memory tasks is of interest. In terms of the participants' response to the intervention, it should be noted that the ZingUp platform was a prototype version, not yet publicly available and in the process of substantial development and improvement. A sizeable minority of the ZingUp participants reported difficulties in accessing the system initially, though subsequently problems were relatively slight.

It is important to acknowledge the limitations of this study. First, the population sampled was by no means random, involving respondents to a circular. They should therefore be seen as relatively high functioning and with good self-efficacy. Furthermore, they represented a spread of ages, with 2 under 55, 27 aged 55 to 64, 55 aged 65 to 74, and 15 aged 75 and over. There was a considerable imbalance between the sexes, with 30 male and 68 female. All were living at home in reasonable health. All of these factors reduce the strength of inferences that can be made regarding generalization to the full population of community based older adults, and highlight the need for further research.

4.6.1 Conclusion

Prior research has established that home-based balance exercises are among the most cost-effective methods of improving balance ability and hence reducing falls in older adults. Recent developments in cognitive neuroscience have revealed that 'coordinative' balance training is likely to have beneficial effects, not only on physical coordination, but also on hippocampal function. Our theoretical analyses suggested that a multi-component, cerebellar challenge intervention should prove maximally effective, combining the effectiveness of coordinative exercise with that of direct cerebellar stimulation, and therefore improving function in the intrinsic connectivity networks involving the cerebellum. The study design did not include brain imaging, and therefore it is not possible to assess directly any underlying neural changes. Nonetheless, the results were encouraging.

The present study is unique in two ways: first we investigated a highly cost-effective internet-based 'cerebellar challenge' intervention, 'ZingUp'. Second we investigated physical coordination, mental coordination, language, fluid thinking and affect using a specially developed suite of tests. Significant benefits (comparing initial performance with post-intervention performance) were found for the intervention group on the majority of the tests, excluding only those of affect. Furthermore significantly greater improvements were found

for the intervention group (compared with the control group) for balance, for physical coordination, and for delayed declarative memory retrieval.

Further research, including research using an active control intervention, would be needed to pinpoint the theoretical causes of the improvements obtained. Nonetheless, given the minimal cost and considerable ease of access of the intervention, it provides a promising approach to improving the overall cerebellar-related function, protecting against subsequent balance problems, and may also benefit declarative memory in older adults.

5 Chapter 5: Overall Discussion

It has already been established that cognition and motor function generally decline with advancing age, but the relationship between domains and precise mechanism for how this occurs remains to be confirmed. This thesis sought to address three main issues:

1) To establish the potential role of tests sensitive to the cerebellum in general cognitive ageing, and how this could motivate specific approaches to screening and intervention.
2) To be able to accurately determine who is most at risk of cognitive decline. This should be done through a short, easy to administer, but highly predictive screening test, which would act as the first step before further testing.
3) Once we are able to reliably predict who is most likely to decline, to then be able to offer a suitable intervention to prevent it.

Three studies were carried out in order to enable this, all designed to focus on the role of the cerebellum in ageing. Study one was exploratory in nature, and tested participants of various ages on 10 subtests from the Dyslexia Adult Screening Test (DAST). Correlations with age and effect size analysis of age groups revealed significant declines in processing speed, motor function and fluid intelligence with increasing age, while crystallised skills remain intact. Surprisingly, this was also true for fluency tasks. Analysis revealed that fluid intelligence showed age-related differences across the lifespan, but substantially dropped after the age of 50, while difficulties with processing speed and motor function appeared at an earlier age. Study two expanded the number of cognitive tasks used; again confirming that decline is seen in both cognitive and motor domains with age, though the latter showed the most decline. When age is controlled for, motor function is predictive of some aspects of memory function. The final study tested an at home intervention, designed to challenge and train cerebellar function. While the 'life as usual' control group showed no significant change for 17 of the 18 cognitive and motor tests after three months, the intervention group showed significant improvement in 12 of the 18 tests. Furthermore, the intervention group improved significantly more than the control group on the four physical coordination tests, and one of the memory tests. Taken together, these results suggest that motor function declines before cognitive function, that motor function can be used as a predictor of cognitive function, and that an at home cerebellar challenge intervention can be used to improve the decline across both motor and cognitive domains.

The first aim of this thesis was to establish the potential role of the cerebellum in cognitive ageing, and how this could motivate specific approaches to screening and intervention. To date, there is no consensus as to the exact pattern of degeneration seen in normal ageing. The frontal lobe hypothesis, based on the fact that this region shows the most atrophy with age, has wide ranging support given that many frontal and prefrontal based processes show marked decline with age, and these may lead to more specific cognitive deficits (West, 1996; Drag & Bieliauskas, 2010; Albinet, et al., 2012). However, the main criticism levelled at this theory is that functions largely independent of prefrontal areas are also significantly impaired in ageing, therefore a global mechanism, such as the processing speed theory of ageing, would more accurately account for age-related impairments in more varied cognitive domains (Greenwood, 2000; Drag & Bieliauskas, 2010; McKinlay et al., 2009; Park et al., 2002). Results from the first study of this thesis not only support previous findings in that a global deficit across the motor and cognitive domain is present, but also found a significant decline in processing speed and motor function, in addition to the well-established frontal executive difficulties.

What is of great importance here though is the fact that motor function appears to show differences between age groups before frontal executive functions and processing speed. Caution has previously been urged when interpreting studies reporting processing speed changes as accounting for the variance seen in cognitive function, as cross-sectional studies are likely to overestimate these proportions, with the need for additional factors to be taken into account (Sliwinski & Buschke, 1999; Lemke & Zimprich, 2005; Drag & Bueliauskas, 2010). Of the proposed theories, the fronto-cerebellar theory of ageing encompasses the difficulties experienced in frontal executive functioning, while describing a mechanism that accounts for overall decline, and is likely to also explain why deficits in motor function are noticeable first. It is recognised that the cerebellum not only acts a precise timing mechanism for the brain, but that it is well connected with all other regions of the brain as well (Gordon, 2007). While its role in motor function is well-known, more recent research suggests that the circuits that allow for precise motor control, also exist as cortico-cerebellar loops responsible for precise cognitive control (Timmann & Daum, 2007; Schmahmannn, 1998; Leiner et al., 1986; Kelly & Strick, 2003; Allen et al., 2005; Hayter et al., 2007; Balsters & Ramnani, 2008; Stoodley & Schmahmann, 2009; Leiner et al., 1986; Ramnani et al., 2006; Schmahmann & Sherman, 1998; Botez et al., 1989).

It is disruption of these networks that likely cause the difficulties seen across multiple domains (Hogan, 2004). With the cerebellum playing such a large role in motor function, it is

plausible that deficits in this domain are demonstrated prior to deficits in cognitive domains, due to a lack of compensatory mechanisms to account for this. So while the findings of this thesis offer strong support from the fronto-cerebellar theory of ageing, more research into the functional connectivity of the cerebellum with other brain structures is needed to develop this further.

The second aim of this thesis was to be able to accurately determine who is at risk of cognitive decline. This should be done through a short, easy to administer, but highly predictive screening test, which would act as the first step before further testing. As previously described, study one revealed that deficits in motor function are likely to be detectable before deficits in cognition manifest. DAST provided a quick and easy to administer battery that tested multiple tasks across various domains, although it is acknowledged that not all tests were found to be predictive within the studies presented here. Studies two and three saw the addition of further cognitive tests, as well as the Purdue Pegboard (Lafayete Instrument Co.). Dexterity tasks have been found to be sensitive in identifying age-related decline, and it has been suggested that difficulties in fine motor skills might actually be predictive of cognitive decline (Carment et al., 2018; Vasylenko et al., 2018b; Curreri et al., 2018), and study two found evidence to support this. When age was controlled for, motor function was found to be predictive of some aspects of cognitive function. This finding provides strong evidence for including motor tests in screening tasks, which importantly, unlike many tests of executive functioning, are likely to be independent of education (Kluger et al., 1997). This thesis has demonstrated that it is possible to do this using tests that replicate movements in everyday life, while being suitable for rapid quantification (Carament et al., 2018; Yan & Zhou, 2009).

The final aim of this study was that once we are able to reliably predict who is most likely to decline, to then be able to offer a suitable intervention to prevent it. If improvements to the way we predict and detect cognitive decline with age are made, morally, we must also seek to improve the protection we provide against this. Working with the hypothesis that the cerebellum is involved in both sensorimotor and cognitive function through multiple cortico-cerebellar loops, repair to any age related damage should in turn strengthen the connections and improve function. Study three provides evidence that an at home intervention designed to train cerebellar function, led to improvements in various cognitive tasks, but in particular balance, physical coordination and delayed declarative memory retrieval. This is of great importance to people of all ages, but may be particularly relevant to those of advancing age. Older adults have been shown to have diminished postural control and thus problems with

balance as a result of degraded compensatory mechanisms to correct for disruptions to sensory output (Teasdale, Stelmach & Brueunig, 1991). Poor balance and physical coordination then leads to an increased risk of falls and physical harm to an already physically weakened body, while memory complaints are commonplace in older age. While younger adults also have memory complaints, these are usually attributed to stress. By training the cerebellum to act more efficiently when ageing, it seems possible that the connections on which both cognitive and motor function rely, execute cognitive and motor commands more efficiently and performance is increased as a result. Further research is needed to examine the precise mechanisms underlying these behavioural findings.

5.1 Limitations and Future Directions

The limitations of each study were addressed by the following one, however some issues remain. Difficulties in recruiting those of the oldest age and of an even spread of genders could be addressed by using larger sample sizes than were practically possible for the purposes of this thesis. It remains unclear as to precisely what the differences are in cerebellar size and degeneration with age are between the genders, and also which in which direction the differences are, but clear differences have been found (Rhyu et al., 1999; Escalona et al., 1991; Hogan, 2004). Gender differences in age related loss in the frontal and temporal lobes, the hippocampus and parietal lobes has also been reported (Greenwood, 2000). Therefore, larger sample sizes could allow for comparison of male and female participants to help clarify how these differences manifest behaviourally in the cognitive and motor domains. Recruiting more participants who meet the exclusion criteria for health, but are of the eldest ages in society, would help to further explore the lifespan in more fullness.

This thesis explored behavioural changes across the lifespan, looking for potential predictors of cognitive decline and investigating the effectiveness of a cerebellar based intervention. While evidence was found to support a causal role for the cerebellum in cognitive ageing, anatomical evidence to support this is needed to explain the mechanisms behind the behavioural findings. By repeating the final study, but including neuroimaging, it would be possible to examine the structural changes that occur in the brain following cerebellar stimulation. Previous studies have revealed that relatively short doses of balance training can result in growth of specific brain regions, when used within special groups. Burciu et al. (2013) found increased grey matter volume in the dorsal premotor cortex and the cerebellum in both cerebellar patients and age-matched controls, while Sehm et al. (2014)

reported improved balance which was maintained for a year, as well as increased grey matter in the hippocampus for the controls, and in several brain regions for the patients. Given that the final study of this thesis found improvement in both motor control and memory performance in a group of healthy older adults, it would be of the utmost importance to investigate whether structural growth in the cerebellum and hippocampus is replicated with this intervention. Including an active control group in future studies would also be beneficial, to be more certain that the type of intervention is driving the improved results, rather than the mere supply of an intervention being responsible for the changes described. The present study found no significant multivariate improvement in affect for the intervention group, thus suggesting an affective active control task may satisfy this need. Furthermore, having established the benefit of using motor tests as a predictive tool, it would be sensible to extend the research in this direction too. Dexterity tasks comprise of many different types of movements, which may show varying degrees of decline in older adults (Vasylenko et al., 2018b). More precise measures of motor timing (such as a finger tapping task), motor learning (using a motor sequence task) and balance (using a Wii fit balance board) would enable more accurate pre and post comparisons, while still allowing for fast quantification of results for clinical use. Work to address these issues has already begun, however were unable to be included in this thesis due to practical limitations.

5.2 Conclusion

Ageing is a difficult concept to define, with the only certainty being that the precise mechanisms behind cognitive ageing are as yet unclear. While structural changes at both macro- and micro-level are described, and neurochemical changes illustrated, the debate over the compensatory activation models that explain the differences between younger and older adults continues. The need for a single unifying theory is as great as ever in an ageing Western population, in an attempt to best support the oldest adults in our society.

Behaviourally, it is well documented that fluid intelligence is susceptible to the effects of ageing, while crystallised abilities remain intact. Difficulties in attention, memory, language and motor function are again well established as degenerating with normal ageing. While the cerebellum has traditionally been thought of as a motor structure, there is now evidence to imply it plays a similar role in cognition as it does in motor function. Multiple cortico-cerebellar loops may be responsible for the smooth running and accuracy of complex cognitive, as well as motor functions. Disruptions of these loops is likely increased in ageing,

as a result of the cerebellum's inability to precisely keep time of every action that needs to be executed. Thus, the cerebellum provides a logical place to begin describing a unifying theory of ageing.

The three studies presented in this thesis provided evidence that motor function declines before cognitive function, motor function can be used as a predictor of cognitive function, and that an at home cerebellar challenge intervention can be used to improve the decline across both motor and cognitive domains. By including motor tasks in ageing test batteries, it is plausible that those most at risk of cognitive decline are identified *before* behavioural changes are self-reported. Moreover, once these individuals have been identified, there is again evidence to suggest that a simple at home intervention can at worst limit the damage, and at best repair it. Further research is needed to understand more about the mechanisms behind this, but it now seems highly likely that cerebellar testing and training holds the key to the societal problem of how to ensure we continue to age well.

6 Declarations

Study One
This dataset is taken from the normative testing data obtained during the development of the Dyslexia Adult Screening Test (DAST, Fawcett and Nicolson, 1998).

Study Two
Dataset taken from the unpublished doctoral thesis of Drew Tarmey (2012), although partially collected by Zoë Gallant as a Graduate volunteer, then later as part of her Master's degree.

Study Three
Zoë Gallant was the primary contributor for this study. Rod Nicolson was not involved in the data collection, but made revisions to the paper in preparation for journal submission.

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