Lifestyle factors and neuroimaging metrics as predictors of cognitive performance in healthy aging

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Abstract

Despite all the advances made in health-related and psychological sciences, advancing age continues to be accompanied by cognitive decline. Aging is usually associated with major changes in the structure and functioning of the brain that lead to impairments in multiple cognitive functions. The trajectories of age-related effects on the brain and cognition exhibit considerable differences across cognitive domains and across individuals, and investigating approaches and factors that might prevent brain and cognitive decline during aging is considered a topic of great scientific and public health relevance. The overall goal of this thesis was to evaluate age-related differences in brain structure and functional connectivity to further our understanding of the neural mechanisms involved in age-related declines in cognition. This thesis also aimed to investigate the influence of lifestyle factors on age differences in cognition, and in that regard, I focused on the effects of sleep quality and physical activity on memory.

In Study 1, I assessed the impact of aging on grey matter volume of the medial temporal lobe MTL and prefrontal cortex PFC and compared the relative contributions of MTL and PFC structures to age differences in associative memory. My findings emphasize the critical role of the frontal lobes, and the control processes they subserve, in determining the detrimental effects of age on memory. Additionally, I observed that the relationship between frontal grey matter volume and memory was not moderated by age or sex, suggesting that greater volume in PFC structures relates to better memory performance across the lifespan and in both sexes. In Study 2, I assessed the effects of age on functional brain networks. Given the essential role of the arousal system (ARAS) in cortical activation and previous findings of disrupted ARAS functioning with age, I investigated the hypothesis that age-related changes in ARAS-cortical functional connectivity may contribute to commonly observed age-related differences in cortical connectivity. The findings of this study showed that the arousal system is functionally connected to widespread cortical regions and suggest

that age differences in functional connectivity within the cortex may be driven by age-related changes in the brainstem and these altered connectivity patterns have important implications for cognitive health. In Study 3, I investigated the relationship between sleep quality, physical activity, and memory in middle-age and older adults, in addition to assessing the impact of the COVID-19 pandemic on participants' mood and sleep quality. Our results showed that people who were more active reported better sleep quality and showed better memory, and better sleep quality was associated with better memory. Moreover, our findings also showed that some of the beneficial effects of physical activity on cognition are partially mediated by improved sleep. Additionally, this study indicated that the COVID-19 pandemic had a deleterious effect on people's sleep quality and overall well-being.

Taken together, these studies suggest that aging is associated with disruptive effects on brain structure and function, and that these changes are associated with age-related cognitive decline. Additionally, our study supported the association between lifestyle factors, more specifically, sleep quality and physical activity, and cognitive performance during aging.

Keywords: *aging, brain health, cognitive maintenance, neuroimaging, memory, lifestyle, sleep, physical activity.*

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COVID-19 Thesis Impact Statement

This research was conducted during the COVID-19 pandemic. While the pandemic afforded the unique opportunity to study how a global health crisis affects mental health, cognition, and well-being, it did pose a significant challenge to my research.

Study 3 was originally designed as an intervention study to evaluate the effects of exercise training on sleep quality, memory, and well-being in middle-aged and older adults. This would have been a 3-week study recruiting participants from the local community to come into the lab for pre and post-intervention cognitive testing, 4 sessions of 40 minute moderate-intensity cycling training (with our collaborators at the Brock-Niagara Centre for Health and Well-Being), and the use of actigraphy to monitor sleep quality (along with a sleep diary). However, in response to COVID-19, Study 3 had to be totally adapted. Unfortunately, we were unable to test participants in person, so we switched to an observational design run entirely online as described in this thesis. In addition to this structural impact in Study 3, the pandemic has also impacted the development of this thesis in other indirect ways, such as increasing levels of stress associated with the required changes at professional and personal levels.

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Chapter 1: General Introduction

The proportion of older adults is growing in the global population and despite all the advances made in health-related and psychological sciences, advancing age continues to be accompanied by cognitive decline. Aging is usually associated with major changes in the structure and functioning of the brain that lead to impairments in multiple cognitive functions. The trajectories of age-related effects on the brain and cognition, however, exhibit considerable differences across cognitive domains and across individuals, and investigating approaches and factors that might prevent brain and cognitive decline during aging is considered a topic of great scientific and public health relevance. The present thesis examines age-related effects on brain structure and functional connectivity to better understand the neural mechanisms underlying age differences in cognition and the potential benefits of lifestyle factors for cognitive longevity.

Literature Review

Effects of aging on cognition

The effects of aging on cognition have been demonstrated by decades of research, and it is well known that older adults have impaired cognitive abilities relative to younger adults (Grady, 2012). Even healthy aging is typically accompanied by impairments in multiple cognitive functions, and the trajectories of these age-related effects exhibit substantial differences across cognitive domains and across individuals (Lindenberger & von Oertzen, 2012). Thus, as individuals age, many aspects of cognitive processing become less efficient, while some cognitive abilities remain preserved (Glisky, 2007). Most commonly, older adults show impairments on functions like speed of processing, inhibitory control, working memory, attention, task-switching, and episodic memory. In contrast, implicit memory, semantic memory, and emotion regulation are relatively resistant to the deleterious effects of aging (Glisky, 2007; Grady, 2012; Park & Reuter-Lorenz, 2009). An ongoing

challenge for cognitive aging research is determining *why* some cognitive functions are preserved while others decline.

Multiple factors, such as genetics, lifestyle, health, education, and socioeconomic status, may influence the trajectory of cognitive aging, and some people are more resistant than others to the detrimental effects of age on cognition (Glisky, 2007; Grady, 2012; Gutchess & Thomas, 2020). Hence, advancing age is associated with increased inter-individual variability for different cognitive domains (Baghel et al., 2017), and some people show little cognitive decline with age, while other experience remarkable cognitive impairment and may even develop dementia (Cabeza et al., 2018). There may even be variability across individuals in the types of cognitive functions that are affected by age. For instance, some older adults show preserved episodic memory but impaired executive function, and vice-versa (Glisky, 2007). Determining the factors that account for this variability is considered an important matter for research, as it may help to guide the development of early interventions that support cognitive longevity (Livingston et al., 2020).

Aging and Memory

Memory loss is one of the most common concerns among older adults (Reese et al., 1999). The deleterious effects of age on memory performance, however, are not homogeneous, and different aspects of memory are affected to greater or lesser extents as people age (Larrabee, 2019). The different types of memory (or "memory systems") are underpinned by different regions of the brain, which in turn have different levels of vulnerability to aging (Luo & Craik, 2008). Memory systems are characterized in terms of duration and storage capacity, and can be separated into short- and long-term-memory systems (Gazzaniga, et al., 2014). Short-term (or working) memory involves the temporary retention of visuospatial and phonological information, as well as some sort of executive component (Baddeley, 2021). Long-term memories can be divided into declarative (explicit) and non-declarative (implicit) memory systems. Declarative memory can be further divided into episodic

memory (memory for personal experiences and events) and semantic memory (memory for factual knowledge). Implicit memory includes memory for procedures, priming, and conditioning. Among the different types of memory, episodic memory is the most affected by healthy aging, as it shows the largest degree of age-related decline (Nyberg et al., 2012; Wang & Cabeza, 2016).

Episodic memory refers to the ability to encode and retrieve the details and associations of personally experienced events (Gazzaniga et al., 2014), and ontogenically, it is a late-developing, and early deteriorating retrograde memory system (Tulving, 2002). In our daily lives, episodic memory supports, for example, remembering what to buy at the grocery store and where the car was parked, as well as, for instance, recalling the details of an event that occurred many years ago (e.g., a conversation one had at a party). In research settings, episodic memory can be tested with recall and recognition tasks using different types of stimuli (e.g., words, objects, scenes, and faces) (Nyberg & Pudas, 2019). In these cases, the information stored in an episodic memory may include memory for items, context (spatial, temporal, etc.), and associations (item-item, item-context) (Wang & Cabeza, 2016).

Evidence from numerous studies shows that episodic memory is primarily dependent on the medial temporal lobe (MTL), prefrontal cortex (PFC) and posterior cortices (Duarte & Dulas, 2020; Wang & Cabeza, 2016). During encoding, the MTL, particularly the hippocampus, is assumed to facilitate the binding of multiple features from distinct content domains (e.g., visual, auditory, etc.) into episodic representations, and posterior cortical regions are thought to support processing and storage of memory traces in a domain-specific manner (e.g., occipital regions for visual representations) (Wang & Cabeza, 2016). The anatomic organization of the MTL memory system suggests the use of hierarchical processing, in which information from neocortical association areas converge onto the perirhinal and parahippocampal cortices, then pass to the entorhinal cortex, and finally reaching subdivisions of the hippocampal formation. Feedback signals from the hippocampus

are then sent back to the entorhinal, perirhinal and parahippocampal cortices, which in turn project back to neocortical association areas (Dickerson & Eichenbaum, 2010; Raslau et al., 2015). During encoding, the PFC also supports episodic memory function through cognitive control processes (e.g., semantic processing, evaluation of relationships between stimuli and concepts, selection of to-be-attended information) (Campbell et al., 2012; Duarte & Dulas, 2020). During retrieval, structures of the MTL mediate the reactivation of posterior cortical regions to recover memory traces, while the PFC is thought to guide memory search and monitoring processes (Wang & Cabeza, 2016).

The effects of aging on episodic memory tend to be more pronounced for associative information than individual items, and the observed age-related decline in episodic memory has been attributed to deficits in the ability to form new associations (Old & Naveh-Benjamin, 2008). Overtime, researchers have proposed different mechanisms to explain the deficits in episodic memory associated with aging; these includes disruption of the binding process, reduced attentional control, and loss of inhibitory functions (Hasher & Campbell, 2020; Luo & Craik, 2008; Naveh-Benjamin & Mayr, 2018; Wang & Cabeza, 2016). The associative deficit hypothesis (ADH) suggests that age-related declines in episodic memory are largely due to impaired associative binding at encoding in older adults, and their limited access to the bound information during retrieval (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000). An alternative hypothesis suggests that reduced inhibitory control with age leads older adults to process more irrelevant information (Hasher & Zacks, 1988). This in turn results in older adults forming more irrelevant associations at encoding (i.e., hyper-binding) and ultimately, greater interference and lower performance at retrieval (Campbell et al., 2010; Davis et al., 2021). Impaired cognitive control with age is also thought to affect retrieval from episodic memory (Castel & Craik, 2003; Cohn et al., 2008; Healey et al., 2013; Luo & Craik, 2008). For example, older adults show impaired strategic (intentional) memory retrieval while automatic (spontaneous) memory retrieval remains intact (Cohn et al., 2008; Luo & Craik, 2008).

These different explanations are not mutually exclusive, and it is likely that various processes contribute to age-related declines in episodic memory. Understanding how age affects the neural structures and processes underlying memory is likely to be informative about their relative contributions, and I turn to how age affects the brain next.

Effects of aging on the brain

Age-related cognitive changes result from multilevel effects of aging on the central nervous system, including altered expression of genes and functions of cells that ultimately lead to changes in the structure and function of the brain (Cabeza et al., 2018). Over the past decades, numerous advances have been made in the field of neuroimaging, substantially contributing to the advancement of the neuroscientific field (Cope et al., 2021; Ding et al., 2022; Morita et al., 2016). These technological advancements have allowed researchers to observe and analyze the structure and functioning of a living human brain and have led to the exponential growth of neurocognitive research (Morita et al., 2016; Poldrack, 2012). In the field of aging, neuroimaging studies have provided substantial evidence of the effects of age on the brain, and different theories have been developed to explain the association between age-related changes in cognition and changes that occur in the brain (Liem et al., 2019; Lockhart & DeCarli, 2014; Spreng & Turner, 2019).

A large body of cross-sectional and longitudinal research with healthy adults shows that advanced age is associated with global and regional brain volume loss (Lockhart & DeCarli, 2014; Raz et al., 2010). Global shrinkage of grey and white matter volumes and the enlargement of the ventricles are well established hallmark of normal aging (Spreng & Turner, 2019). Along with global shrinkage, evident regional differences are observed, with the frontal lobes showing the greatest volume decline with age overall, followed by less pronounced declines in the temporal lobes, and modest changes in the parietal and occipital lobes (Lockhart & DeCarli, 2014; Raz et al., 2005, 2010). This age-related reduction in gray matter volume is thought to represent neuronal degeneration and

synaptic density reduction, while white matter loss is associated with reductions of myelinated fibers and increased perivascular spaces (Lockhart & DeCarli, 2014). Longitudinal work also demonstrates substantial inter-individual variability in the rates of decline, and potential modifiers of brain aging include genetics, cardiovascular health status, and lifestyle factors (Bittner et al., 2019; Raz et al., 2010; Smith et al., 2020).

Functional magnetic resonance imaging (fMRI) has been one of the most widely used modalities for investigating human brain function (Bandettini, 2012). As in the structural neuroimaging literature, functional neuroimaging research has provided extensive evidence of the effects of age on functioning of the brain from both task and resting state studies (Liem et al., 2019; Spreng & Turner, 2019). Interpretating the effects of age on brain function and its relationship to cognitive performance is, however, challenging. Different patterns of activation (reduced or increased activity with age) and changes in the connectivity between brain regions are observed in older adults across studies, and, as a result, distinct theories have been proposed to explain the relationship between brain functioning and cognition with age (Grady, 2012). In terms of neural activity, age-related decreases in regional brain activation during task have been interpreted as the cause of reduced cognitive performance in older adults (Rond et al., 2021; Grady et al., 1995). On the other hand, age-related increases in brain activity have been interpreted as a compensatory mechanism (referred to in the literature as 'compensation'), as it often relates to better performance in older adults (Cabeza et al., 2002). Alternatively, increased brain activity with age has also been interpreted as either reduced efficiency in the use of neural resources (inefficiency) or decreased selectivity in neural activity (dedifferentiation) when it is not associated with a gain in cognitive performance (Grady, 2012).

One of the most consistently observed patterns of age effects is known as the "posterior–anterior shift with ageing" (PASA), which involves an age-related reduction in occipitotemporal activity coupled with increased frontal activity (Davis et al., 2008; Grady et al., 1994). The PASA

pattern has been found across a variety of cognitive functions (attention, visual perception, visuospatial processing, working memory, episodic memory encoding, and episodic memory retrieval), and since it tends to correlate with better cognitive performance, increased frontal activation was suggested to compensate for processing deficits in occipitotemporal regions (Davis et al., 2008). Conversely, other studies provided evidence that additional brain activation does not necessarily lead to better task performance and suggested that over-activation reflects inefficient use of neural resources (Morcom & Henson, 2018; Rypma et al., 2007; Stevens et al., 2008; Zarahn et al., 2007). In summary, it has been shown that increased frontal activity in older adults is sometimes associated with better task performance, but other times, this additional recruitment may be due to greater demand of neural resources with no relation to performance (Campbell et al., 2016; Davis et al., 2014).

An alternative hypothesis that considers the compensatory mechanism of the aging brain is known as the "compensation-related utilization of neural circuits hypothesis" (CRUNCH) (Reuter-Lorenz & Cappell, 2008). According to CRUNCH, older adults recruit more neural resources at lower levels of cognitive load (i.e., easier tasks) than younger adults; however, at higher levels of cognitive load (i.e., harder tasks), they are unable to activate these compensatory mechanisms any further. Studies have supported this hypothesis in working memory and episodic memory tasks (Schneider-Garces et al., 2010; Spaniol & Grady, 2012). In the episodic memory study, for example, younger adults showed bilateral activation of the PFC during the difficult version of the task, while older adults showed this activation pattern during both the easy and difficult versions of the task (Spaniol & Grady, 2012).

Neural dedifferentiation is another idea that provides a reasonable explanation for some of the commonly observed age differences in brain activity. Age-related neural dedifferentiation refers to a decline in the brain's functional specialization, such that the regions that are usually activated for

specific cognitive functions in younger adults are coactivated in older adults to support multiple cognitive functions (Koen & Rugg, 2019). Examples of neural dedifferentiation include bilateral activity associated with cognitive demands that are typically associated with lateralized activity in younger adults (such as language comprehension; (Tyler et al., 2010), and other diffuse activation patterns in task-relevant regions across a variety of tasks (Grady, 2012; Spreng & Turner, 2019). During memory retrieval, for instance, younger adults have been shown to activate the hippocampus for explicit learning and have more activity in the striatum for implicit learning, whilst older adults show activation in both regions during the two tasks (Dennis & Cabeza, 2011). While some work shows a positive association between neural differentiation and cognitive performance in older adults, more often dedifferentiated neural responses are associated with poorer cognitive performance (Spreng & Turner, 2019). Thus, neural dedifferentiation is generally considered to reflect neuronal and cognitive dysfunction in older age (Koen & Rugg, 2019).

In addition to localized brain activity, over the past decade, several neuroimaging studies have focused on coordinated activity within the brain's functional networks (Farahani et al., 2019). The study of functional connectivity under the lens of large-scale networks has facilitated novel insights into brain functioning and how the communication between distant areas supports cognitive functions (Menon, 2015). The most commonly observed large-scale functional networks include the somato-motor, visual, dorsal attention, default mode, salience, fronto-parietal, limbic, and language networks (Zabelina & Andrews-Hanna, 2016).

Investigations of the effects of age on functional brain networks have revealed alterations to connectivity within brain networks, as well as in the dynamic interactions between them (Damoiseaux, 2017; Geerligs et al., 2014; Liem et al., 2019; Spreng & Turner, 2019). One of the most fundamental features of neural network functioning is the balance between functional segregation and functional integration (Sporns, 2013; Tononi et al., 1994). Functional segregation refers to

functionally connected regions clustered in modules (also called communities) that are characterized by high connectivity among nodes of the same module and low connectivity among nodes of different modules, while functional integration refers to the connectivity and communication between different modules (Sporns, 2013). Age-related functional brain reorganization has been frequently reported, and a considerable amount of evidence suggests that global network architecture changes across the lifespan (Edde et al., 2021). Briefly, during the first years of life, there is a broad organization of functional networks that start to segregate with age; these networks and their interconnections are further refined from adolescence to adulthood. Then, middle age consists of a critical period during which there is an inversion of the developmental trajectory, with a decrease in network segregation and increased between network connectivity with increasing age (Chan et al., 2014; Edde et al., 2021; Geerligs et al., 2014). This means that during older age, brain networks become less specific and more integrated with one another, resulting in a more diffuse connectivity pattern.

Functional networks can also be classified into sensory-motor or association networks, and there is evidence these two classes of networks exhibit different patterns of age-related changes in segregation (Chan et al., 2014; Geerligs et al., 2014). Sensory-motor systems include the auditory, somato-motor, and visual systems, while association systems include the dorsal attention, ventral attention, fronto-parietal control, salience, cingulo-opercular control, and default systems (Chan et al., 2014). Sensory-motor systems show a linear age-related decline in network segregation, while the decrease in segregation of the association networks shows an inflexion point at approximately age 50, reflecting accelerated reduction at that point (Chan et al., 2014; Geerligs et al., 2014). Thus, middle-age may serve as a transition point, with accelerated decline of association network segregation, and concomitant changes in cognitive performance observed around the same time (Edde et al., 2021). Indeed, the level of segregation of the association systems has been shown to predict episodic memory across the adult lifespan, with greater levels of association network segregation

relating to higher episodic memory scores (Chan et al., 2014). Taken together, this work suggests that middle-age may be a critical period during which the introduction of preventative lifestyle factors may alter the course of neurocognitive aging. I turn to some of these preventative factors next.

Cognitive Reserve

Although typical healthy aging is accompanied by age-related changes in the brain, which in turn are associated with declines in multiple cognitive functions, some individuals with considerable brain deterioration have been found to show relatively well-preserved cognition (Stern, 2002; Stern et al., 2019). To explain this phenomenon, the concept of "cognitive reserve" was introduced (Cabeza et al., 2018; Stern, 2002; Stern et al., 2019). The term cognitive reserve refers to the adaptability of cognitive processes (i.e., efficiency, capacity, flexibility), and attempt to explain the different levels of susceptibility of cognitive abilities to brain aging, insult, or pathology (Stern et al., 2020), and supports the idea that certain lifestyle factors (such as education, high occupational attainment, and social interaction) enable some people to remain cognitively healthy despite displaying neuropathology indicative of dementia. Cognitive reserve became an important concept in the field of neurocognitive aging, and its concept is evolving along with other constructs such as compensation, brain maintenance, and brain reserve as they are studied (Cabeza et al., 2018; Nogueira et al., 2022; Stern et al., 2019, 2020).

As mentioned previously, compensation refers to cognitive-enhancing recruitment of alternative neural resources in response to relatively higher cognitive demands. The term brain maintenance is used to refer to the preservation of neural resources that might occur throughout the lifespan through ongoing repair of the brain in response to damage occurring at molecular and cellular levels (Cabeza et al., 2018). The concept of brain reserve is based on the fact that people have differential susceptibility to brain damage, and when aging or pathology affect the brain (or reduce its reserve capacity) to a critical threshold, decline occurs (Barulli & Stern, 2013). Brain reserve is

considered a “passive” form of reserve, or capacity, that depends on the structural properties of the brain (such as the number of neuron and synapses, the overall size of the brain, etc.) and people with less brain reserve (e.g., less synaptic density) would have a lower threshold for manifestation of cognitive impairments following the onset of brain deterioration (Barulli & Stern, 2013). The brain reserve model explains how people with similar levels of neurodegeneration can exhibit dramatically different levels of cognitive performance and has found support in cohorts with Alzheimer’s disease (Murray et al., 2011; Perneczky et al., 2010). In contrast to brain reserve, cognitive reserve is considered an “active” model of reserve and is based on the functionality, plasticity, flexibility, and adaptability of cognitive functions and brain functional networks that support resistance to the deleterious effects of age on brain structure (Stern, 2002; Stern et al., 2019). Thus, individuals with the same amount of brain reserve can have different levels of cognitive resistance to the effects of age, depending on their cognitive reserve (Barulli & Stern, 2013). Cognitive reserve is influenced by life experiences throughout the lifespan, and those with higher cognitive reserve tend to have higher levels of education, higher occupation attainment, and are engaged in late-life leisure activities and social interactions (Medaglia et al., 2017; Tucker & Stern, 2011). The underlying assumption of cognitive reserve is that some aspects of these lifetime experiences provide people with better mechanisms to cope with age or disease-related impairments (Stern et al., 2019).

The influence of lifestyle on brain and cognitive health during aging

Inter-individual variability in age-related changes in the brain and cognition is associated with many different factors, including genetic makeup, environmental factors, lifestyle, education, physical and mental health, socio-economic status, etc. (Ngandu et al., 2015; Zoccola et al., 2018). As life expectancy of the world’s population increases and neurodegenerative diseases become increasingly widespread, lifestyle interventions are increasingly explored as key components in preserving brain health and delaying cognitive decline (Kempermann, 2019; Mintzer et al., 2019;

Toman et al., 2018). Multidomain lifestyle interventions have been shown to benefit older populations at risk for cognitive decline and dementia, and a growing number of studies have investigated the extent to which specific lifestyle factors are associated with brain and cognitive health (Bott et al., 2019; Rosenberg et al., 2020). Lifestyle factors such as physical activity, diet, sleep, social interaction, education, cognitive engagement, and management of health issues are amongst the most influential factors on brain health and cognitive longevity (Kempermann, 2019; Rosenberg et al., 2020). In this thesis, I focus on sleep quality and physical activity, as both are strongly related to neurocognitive health with age and are modifiable in later life.

Sleep is essential for health and well-being throughout the lifespan, in addition to being associated with human longevity (Grandner, 2012; Mazzotti et al., 2014; Ramar et al., 2021; Worley, 2018). Decades of research on sleep and cognitive functioning in aging have shown that, good sleep quality promotes better cognitive functioning in both older and younger adults and might serve as a protective factor against age-related cognitive decline (Scullin and Bliwise, 2015). The sleep–wake cycle is regulated by complex neural circuits and neurotransmitter systems, many of which have been shown to be important for optimal cognitive function (Guardia et al., 2021; Mander et al., 2017; Wright et al., 2012). The ascending arousal system, for example, is composed of a set of neurotransmitter pathways from the brainstem to the cortex that affects brain functioning, promotes cortical arousal, and influences many aspects of cognition (Briand et al., 2007; Handra et al., 2019; Lobo & Summavielle, 2015). Sleep also directly supports the formation of long-term memories (Diekelmann & Born, 2010; Rasch & Born, 2013). According to the active system memory consolidation model, the consolidation of declarative memories during sleep is regulated by the temporal coupling of sleep electrophysiological oscillations, which in turn promote the reactivation and redistribution of hippocampal memory traces across cortical networks (Born & Wilhelm, 2012; Klinzing et al., 2019). Thus, sleep is essential to episodic memory consolidation and sleep disruptions

should be associated with poorer memory performance.

Aging is usually accompanied by several changes in behavioral and physiological sleep quality, and some of the most commonly observed changes include longer sleep-onset latency, decreased total-sleep-time, increased sleep fragmentation, and decreased sleep efficiency (Mander et al., 2017; Pace-Schott & Spencer, 2015). Additionally, decreased amounts of deeper NREM (i.e., slow-save sleep [SWS]), reduced amplitude and density of SWS, as well as reduced amplitude and durations of sleep spindles also characterize the effects of age on sleep architecture (Mander et al., 2017). Based on the importance of sleep for consolidation and the fact that age is associated with declines in sleep quality (Scullin, 2013), emerging studies are focused on investigating the importance of sleep and its mechanisms not only as a predictor of cognitive decline, or an early biomarker of dementia, but also as a potential therapeutic intervention for preventing or slowing the progress of cognitive decline and neurodegenerative conditions (Bellesi et al., 2014; Cellini & Mednick, 2019; Helfrich et al., 2018; Mander et al., 2013, 2014, 2016; Ngo et al., 2013; Pace-Schott & Spencer, 2015; Salfi et al., 2020; Scullin, 2013; Scullin & Gao, 2018; Wilckens, et al., 2018).

Another lifestyle factor that has been shown to benefit cognition across the lifespan is physical activity (Engeroff et al., 2018; Erickson et al., 2019; Gomes-Osman et al., 2018). Physical activity is defined as any "bodily movement produced by skeletal muscles that results in energy expenditure" (WHO, 2010, p. 53), and includes both daily tasks and leisure activities that involve motor behavior. Physical exercise is considering a sub-classification of physical activity and it is defined as “physical activity that is planned, structured, repetitive, and has as a final or an intermediate objective: the improvement or maintenance of one or more components of physical fitness”. Although several studies suggest that good sleep and physical activity relate to better cognitive performance, these effects tend to be most consistent in young adults, and more evidence is needed to support this connection in middle-aged and older adults (Scullin & Bliwise, 2015; Stillman et al., 2020).

Rationale (Summary of the thesis)

Across three cross-sectional studies, this thesis examines the effects of age on brain structure and functional connectivity in relation to cognition and explores the potential influence of sleep quality and physical activity on age-related differences in memory. To this end, I assessed structural and functional magnetic resonance imaging (MRI/fMRI) and behavioral data obtained from the population-derived Stage 2 sample of the Cambridge Centre for Aging and Neuroscience (Cam-CAN; www.cam-can.org) project (Shafto et al., 2014) for Studies 1 and 2, respectively. In Study 3, self-report measures of sleep quality and physical activity, as well as behavioral measures of episodic and working memory were collected from the online platform Prolific (https://www.prolific.co/).

Study 1: Study 1 aimed to compare the relative contributions of medial temporal lobe (MTL) and prefrontal cortex (PFC) structures to age differences in associative memory, and to test for potential sex-related differences in the effects of age on memory and brain structure, as well as the relationship between them. To this end, I used T1-weighted structural images and behavioral data from over 300 individuals uniformly spread across the adult lifespan (18–87 years old) from the Cam-CAN project and tested the multivariate relationship between grey-matter volumes and item/associative memory scores using canonical correlation analyses.

Study 2: Study 2 aimed to examine age-related differences in resting state functional connectivity of cortical networks and how these relate to concomitant differences in functional connectivity of the ascending reticular activating system (ARAS). The ARAS is involved the regulation of sleep-wake cycles and is responsible for cortical arousal, affecting brain functioning and influencing many aspects of cognition (Jones, 2003; Lobo & Summavielle, 2015). During the aging process, there is a clear disruption to ARAS functioning (Mather, 2020), however, neuroimaging studies that investigate the effect of age on functional connectivity of the arousal system are still scarce. Thus, given the essential role of the arousal system in cortical activation and previous findings

of disrupted ARAS functioning with age, I hypothesized that age-related declines in functional connectivity between the ARAS and cortex may contribute to commonly observed differences in cortical connectivity (e.g., decreased network segregation with age; (Chan et al., 2014). This hypothesis was tested using resting state fMRI data from over 500 individuals across the lifespan (18–88 years old) from the Cam-CAN cohort. This study characterized age-related differences in functional connectivity of the entire ARAS system and tested the influence of ARAS-cortical connectivity on age-related differences in connectivity within and between cortical networks. I also assessed the multivariate association between ARAS-cortical network connectivity and age-related differences in cognitive performance across a range of tasks.

Study 3: Finally, Study 3 aimed to investigate the relationship between sleep quality, physical activity, and memory in middle-age and older adults. To this end, I assessed self-reported measures of physical activity, sleep quality, self-perception of memory abilities, and objective measures of working memory and associative memory in a sample of over 300 middle-aged and older adults (45 - 75 years old). Additionally, I also assessed the impact of the COVID-19 pandemic on participants' mood and sleep quality by comparing them to an age- and education-matched reference sample from the CamCAN project. We hypothesized that higher levels of physical activity would be associated with better sleep quality, better memory performance, and better well-being in middle-aged and older adults. Similarly, we predicted that better sleep quality would correlate with higher memory performance and well-being. Additionally, we hypothesized that sleep would partially explain the relationship between physical activity and cognition.

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Chapter 2: Age-related decreases in associative memory more strongly predicted by atrophy in the prefrontal cortex than medial temporal lobes

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Abstract

It is well established that episodic memory declines with age and one of the primary explanations for this decline is an age-related impairment in the ability to form new associations. At a neural level, both the medial temporal lobe (MTL) and lateral prefrontal cortex (PFC) are thought to be critical for associative memory, and grey-matter volume loss in these regions has been associated with age-related declines in episodic memory. While recent work has compared the relative contributions of grey-matter volume in the MTL and PFC to item and associative memory, these studies only assessed older adults. In this study, we use a lifespan approach to examine the relationship between grey-matter volume within substructures of the MTL and PFC on the one hand and item and associative memory on the other. To this end, we used data from over 300 individuals uniformly spread across the adult lifespan from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) and tested the multivariate relationship between grey-matter volumes and item/associative memory scores using canonical correlation analysis. We found that structures of the PFC alone predicted memory performance better than either structures of the MTL alone or PFC and MTL combined. Moreover, our results also indicated that grey matter volume in the inferior frontal gyrus - pars opercularis, middle frontal gyrus, and superior frontal gyrus, related most strongly to memory (particularly associative memory) and this effect persisted when controlling for age and education. Finally, we also found that the relationship between frontal grey matter volume and memory was not moderated by age or sex. Taken together, these findings emphasize the critical role of the frontal lobes, and the control processes they subserve, in determining the effects of age on memory.

Keywords: *aging, grey matter volume, memory*

Introduction

Episodic memory refers to the ability to encode, store and retrieve the details of personal experiences and events within their temporal and spatial contexts (Tulving, 2002). It is well established that aging is associated with episodic memory decline (Nyberg et al., 2012). This age-related decline in episodic memory has been attributed to a specific deficit in the ability to form new associations (Naveh-Benjamin, 2000), because age differences in item memory tend to be less pronounced than age differences in associative memory (Old & Naveh-Benjamin, 2008). This view places emphasis on the memory binding process itself (Chalfonte & Johnson, 1996), which associates individual items to each other or their context at encoding and is thought to depend on the medial temporal lobe (particularly, the hippocampus; Ranganath, 2010). However, other accounts of age differences in associative memory attribute a greater role to age-related declines in attention (for a recent review, see Naveh-Benjamin & Mayr, 2018), which may lead older adults to form more irrelevant associations at encoding (Campbell et al., 2010; Davis et al., 2021) and/or hinder control processes at retrieval (Castel & Craik, 2003; Cohn et al., 2008; Healey et al., 2013). In adjudicating between these different cognitive accounts, it may be useful to turn towards the brain (Pudas et al., 2013).

Regarding the neural substrates of associative memory, the involvement of the medio-temporal lobe (MTL) and the lateral prefrontal cortex (PFC) has been well documented through neuroimaging studies and brain damage case studies (Noulhiane et al., 2007; Simons & Spiers, 2003; Squire, 2009). Overall, there is an established consensus on which functions the MTL and PFC serve: the MTL is critical for the binding process (item-item; item-context) in long-term memory, and the lateral PFC is known to be important for attentional control functions that support binding through the creation, maintenance, and selection of memory representations (Cabeza, 2006; Simons & Spiers, 2003). Older age leads to a loss of total brain volume, but the degree of change is highly heterogeneous

across different structures, with the MTL and PFC demonstrating marked age-related declines in grey matter volume, along with increased inter-individual variability (Raz et al., 2005). Comprehensive reviews suggest that healthy aging has the largest effect on the frontal cortex, followed by more moderate effects in the temporal lobes, posterior association cortex, and occipital regions (Freund & Pettman, 2010; MacDonald & Pike, 2021).

Grey-matter volume loss has been associated with age-related decline and inter-individual differences in episodic memory, however, most structural studies have focused exclusively on the link between hippocampal volume and associative memory functioning in young and older adults, and thus far, results have been mixed (Becker et al., 2015; Carr et al., 2017; DeMaster et al., 2014; Grady & Ryan, 2017; Poppenk & Moscovitch, 2011; Rajah et al., 2010; Schlichting et al., 2017). In young adults, these studies range from finding no link between hippocampal volume and associative memory, to a positive, or even a negative association (DeMaster et al., 2014; Poppenk & Moscovitch, 2011; Rajah et al., 2010; Schlichting et al., 2017). In older adults, findings range from no link to a positive link between hippocampal volume and associative memory (Becker et al., 2015; Carr et al., 2017). This could be because previous studies have tended to look at the hippocampus as a whole (Head et al., 2008; Rodrigue et al., 2013; Ward et al., 2015) or simply divided the hippocampus into anterior vs posterior sections (Driscoll et al., 2003; Rajah et al., 2010; Ta et al., 2012). Importantly, recent work suggests that other subregions of the MTL (such as the entorhinal cortex) may also play a critical role in associative binding (Nilssen et al., 2019; Yeung et al., 2019), suggesting that we should maybe look beyond the hippocampus when examining structural correlates of associative memory in aging.

Moreover, previous work on the structural correlates of age differences in associative memory rarely considers the joint contribution of MTL and PFC regions. To the best of our knowledge, only two studies have compared the contributions of regional grey-matter volume in the MTL and PFC to

item memory and associative memory (Becker et al., 2015; Brehmer et al., 2020). Both of these studies found that grey-matter volume in the PFC is a better predictor of individual differences in associative memory functioning than grey-matter volume in MTL regions. However, these studies only assessed older adults, thereby leaving a gap in our understanding of the relevance of MTL and PFC structures for item and associative memory across the lifespan.

Finally, recent work suggests that biological sex and gender (hereafter we will mainly focus on biological sex) may also play an important role in how memory and the brain change with age. For instance, accelerated brain aging in men compared to women is commonly observed (Cowell et al., 1994; Zheng et al., 2017), and behaviorally, older women generally perform better than older men on associative memory tasks (Herlitz & Rehnman, 2008) though this may depend on the material being tested (Asperholm et al., 2019; Subramaniapillai et al., 2022). Some studies, however, did not find such a sex difference in episodic memory (McDougall et al., 2014). Unfortunately, few studies have looked at sex differences in the relationship between MTL and PFC structures and individual differences in item and associative memory. One study demonstrated that hippocampal volume predicts associative memory in older women, but not in older men (Zheng et al., 2017), but further work is needed on the moderating role of sex in the relationship between grey-matter volume and episodic memory performance with age.

The aim of this study was to investigate the contribution of grey-matter volume within substructures of the MTL and PFC to age-related differences in item and associative memory across the adult lifespan, and to assess the effects of sex on these relationships. To this end, we used data from over 300 individuals uniformly spread across the adult lifespan (18-87 years) from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN; www.cam-can.org) project (Shafto et al., 2014). Structural images were submitted to the Automatic Segmentation of Hippocampal Subfields (ASHS; Yushkevich et al., 2015) software package to obtain volume estimates for several

MTL regions (including the anterior and posterior hippocampi, entorhinal cortex, perirhinal cortex – Brodmann areas 35 and 36, parahippocampal cortex, and an estimate of intracranial volume). We also extracted grey matter volume estimates of the same PFC regions as Brehmer et al. (2020; detailed below) using FreeSurfer (Fischl et al., 2004). Measures of item and associative memory were obtained from the emotional memory task previously reported by Henson et al., (2016). We tested the multivariate relationship between grey-matter volumes and item/associative memory scores using a series of canonical correlation analyses, comparing MTL-only and PFC-only models to one that combined both MTL and PFC regions together. We hypothesized that grey-matter volume of structures in the PFC would be more strongly related to associative memory performance than structures in the MTL (Becker et al., 2015; Brehmer et al., 2020), which would suggest a critical role for attention and executive functions in age-related differences in associative memory. Moreover, we expected sex to moderate the effect of age on both grey-matter volume and memory scores, and possibly the relationship between them.

Methods

Participants. An initial sample of 312 participants (18–87 years old; mean 54.24; SD 18.22; 158 men and 154 women; approximately equally distributed across the lifespan) was taken from the population-derived Stage 2 sample of the Cambridge Centre for Aging and Neuroscience (Cam-CAN) project (Shafto et al., 2014). Participants reported their sex during the home interview phase (Stage 1) but were not asked about their gender identity. After image processing and outlier removal (described below), our final sample included 307 participants (18–87 years old; mean 54.43; SD 18.26; 155 men and 152 women). Demographic information of the final sample is provided in Table 2.1 (divided into age groups for illustrative purposes, but all analyses used age as a continuous variable). Participants were included if they had no contraindications to MRI, no self-reported history of drug or alcohol abuse, no neurological disorders, and no brain abnormalities detected. Participants

were native English speakers, had normal or corrected-to-normal vision and hearing, and scored 25 or higher on the Mini Mental State Exam (MMSE; Folstein et al., 1975). Informed consent was obtained from all participants and the study was approved by the Cambridgeshire 2 Research Ethics Committee, United Kingdom (Shafto et al., 2014).

Table 2.1 - Participant demographics and cognitive scores

Age group	**Young**	**Middle**	**Older**	**Total**
n	117	98	92	307
Age range (years)	18-47	48-67	68-87	18-87
Sex (men/women)	58/59	49/49	48/44	155/152
Highest education				
University	86 (73.5%)	65 (66.3%)	38 (41.3%)	189 (61.6%)
A' levels	19 (16.2%)	16 (16.3%)	23 (25%)	58 (18.9%)
GCSE grade	12 (10.3%)	14 (14.3%)	13 (14.1%)	39 (12.7%)
None over 16	0 (0.0%)	3 (3.1%)	17 (18.5%)	20 (6.5%)
Cognitive Scores				
MMSE	29.21 (1.12)	29.14 (1.11)	28.22 (1.51)	28.89 (1.32)
ACE-R	96.61 (3.64)	95.89 (3.64)	92.73 (5.21)	95.22 (4.47)

Note. Participants are divided into age groups for descriptive purposes, but all analyses used age as a continuous variable. [*]*Education, MMSE, and ACE-R data missing for one participant. GCSE = general certificate of secondary education. MMSE* = Mini-Mental State Exam. *ACE-R = Addenbrooke's Cognitive Examination-Revised* (Mioshi et al., 2006b).

Memory Assessment. Item and associative memory performance were assessed by a task previously described in Henson et al., 2016. To summarize, the study phase was comprised of 120 trials, split into two blocks, with a short break between blocks. Each trial began with a background scene that could have positive, negative, or neutral valence (40 trials per valence; scenes taken from the International Affective Pictures System (Lang et al., 1997). After 2s, a neutral object was superimposed on the scene for 7.5s. Participants were instructed to press a key when they had mentally formed a story that linked the object to the scene and continue to elaborate the story until the images disappeared. A 0.5s blank screen was shown between trials. Participants were not informed

that their memory would be tested later. The test phase was given after a 10-minute break and was comprised of 160 trials (using 120 objects from the Study phase and 40 new objects), split into 4 blocks. On each trial, measures of object priming, item recognition, and associative memory were obtained. First, a pixilated version of the object appeared, and participants had to respond as quickly as they could to identify the object (this measure of object priming is not used in the current analyses). Next, the pixilation was removed, and a clear version of the object was shown to test item memory. Participants indicated whether the object had been shown in the Study phase and their level of confidence in their response ("sure new", "think new", "think studied", "sure studied"). If participants selected "think studied" or "sure studied", then associative memory was tested by asking participants to first report the valance of the background scene that the object had been paired with (positive, neutral, negative, don't know) and then describe the scene.

Memory Accuracy. For Item memory, we used d' as a measure of discriminability (Green et al., 1966), calculated as the difference in inverse normal transformed probabilities of Hits and False Alarms. Hits and False Alarms were collapsed across "sure" and "think" confidence levels (the number of low confidence answers was too small to perform separate analysis). For associative memory, the number of correctly described background scenes was used as our measure of interest[1]. Participants needed to describe the background scene in enough detail to distinguish it from other background images.

MRI Data. Gray-matter volume (GMV) was estimated from the segmented T1-weighted MR images ($1mm^3$). Scanning took place at the Medical Research Council Cognition and Brain Sciences Unit (MRC-CBSU) in a 3T Siemens TIM Trio, with a 32-channel head-coil. The 3D T1-weighted structural image (field of view - FOV = 256mm x 240mm x 192mm; voxel size = $1mm^3$) was acquired

[1] Note. The same pattern of results is found if we use a proportional score for associative memory instead (i.e., the number of backgrounds correctly described out of the total number of possible trials, which was dependent on correctly identifying the cued object as "old").

using a Magnetization Prepared RApid Gradient Echo (MPRAGE) sequence. T1 images were coregistered to the Montreal Neurological Institute - MNI template. For details of the MRI sequences, see Shafto et al., 2014; for details of the MRI preprocessing, see Taylor et al., 2017. The Automatic Segmentation of Hippocampal Subfields (ASHS) software (Yushkevich et al., 2015) (https://sites.google.com/view/ashs-dox/home) and the ASHS-PMC-T1 atlas (Xie et al., 2016) (https://sites.google.com/view/ashs-dox/mri-data/ashs-pmc-t1-atlas-requirements) were used to estimate volumes of the following MTL structures (left and right separately): anterior and posterior hippocampi, entorhinal cortex, Brodmann areas 35 and 36 (both subregions of the Perirhinal cortex), parahippocampal cortex, and an estimate of intracranial volume (eICV). For the purpose of quality control (QC), all segmentations obtained from ASHS were visually inspected and scored by two raters who were blind to participant age and sex. A five-point rating scale was used based on the number of voxels that were over/undersegmented for a given structure (1 - Perfect, or near-perfect outputs; 0.75 - Small, contained errors; 0.5 - Moderate errors; 0.25 - Large and expansive errors; 0 - Totally misses the mark). Only participants with segmentations score of 0.5 and above were kept for volume assessment and statistical analysis (no participants needed to be excluded). The rating reliability between raters was assessed through Intraclass Correlation Coefficient (ICC) (Koo & Li, 2016; Liljequist et al., 2019), and the average ICC across ratings for the assessed brain regions was 0.783, indicating moderate to good reliability (Koo & Li, 2016). FreeSurfer v7 (Fischl et al., 2004) (https://surfer.nmr.mgh.harvard.edu/) and the ‘Segmentation of hippocampal subfields and nuclei of the amygdala tool’ (Saygin et al., 2017) were used to estimate volumes of the amygdala. Free-Surfer was also used for the following frontal lobe structures (same ones used by Brehmer et al., 2020): superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus - pars orbitalis, inferior frontal gyrus - pars triangularis, inferior frontal gyrus - pars opercularis, and orbital sulci (H-shaped sulci) (Maillet & Rajah, 2014). Five participants were excluded from the original sample due to extreme

MTL structure volume values (values that were more than 3.0 times the interquartile range below the first quartile or above the third quartile). All volumes were corrected for head size using the linear regression method, in which each volume of interest and eICV are used to predict ICV-adjusted volumes as follows: [$Volume\_adjusted_{(i)} = Volume\_raw_{(i)} - \beta(ICV\_raw_{(i)} - ICV\_mean)$], where β is the slope of the regression line between ICV and the volume of interest (Voevodskaya, 2014).

Statistics. We first used a series of linear regression analyses to predict item memory, associative memory, and grey matter volumes from age, sex, and the age x sex interaction (controlling for education). The multivariate association between brain volumes and memory performance was tested using a multivariate approach. We adopted a two-level procedure (Passamonti, et al., 2019; Tsvetanov et al., 2016, 2021, 2022). In the first-level analysis, the relationship between brain volumes and memory performance were identified using canonical correlation analysis (CCA) (Hotelling, 1936; Zhuang et al., 2020). The goal of CCA is to compute the linear combination of variables that maximizes the correlation between two multivariate data sets (X and Y) without assuming any form of directionality. In our study, the relationship between GMV in multiple brain regions of interest (X) and six memory scores (Y) were evaluated in three distinct models (see Table 2.2). To determine the best set of regions that predicts memory performance (MTL-only regions or PFC-only or MRL and PFC regions together), we compared model fits between the three models with a boostrapping approach and determined the significance of the loadings of the best fit model with a permutation-based cross-validation approach (Tsvetanov et al., 2018).

Next, we tested whether relationship between GMV and memory performance identified by the winning model 1) remains after controlling for age and education, and 2) is moderated by age and sex. To this end, we performed a second-level analysis using multiple linear regression. Predictor variables included subject GMV scores (from the winning CCA model), age, sex, their interaction terms (GMV x age, GMV x sex). The dependent variable was subject memory scores (from the

winning CCA model). Education was entered as a covariate of no interest. The model therefore can identify the unique variance explained by each of the predictors, i.e., whether GMV scores predicted memory scores over and above age, or evidence for moderation by age and/or sex.

Table 2.2 – CCA Models

Models	X (Brain Regions)	Y (Memory Scores)
Model 1	MTL only model • Anterior hippocampus • Posterior hippocampus • Entorhinal cortex • Perirhinal cortex - Br35 • Perirhinal cortex - Br36 • Parahippocampal cortex • Amygdala	• Item Memory - Positive Background • Item Memory - Neutral Background • Item Memory - Negative Background • Associative Memory - Positive Background • Associative Memory - Neutral Background • Associative Memory - Negative Background
Model 2	PFC only model • Superior frontal gyrus • Middle frontal gyrus • Inferior frontal gyrus - Pars orbitalis • Inferior frontal gyrus - Pars triangularis • Inferior frontal gyrus - Pars opercularis • Orbital sulci (H-shaped sulci)	• Item Memory - Positive Background • Item Memory - Neutral Background • Item Memory - Negative Background • Associative Memory - Positive Background • Associative Memory - Neutral Background • Associative Memory - Negative Background
Model 3	MTL and PFC model • Anterior hippocampus • Posterior hippocampus • Entorhinal cortex • Perirhinal cortex - Br35 • Perirhinal cortex - Br36 • Parahippocampal cortex • Amygdala • Superior frontal gyrus • Middle frontal gyrus • Inferior frontal gyrus - Pars orbitalis • Inferior frontal gyrus - Pars triangularis • Inferior frontal gyrus - Pars opercularis • Orbital sulci (H-shaped sulci)	• Item Memory - Positive Background • Item Memory - Neutral Background • Item Memory - Negative Background • Associative Memory - Positive Background • Associative Memory - Neutral Background • Associative Memory - Negative Background

Results

Age and sex effects on memory. Figure 2.1 shows mean item and associative memory (averaged across valence) plotted against age (see Figure 2.S1 for each valence separately[2]). For item memory, a regression predicting item memory from age, sex, and the age x sex interaction was significant ($R^2 = 0.23$, $F = 30.2$, $p < 0.001$). Age was the only significant predictor ($\beta = 0.007$, $p < 0.001$). For associative memory, a regression predicting associative memory from age, sex, and the age x sex interaction was significant ($R^2 = 0.358$, $F = 56.4$, $p < 0.001$). This model showed a significant effect of age ($\beta = -0.584$, $p < 0.001$) and an age x sex interaction ($\beta = 0.12$, $p = 0.001$), indicating that the age-related decline in associative memory was slightly steeper in men (see Figure 2.1B). In line with previous findings, age was associated with a decrease in memory performance; however, in contrast to previous work showing a disproportionate age effect on associative relative to item memory, there was no difference in the effect of age on item and associative memory in this case (tested by comparing the correlations between age and item memory, and age and associative memory; $z = 1.44$; $p = 0.15$).

[2] Note: We do not focus on valence effects here as 1) this was not our primary question of interest and 2) this was covered extensively in Henson et al. (2016) using the same data. Nevertheless, each valence was entered into the CCA analyses separately as this method lends itself well to the inclusion of multiple outcome measures.

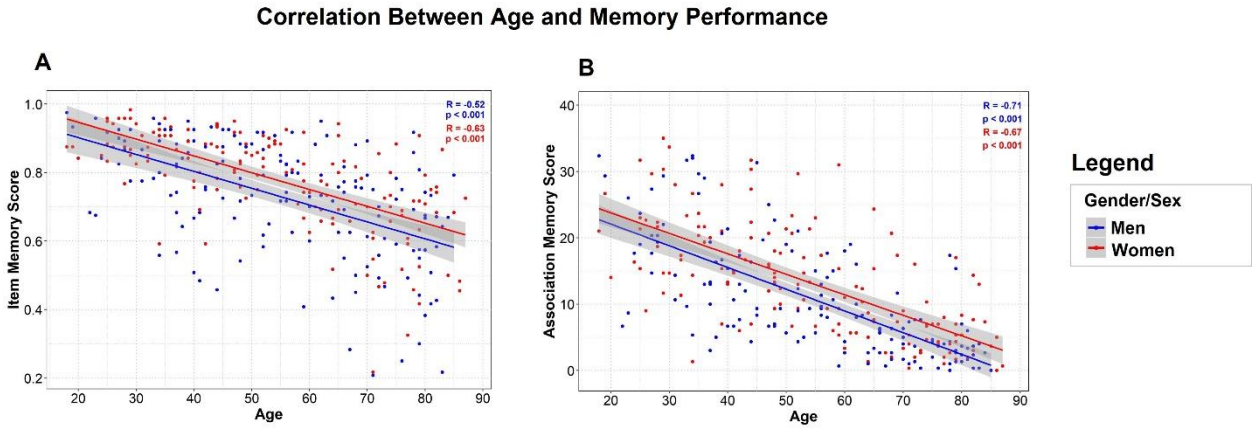

Figure 2.1: Correlation between age and memory performance. A) Item Memory score (hits minus false alarms). B) Association Memory Score (number of background scenes correctly recalled). Memory scores represent the average score across valance of the background image (positive, neutral, and negative). Men are plotted in blue, and Women are plotted in red. Plots for each valence of the background scene (positive, negative, neutral) are available in Figure 2.S1.

Age and sex effects on gray matter volume. Figures 2.2 and 2.3 show mean gray matter volume (averaging across hemisphere) plotted against age for the MTL and frontal lobe structures, respectively (see Figures 2.S2-2.S5 for the left and right hemispheres separately). We performed a series of linear regressions predicting the volume in each structure (averaged across hemispheres) from age, sex, and the age x sex interaction while controlling for False Discovery Rate (FDR) using the Benjamini–Hochberg method (Benjamini & Hochberg, 1995a). As shown in Table 2.3, age was associated with a significant volume decline in all structures (except for the posterior hippocampus), though age-related declines were most pronounced in the perirhinal cortex – Br36, parahippocampal cortex, and amygdala. In the frontal lobes, age-related declines were most pronounced in the middle frontal gyrus, superior frontal gyrus, and inferior frontal gyrus - Pars opercularis. Turning to the effects of sex, none of the main effects of sex nor the interactions between sex and age survived FDR correction. Thus, in the current sample, grey matter volume significantly declined with age in all

structures except the posterior hippocampus and a similar rate of decline was observed for both men and women.

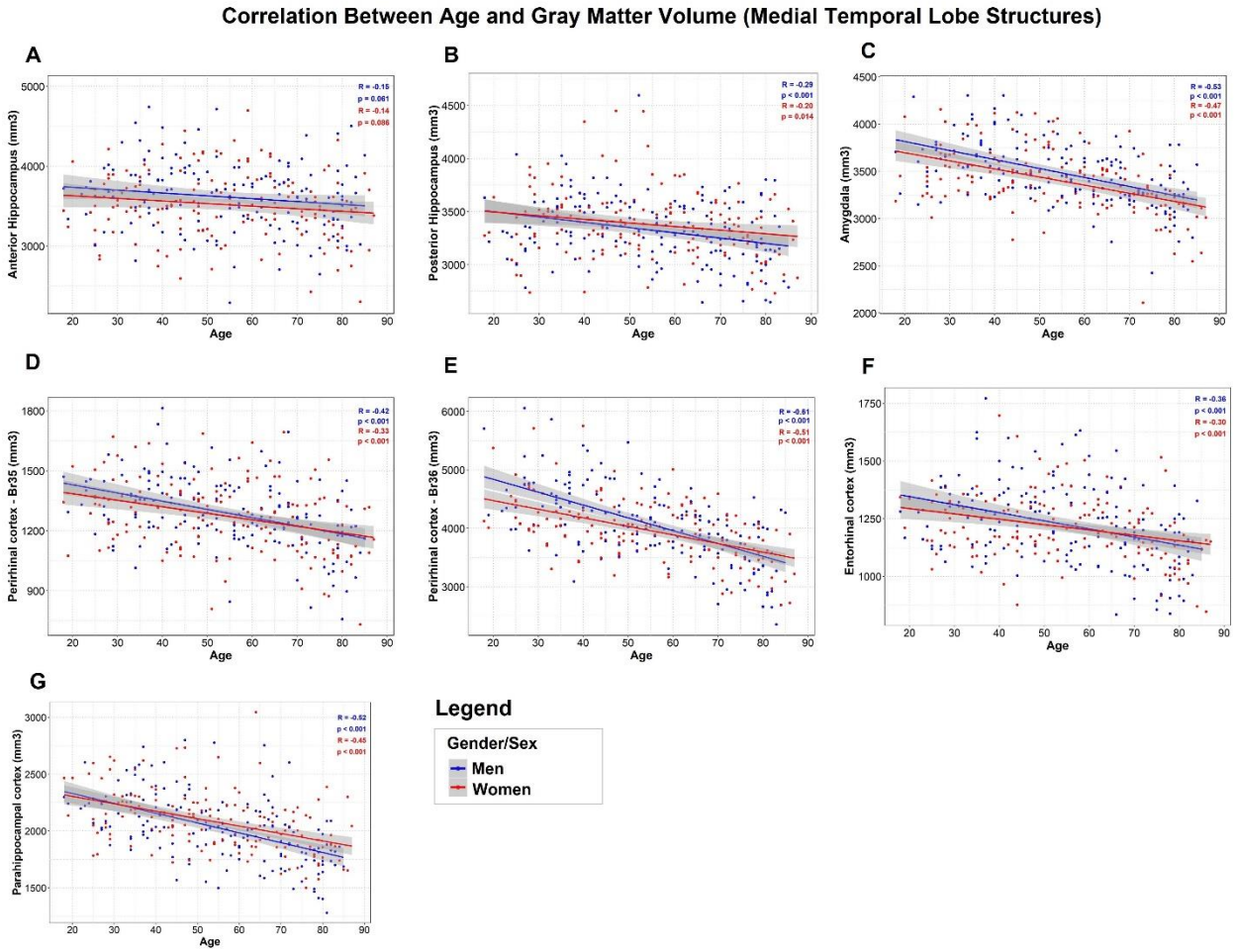

Figure 2.2: Correlation between age and gray matter volume (Medial Temporal Lobe Structures). A) Anterior hippocampus. B) Posterior hippocampus. C) Amygdala. D) Entorhinal cortex. E) Perirhinal cortex - Br35. F) Perirhinal cortex - Br36. G) Parahippocampal cortex. Volumes shown represent the sum of both left and right hemispheres. Plots for each hemisphere are available in Figure 2.S2 and Figure 2.S3.

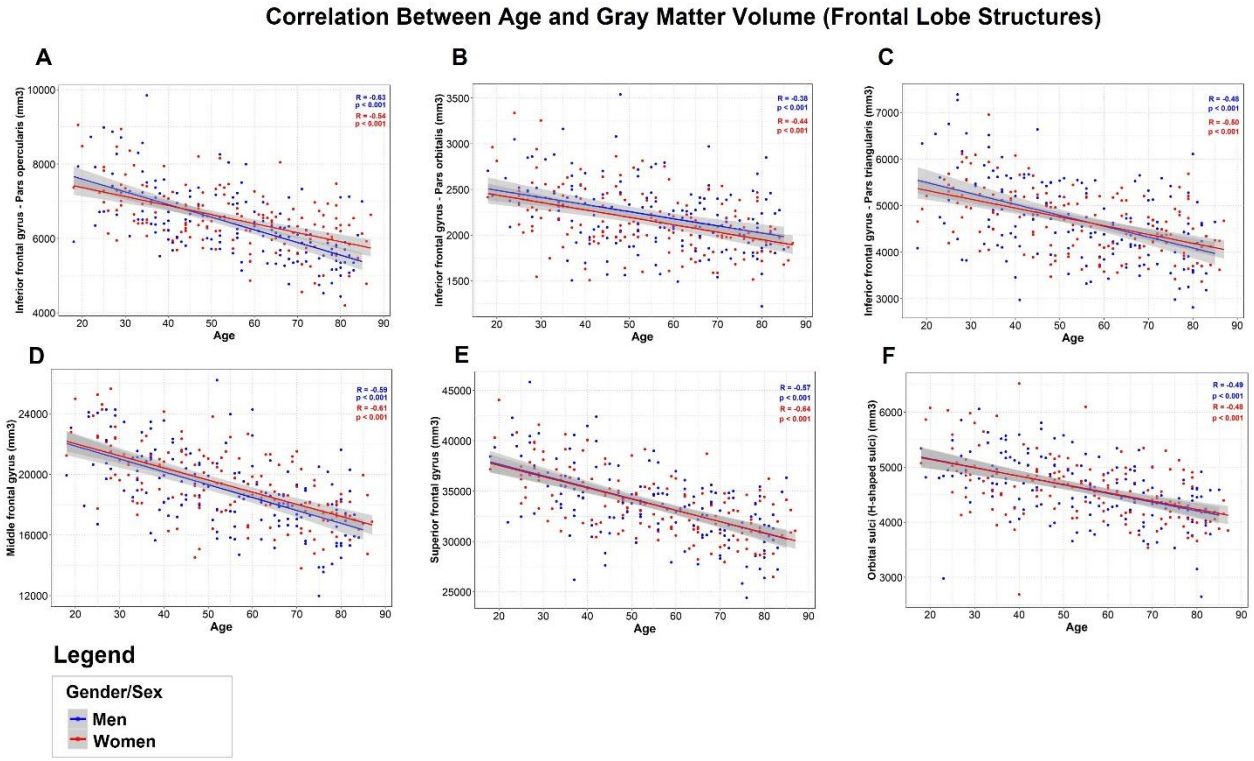

Figure 2.3: Correlation between age and gray matter volume (Frontal Lobe Structures). A) Inferior frontal gyrus - Pars opercularis. B) Inferior frontal gyrus - Pars orbitalis. C) Inferior frontal gyrus - Pars triangularis. D) Middle frontal gyrus. E) Superior frontal gyrus. F) Orbital sulci (H-shaped sulci). Volumes shown represent the sum of both left and right hemispheres. Plots for each hemisphere are available in Figure 2.S4 and Figure 2.S5.

Table 2.3 – List of regression models and significant effects

Region of Interest	Model Fit			Predictor variable p-values			
	R^2	F	p	age		sex	age*sex
Anterior hippocampus	0.036	3.82	0.01	0.003	*	0.138	0.453
Posterior hippocampus	0.015	1.51	0.212	0.562		0.040	0.941
Entorhinal cortex	0.033	3.49	0.02	< 0.001	*	0.669	0.795
Perirhinal cortex - Br35	0.051	5.38	0.001	< 0.001	*	0.257	0.906
Perirhinal cortex - Br36	0.127	14.6	< 0.001	< 0.001	*	0.459	0.920
Parahippocampal cortex	0.04	4.16	0.007	0.003	*	0.055	0.925
Amygdala	0.114	12.9	< 0.001	< 0.001	*	0.632	0.957
Inferior frontal gyrus - Pars opercularis	0.061	6.58	< 0.001	< 0.001	*	0.344	0.234
Inferior frontal gyrus - Pars orbitalis	0.076	8.33	< 0.001	< 0.001	*	0.401	0.933
Inferior frontal gyrus - Pars triangularis	0.067	7.33	< 0.001	< 0.001	*	0.265	0.138
Middle frontal gyrus	0.059	6.33	< 0.001	< 0.001	*	0.404	0.233
Superior frontal gyrus	0.101	11.45	< 0.001	< 0.001	*	0.032	0.505
Orbital sulci (H-shaped sulci)	0.056	5.98	< 0.001	< 0.001	*	0.741	0.402

Note. p-values reported for each predictor in the model. * = significant after FDR correction.

Association between brain volumes and memory performance. The multivariate association between brain volumes of interest and memory scores was evaluated in three distinct CCA models (Fig. 2.4). Model 1 assessed the relationship between structures of the medial temporal lobe and memory performance (Fig. 2.4A-Left). Model 2 assessed the relationship between structures of the frontal lobes and memory performance (Fig. 2.4A-Center). Model 3 assessed the relationship between structures of both the medial temporal and frontal lobes and memory (Fig. 2.4A-Right). When comparing model fit (Fig. 2.4B), we found that Model 2 (which included the frontal regions alone) predicted memory performance better than Model 1 (which included the medial temporal lobe regions alone), $t = -161.77$, $p < 0.001$, and better than Model 3 (which included both medial temporal and frontal regions), $t = -11.06$, $p < 0.001$. Further, Model 3, predicted memory performance better than Model 1, $t = 261.67$, $p < 0.001$ (see Fig 2.4B).

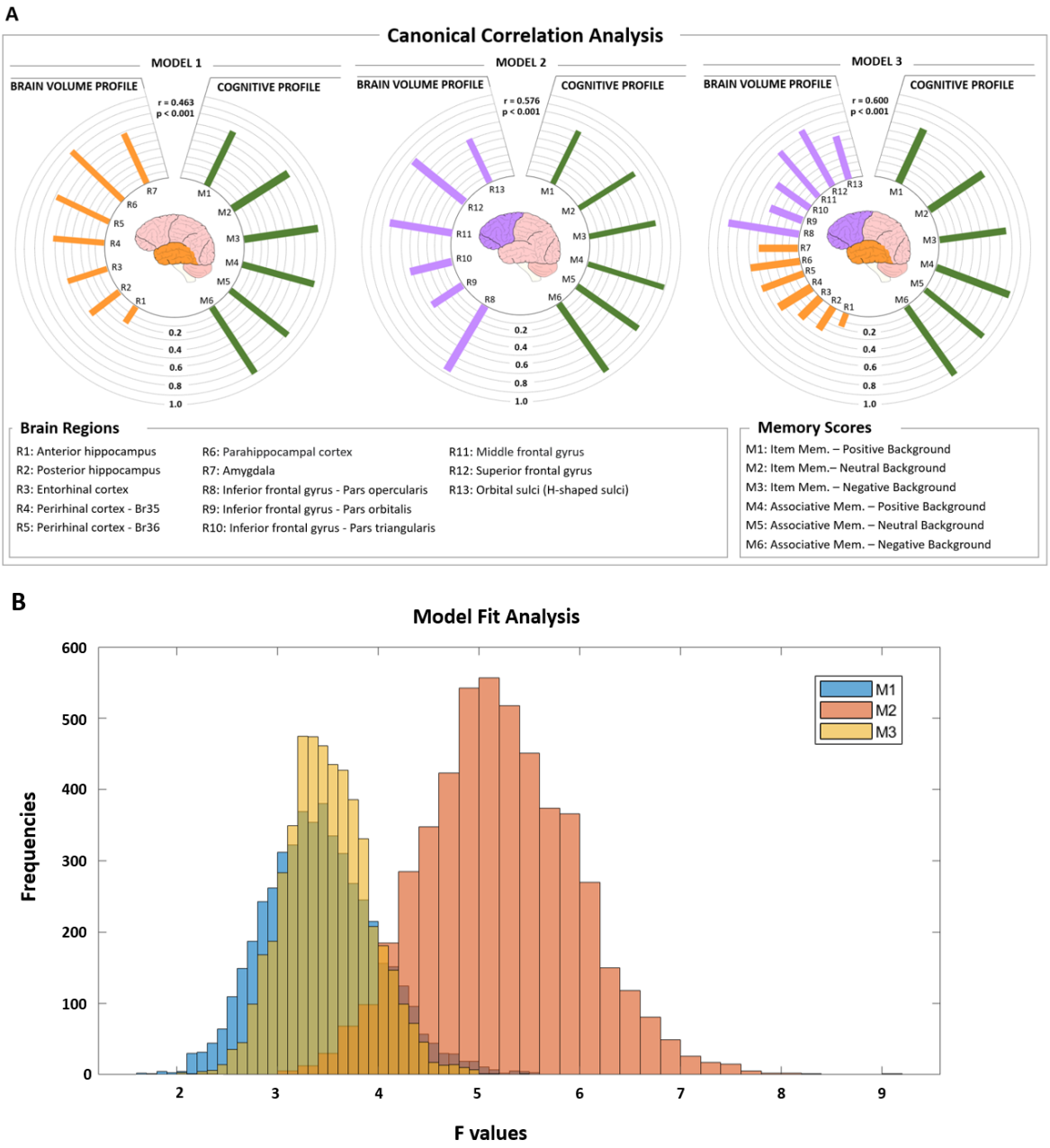

Figure 2.4: Canonical Correlation Analysis (CCA) - The relationship brain structures' volume and memory performance. A) Heliograph of variate loadings (correlations) for the first canonical variate, where the relative size of the correlations is indicated by the relative length of the bars. The statistical relationship between variables of structures' volume (brain volume profile) and memory performance (cognitive profile) is for Model 1 ($r = 0.463$, $p < 0.001$), Model 2 ($r = 0.576$, $p < 0.001$), and Model 3 ($r = 0.600$, $p < 0.001$). B) Model Fit Analysis (Bootstrapping approach). Histogram showing the frequencies of F values (5000 occurrences per model), representing the distribution of the ratio of explained variance to unexplained variance explained by each model.

After assessing model fit, we evaluated the significance of the loadings of the best model (Model 2). Only the first canonical variate was significant ($p < 0.001$), and it explained 33.18% of the covariance between X and Y. As show in Table 2.4, all memory scores (except item memory for objects that were superimposed on a positive background) loaded significantly on this component, though the associative memory scores were numerically higher. In terms of brain regions, the only significant regions were the inferior frontal gyrus - pars opercularis, middle frontal gyrus, and superior frontal gyrus, suggesting that age-related variability in these regions contributes to age-related declines in memory.

While the MTL model (Model 1) showed a poorer fit to the data, this model was still significant, and given the special role of the MTL in memory, it seems fitting to further examine regional differences within this model. Only the first canonical variate was significant ($p < 0.001$), and it explained 21.44% of the covariance between X and Y. Interestingly, the only region of the MTL with significant loadings in Model 1 was the parahippocampal cortex ($p = 0.008$). All of the memory score loadings (except item memory for objects that were superimposed on a positive background) were significant (p's $< .05$) and the difference between item and associative memory loadings was generally less pronounced than it was for Model 2 (see Figure 2.4A).

Table 2.4 – Significance of the loadings of the CCA Model 2

CCA Component	Description	p value (Loadings)
X (Gray Matter Volume)	Inferior frontal gyrus - Pars opercularis	0.011
	Inferior frontal gyrus - Pars orbitalis	0.311
	Inferior frontal gyrus - Pars triangularis	0.215
	Middle frontal gyrus	0.044
	Superior frontal gyrus	0.027
	Orbital sulci (H-shaped sulci)	0.153
Y (Memory Scores)	Item Mem. – Positive Background	0.064
	Item Mem. – Neutral Background	0.043
	Item Mem. – Negative Background	0.028
	Associative Mem. – Positive Background	0.002
	Associative Mem. – Neutral Background	0.004
	Associative Mem. – Negative Background	< 0.001

Moderation Effects. For the best fitting model (Model 2), we also evaluated whether the relationship between PFC volume scores and memory scores remains after controlling for age and education, and whether the volume-performance relationship is moderated by the effects of either age or sex. For this purpose, we ran a moderation analysis testing the moderating effects of age and sex in the same model. Our results show that the model was significant ($R^2 = 0.542$, $F = 58.9$, $p < 0.001$; Table 2.5), with memory subject scores significantly predicted by PFC subject scores, age, sex, and education. However, the relationship between memory and PFC subject scores was not moderated by either age or sex (see Figure 2.5). Importantly, PFC volume scores remained a significant predictor of memory scores ($B = 0.118$, $p = 0.046$), confirming that the relationship between frontal lobe volumes and memory is not simply driven by age.

Table 2.5 – Moderation Analyses

Outcome	Predictors	B	Std. Error	t	Sig.
Y - Cognitive Performance Profile (Memory Scores)	X - Gray Matter Volume Profile (Frontal Lobe Structures)	0.118	0.059	2.007	0.046
	Age	-0.545	0.055	- 9.83	< 0.001
	Gender	0.115	0.039	2.989	0.003
	Volume Profile * Age	- 0.017	0.041	- 0.429	0.668
	Gender * Age	0.022	0.041	0.540	0.590
	Education	0.170	0.041	4.166	< 0.001

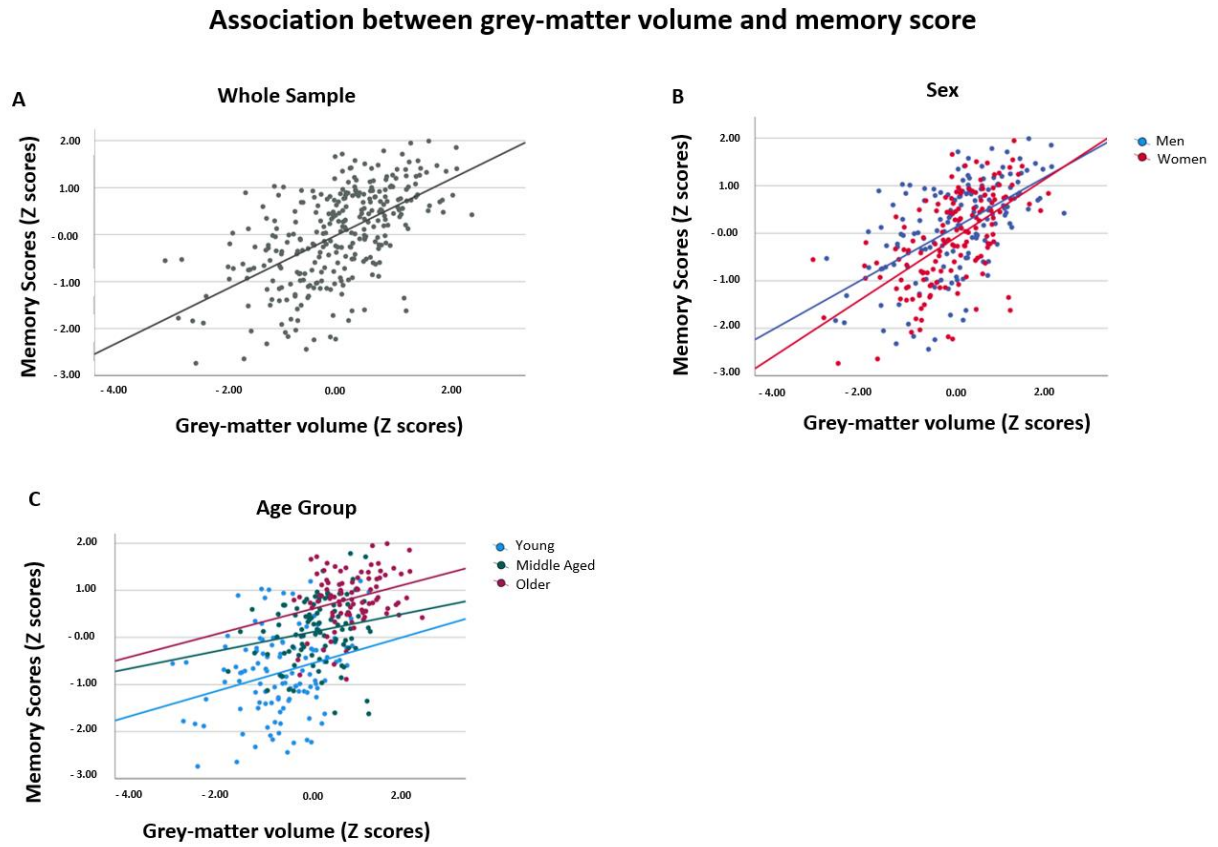

Figure 2.5 – Association between Grey matter volume in frontal lobes (X) and Memory scores (Y) (values expressed in Z scores) for A) Whole Sample. B) Whole sample split by sex. C) Whole sample split by age groups (for illustrative purposes only; age was used a continuous variable in the model).

Discussion

In this study, we evaluated the relationship between grey matter volume within substructures of the medial temporal and frontal lobes and age-related differences in item and associative memory across the adult lifespan. As expected, age was associated with declines in both memory performance and grey-matter volume. Nevertheless, in contrast to previous studies showing a disproportionate age effect on associative relative to item memory, we observed similar effects of age for both item and associative memory. We also observed an interaction between the effects of age and sex for associative memory, indicating that the age-related decline in associative memory was greater in men. Regarding the effects of age on grey matter volume, grey matter volume significantly declined with age in all structures of the medial temporal (except the posterior hippocampus) and frontal lobes, and a similar rate of decline was observed for both men and women. After testing the multivariate relationship between grey matter volumes and memory performance, our results showed that the structures of the PFC alone predicted memory performance better than either the structures of the MTL alone or the structures of the PFC and MTL combined. Our results also indicated that grey matter volume in the inferior frontal gyrus - pars opercularis, middle frontal gyrus, and superior frontal gyrus, related most strongly to memory (particularly associative memory) and this effect persisted when controlling for age. Finally, this relationship between frontal grey matter volume and memory was not moderated by age or sex.

In our study, memory performance was found to relate more strongly to grey matter volume in the PFC than structures in the MTL. This is in line with previous studies showing that grey matter volume in dorso- and ventrolateral prefrontal regions is a better predictor of associative memory performance in older adults than grey matter volume in MTL regions (Becker et al., 2015; Brehmer et al., 2020). The associative deficit hypothesis (ADH) suggests that age-related declines in episodic memory are largely due to impaired associative binding at encoding in older adults (Naveh-Benjamin,

2000). Although the MTL, especially the hippocampus, is critical for the binding process itself, the lateral PFC also supports binding through control functions at encoding and retrieval (Cabeza, 2006; Ranganath, 2010). The PFC undergoes several structural and functional changes during healthy aging that result in impaired aspects of cognitive control, including selective attention and inhibitory control, which in turn may affect long-term memory (Zanto & Gazzaley, 2019). The inhibitory deficit theory suggests that aging impairs the ability to inhibit distraction and maintain focus on relevant information, this way leading older adults to process more information than younger adults (Hasher & Campbell, 2020; Hasher & Zacks, 1988). Relatedly, the hyper-binding hypothesis proposes that memory binding remains relatively preserved with age, and that the age-related declines in associative memory are caused by an impaired ability to ignore distracting information, thereby leading older adults to form more irrelevant associations than older adults (Campbell et al., 2010; Davis et al., 2021). Control processes also play a critical role at retrieval, by guiding the memory search, rejecting familiar but incorrect responses, and overcoming interference (Castel & Craik, 2003; Cohn et al., 2008; Healey et al., 2013). Our findings and those of previous studies emphasizing the role of the lateral PFC in associative memory in older adults (Becker et al., 2015; Brehmer et al., 2020) lend support to the idea that age differences in cognitive control are a primary contributor to impairments in episodic memory (Campbell et al., 2010; Hasher, 2016). This view is also supported by the long-standing 'frontal lobe hypothesis' of aging (West, 2000), which points to the fact that structural declines are most pronounced in the PFC (Raz et al., 2005; Zanto & Gazzaley, 2019).

Among the regions of interest in the PFC, our results show the inferior frontal gyrus - pars opercularis, middle frontal gyrus, and superior frontal gyrus as the significant regions that mostly strongly relate to memory performance. In addition to executive functions (e.g., working memory, inhibitory control, reorienting attention, etc.) and language, these regions have also been associated with semantic retrieval, episodic retrieval, and spatially oriented processing (Boisgueheneuc et al.,

2006; Rajah et al., 2011; Vatansever et al., 2021). Becker et al. (2015) found that both dorsolateral and ventrolateral regions of the PFC, which include all PFC regions of interest in our study, significantly accounted for individual differences in associative memory. In contrast, Brehmer et al. (2020) found the inferior frontal gyrus - pars triangularis and inferior frontal gyrus - pars orbitalis as the regions of the PFC that significantly related to associative memory performance. Methodological differences might explain the differences across studies, including the age range of participants (a lifespan sample in our case vs. just older adults in these previous studies), memory task used (object-scene associations in our case vs. word-word, face-name, and object-scene in these previous studies), and statistical models employed. Despite these differences, it is interesting to note that in all cases, grey matter volume in the PFC was a stronger predictor of associative memory than that in the MTL.

Nevertheless, we know that the MTL is critical for associative memory, as suggested by countless animal studies and brain damage work with humans (Mayes et al., 2007; Olsen et al., 2012), and one of the primary goals of this study was to examine the role of specific subregions within the MTL. Thus, we also evaluated the loadings from the MTL-only model (i.e., Model 1). Interestingly, the only region of the MTL with significant loading values was the parahippocampal cortex (PHC). The PHC encompasses a large area of the MTL and has reciprocal connections within the MTL (which includes projections to and from the perirhinal cortex and parahippocampal cortex itself), in addition to providing a major source of input to the entorhinal cortex and direct connections with the hippocampus (Aminoff et al., 2013). The parahippocampal cortex is also highly connected with the frontal cortex (which includes connections with the medial prefrontal cortex, dorsolateral prefrontal cortex, and orbitofrontal cortex) and the insula (Aminoff et al., 2013). Previous work suggests that the PHC is involved in associative memory (associations between elements, associations between elements and context) and visuospatial processing (e.g., scene perception, spatial representation, and navigation) (Aminoff et al., 2013). The relationship between anatomical integrity of the PHC and

episodic performance in older adults has previously been shown (Gorbach et al., 2017; Köhncke et al., 2021; Snytte et al., 2022). Functional neuroimaging studies also demonstrate the engagement of the PHC in associative memory tasks (M. Li et al., 2016), and in tasks involving spatial information about the environment, including viewing pictures of scenes and landmarks (Epstein & Kanwisher, 1998). Given that our study assessed associative memory for background scenes that were cued by associated objects at retrieval, it seems sensible that grey matter integrity in this region critical for scene processing predicted performance.

As expected, age was largely associated with a decrease in episodic memory performance in both men and women (Duarte & Dulas, 2020). However, our results showed that the age-related decline in associative memory was greater in men. This result is supported by sex differences in episodic memory, which indicated that the magnitude of sex differences tends to vary depending on the material to be remembered, and that across the lifespan, women usually outperform men on tasks that require verbal processing whereas men have the advantage on tasks requiring spatial processing (Asperholm et al., 2019). During the study phase of the current task, participants had to elaborate a story that linked the object to the scene, which relies on verbal processing. Thus, our finding that women outperformed men on this task fits with the general pattern in the literature. Sex differences in the age-related decline in episodic memory have also been attributed to sex difference in hippocampal volume (Zheng et al., 2017). In our study however, we did not observe sex differences in either the relationship between age and grey matter volume or the relationship between grey matter volume and memory performance. Thus, the observed age x sex interaction in predicting associative memory might have been due to some other factor, such as functional differences between men and women. For example, recent functional neuroimaging work has shown that the neural underpinnings of age-related episodic decline differ in men and women (Subramaniapillai et al., 2022). Additionally, female reproductive factors (e.g., age at menarche, reproductive period, age at menopause) might play

an influence on sex differences in episodic memory performance (J. Li et al., 2022).

In this study, we showed that age-related declines in associative memory were more strongly predicted by structural changes in the prefrontal cortex than medial temporal lobes. However, this study is not without limitations. First, we recognize that our cross-sectional design is not ideal for capturing the effects of causality; thus, our results should be interpreted with caution. Second, due to our large sample size, we used automated segmentation tools to obtain measures of grey matter volume in the MTL and PFC. We used the Automatic Segmentation of Hippocampal Subfields (ASHS) software (Yushkevich et al., 2015) to estimate volumes of the MTL structures and FreeSurfer (Fischl et al., 2004) to estimate volumes of the amygdala and structures of the frontal lobe. Although such tools have been widely used, especially in large-scale brain imaging initiatives, and have been reported to have competitive accuracy and reliability when compared to manual segmentation (Sederevičius et al., 2021; Yushkevich et al., 2015), we acknowledge the possibility of potential of bias in these segmentation algorithms. Differences across segmentation protocols, especially regarding the localization of anatomical boundaries among structures might also lead to differences across studies (Snytte et al., 2022; Xie et al., 2016; Yushkevich et al., 2015). In terms of sex differences, we only measured self-reported sex, but this fails to capture any independent effects of gender. The term "sex" refers to the biological characteristic of an individual assigned at birth (e.g., chromosomes, anatomy), while "gender" involves self-identity and is associated social roles (e.g., societal expectations for education, career trajectories, caregiver responsibilities, etc.) (Heidari et al., 2016). Future studies should ask about both sex at birth and gender-related social roles separately to better characterize their potential independent contributions to neurocognitive aging.

Many factors play a role in the age-related decline in episodic memory. Healthy aging seems to affect memory for associations more so than memory for item information. Our findings corroborate with the literature that support the relevance of the integrity of the structures of the frontal

lobe for episodic memory performance.

Supplementary Information

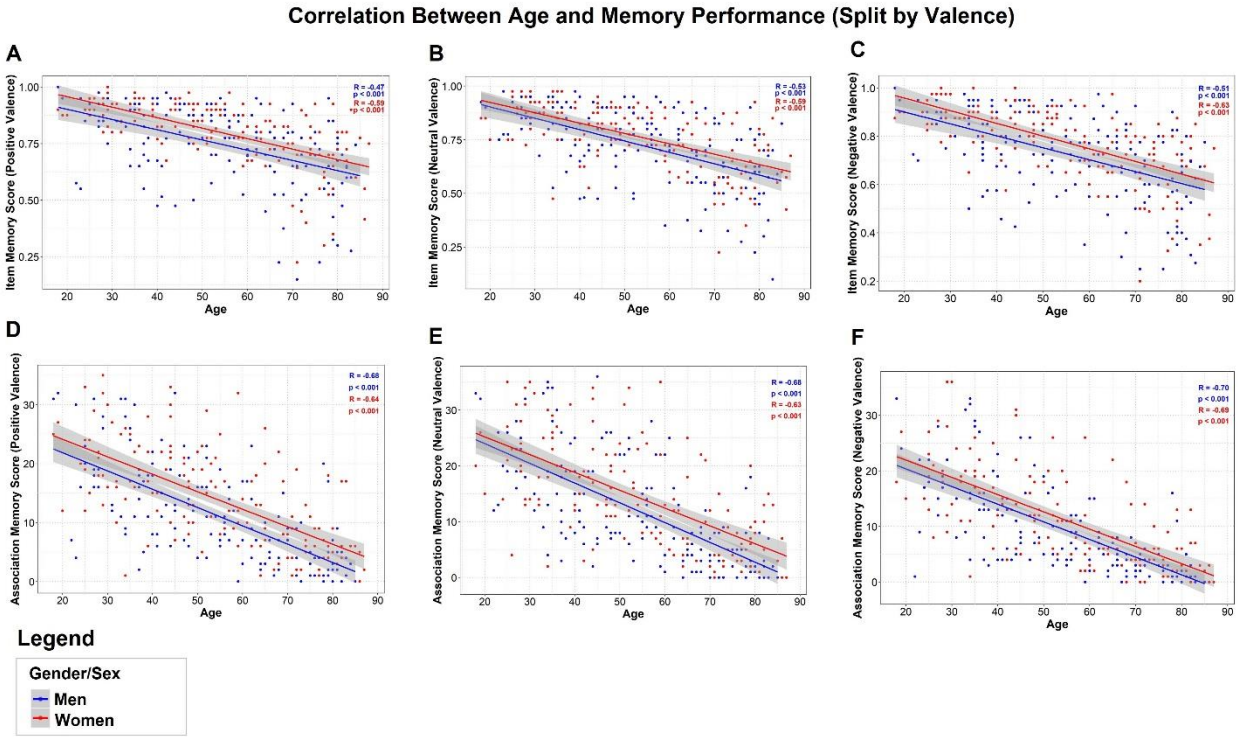

Figure 2.S1: Correlation between age and memory performance split by valance of the background image. A) Item Memory score. B) Association Memory Score.

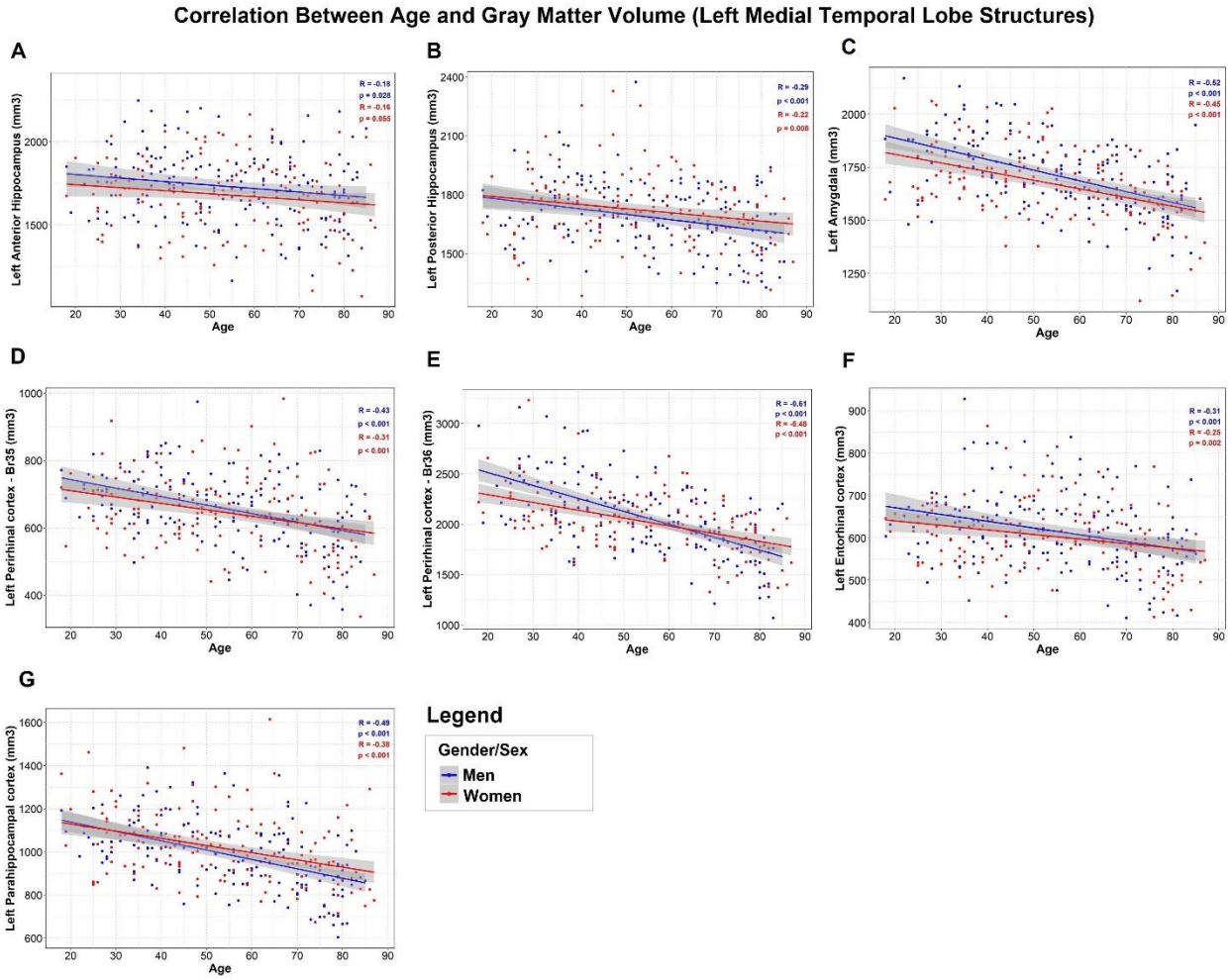

Figure 2.S2: Correlation between age and gray matter volume (Left Medial Temporal Lobe Structures). A) Anterior hippocampus. B) Posterior hippocampus. C) Amygdala. D) Entorhinal cortex. E) Perirhinal cortex - Br35. F) Perirhinal cortex - Br36. G) Parahippocampal cortex.

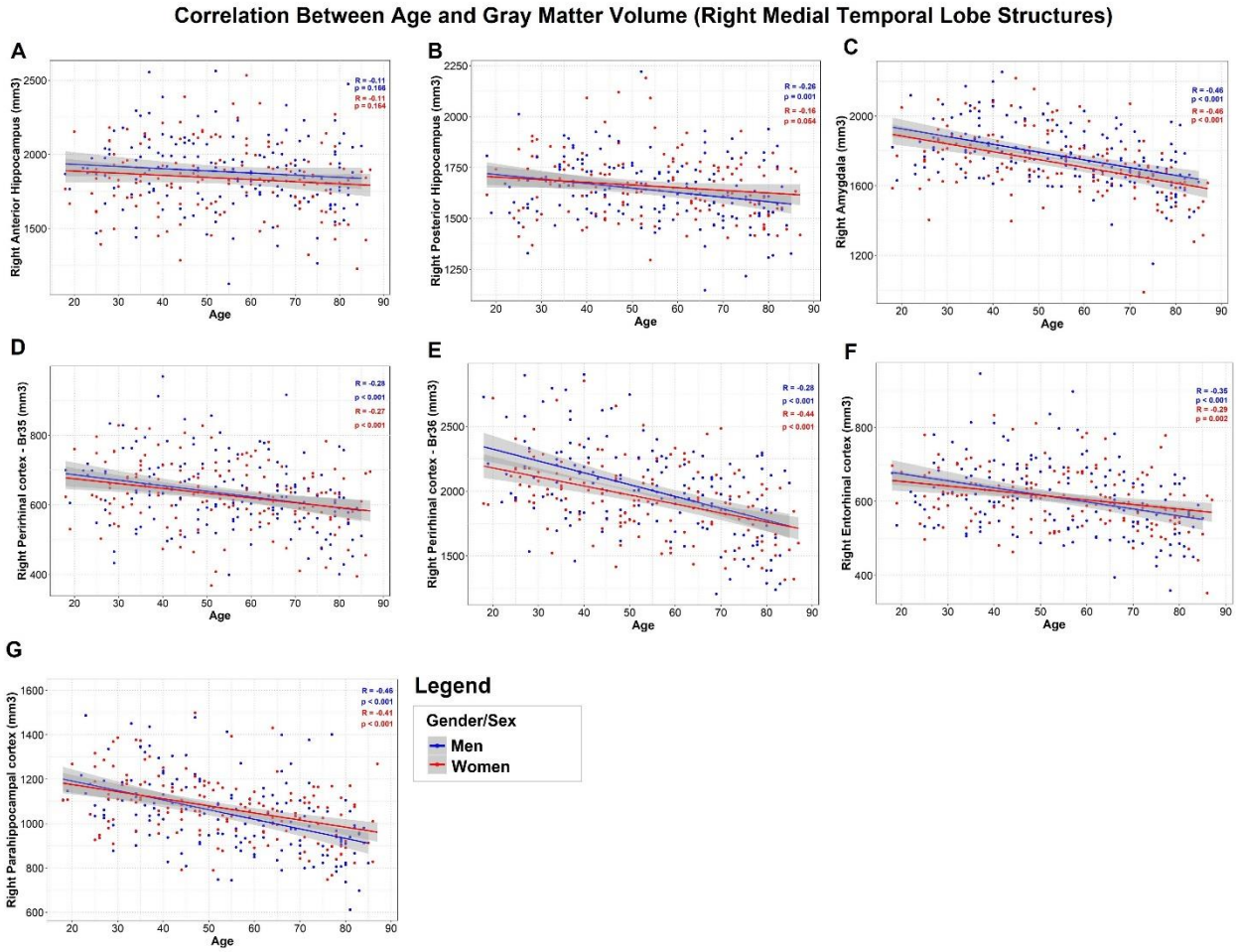

Figure 2.S3: Correlation between age and gray matter volume (Right Medial Temporal Lobe Structures). A) Anterior hippocampus. B) Posterior hippocampus. C) Amygdala. D) Entorhinal cortex. E) Perirhinal cortex - Br35. F) Perirhinal cortex - Br36. G) Parahippocampal cortex.

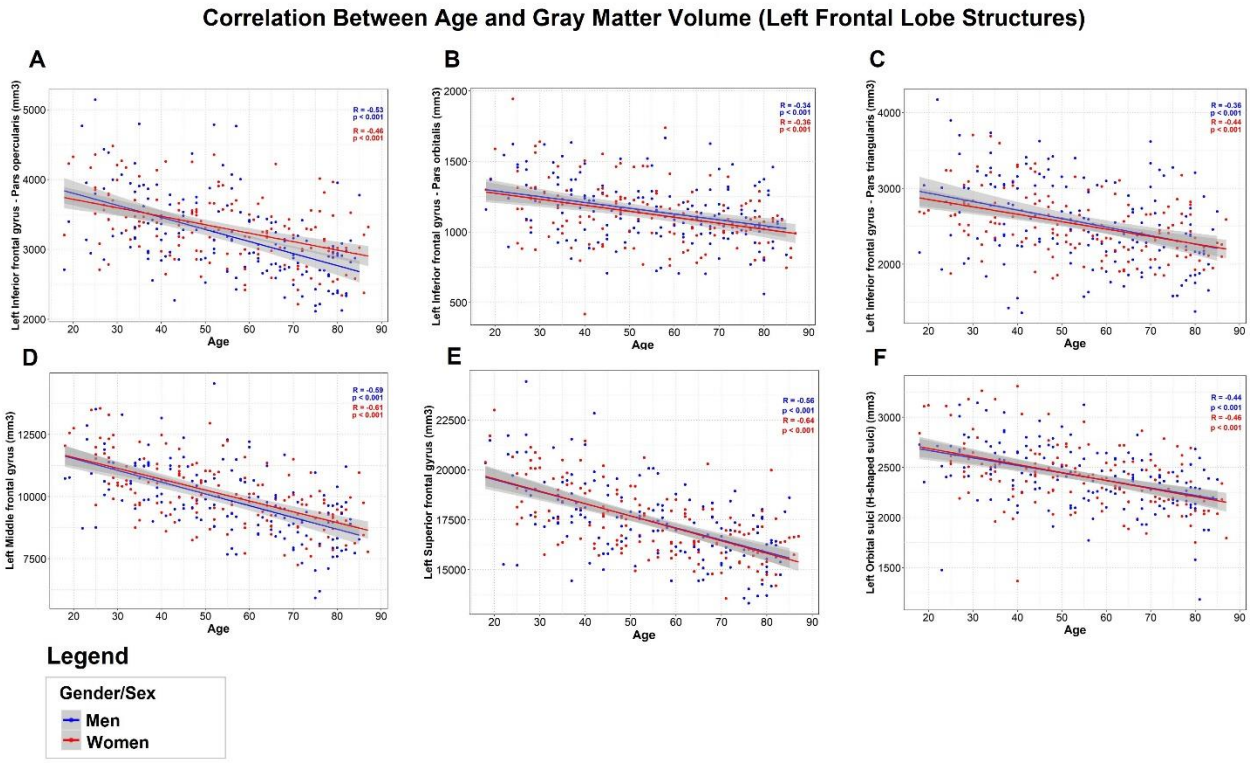

Figure 2.S4: Correlation between age and gray matter volume (Left Frontal Lobe Structures). A) Inferior frontal gyrus - Pars opercularis. B) Inferior frontal gyrus - Pars orbitalis. C) Inferior frontal gyrus - Pars triangularis. D) Middle frontal gyrus. E) Superior frontal gyrus. F) Orbital sulci (H-shaped sulci).

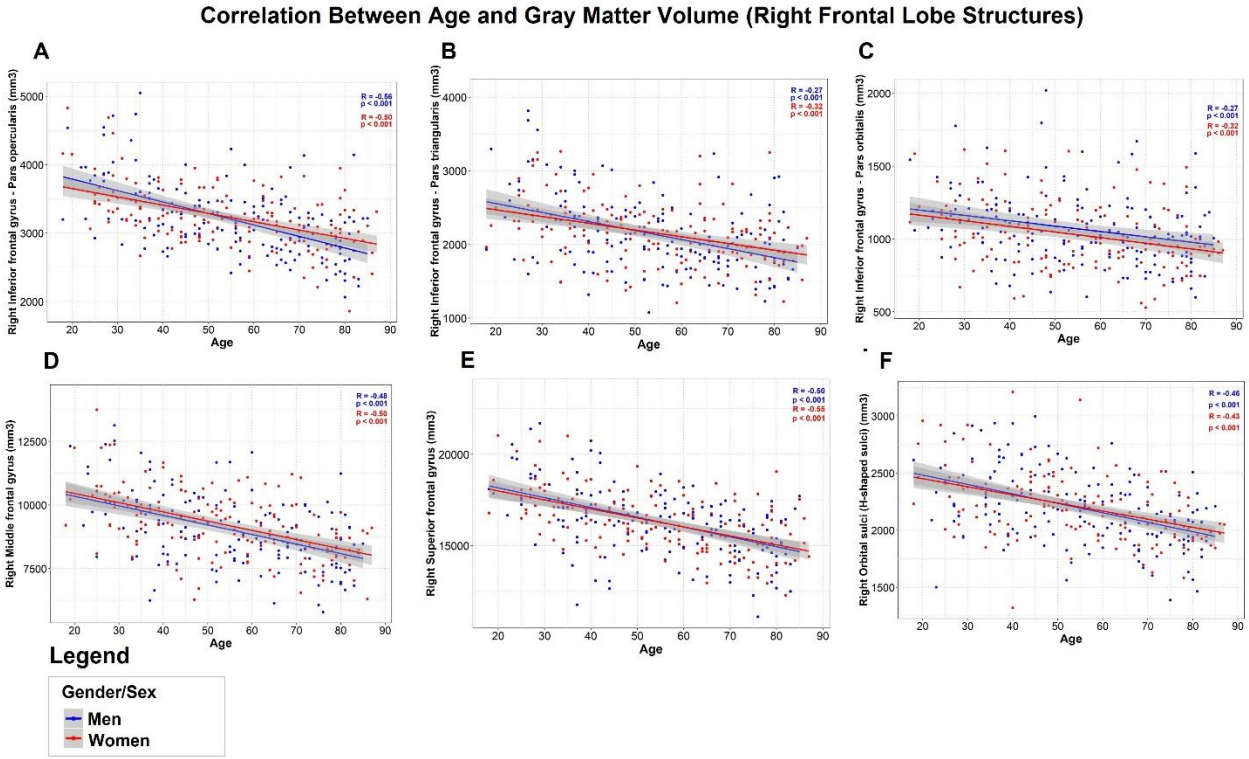

Figure 2.S5: Correlation between age and gray matter volume (Right Frontal Lobe Structures). A) Inferior frontal gyrus - Pars opercularis. B) Inferior frontal gyrus - Pars orbitalis. C) Inferior frontal gyrus - Pars triangularis. D) Middle frontal gyrus. E) Superior frontal gyrus. F) Orbital sulci (H-shaped sulci).

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Chapter 3: The role of the arousal system in age-related differences in cortical functional network architecture

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Abstract

A common finding in the aging literature is that of the brain's decreased within- and increased between-network functional connectivity. However, it remains unclear what is causing this shift in network organization with age. Given the essential role of the ascending arousal system (ARAS) in cortical activation and previous findings of disrupted ARAS functioning with age, it is possible that age differences in ARAS functioning contribute to disrupted cortical connectivity. We test this possibility here using resting state fMRI data from over 500 individuals across the lifespan from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) population-based cohort. Our results show that ARAS-cortical connectivity declines with age and, consistent with our expectations, significantly mediates some age-related differences in connectivity within and between association networks (specifically, within the default mode and between the default mode and salience networks). Additionally, connectivity between the ARAS and association networks predicted cognitive performance across several tasks over and above the effects of age and connectivity within the cortical networks themselves. These findings suggest that age differences in cortical connectivity may be driven, at least in part, by altered arousal signals from the brainstem and that ARAS-cortical connectivity relates to cognitive performance with age.

Keywords: *neurocognitive aging, functional networks, ascending arousal system, fMRI*

Introduction

As people age from young to older adulthood, several changes are commonly observed in the brain´s functional network organization, including reduced suppression of the default mode network during task performance, differences in network interactivity, and decreased network segregation (Bethlehem et al., 2020; Chan et al., 2014; Damoiseaux, 2017; Ferreira et al., 2016; Grady, 2012; Spreng et al., 2010; Turner & Spreng, 2015). Age differences in network segregation are characterized by decreased within-network and increased between-network functional connectivity from adulthood onwards, meaning that functional networks become less distinct in older age. (Chan et al., 2014; Geerligs et al., 2014). This age-related decline in network segregation is particularly pronounced amongst association networks (i.e., the default mode network [DMN], salience network [SN], dorsal attention network [DAN], and frontoparietal control network [FPCN]) (Chan et al., 2014; Geerligs et al., 2014) and has been observed in both task and resting state fMRI studies (Spreng et al., 2016), when controlling for neurovascular coupling of the BOLD signal (Tsvetanov et al., 2016), and when the brain´s electrophysiological signaling is measured directly with EEG (Petti et al., 2016). Moreover, these networks in particular have been consistently related to age-related declines in general cognitive functioning (Grady et al., 2016; Sala-Llonch et al., 2015; Shaw et al., 2015; Siman-Tov et al., 2017). Despite advances in characterizing the effects of age on functional brain networks, a complete understanding of the factors involved in this shifting balance between intra- and inter-network connections is still lacking.

Could one of the factors contributing to altered cortical connectivity be coming from outside the cortex? The ascending arousal system, also known as the ascending reticular activating system (ARAS) is composed of a set of neuroanatomic structures and neurotransmitter systems connecting the brainstem to the cortex and promoting cortical arousal, an essential component of awareness. A diffuse set of neuronal projections from multiple brainstem nuclei stimulate the cerebral cortex via

ascending pathways that project to the thalamus, posterior hypothalamus, basal forebrain and directly to the cortex itself (Jones, 2003). These thalamic and extra-thalamic ascending pathways include, but are not limited to, glutamatergic fibers from the parabrachial complex, cholinergic fibers from the pedunculopontine nucleus, noradrenergic fibers from the locus coeruleus, dopaminergic fibers from the ventral tegmental area, and serotonergic fibers from the raphe nuclei (Edlow et al., 2012). This complex set of neurotransmitter pathways that compose the ARAS continuously interact with and modulate one another on route to the cortex, affecting brain functioning and influencing many aspects of cognition (Briand et al., 2007; Handra et al., 2019; Lobo & Summavielle, 2015).

During the aging process, there is a clear disruption to the ARAS, whereby loss of neurons and receptors is associated with a compensatory increase in neurotransmitter system activity along the ascending pathways (Handra et al., 2019). However, despite recent advances in our understanding of how age affects ARAS functioning (Mather, 2020), neuroimaging studies that investigate the effect of age on functional connectivity of the arousal system are still scarce and restricted to specific nuclei of the system. For instance, in recent years, there has been increased interest in the role of the locus coeruleus (LC) in neurocognitive aging, and structural neuroimaging findings suggest that LC integrity is associated with cognitive reserve and behavioral performance in older adults (Clewett et al., 2016; Dahl et al., 2019; Liu et al., 2020). Recent functional neuroimaging studies have also started to investigate age differences in functional connectivity of brainstem nuclei (Jacobs et al., 2018; Serra et al., 2018; Zhang et al., 2016); but no study to date has examined age differences in functional connectivity across the entire ARAS and determined its relationship to cortical connectivity.

Thus, the first goal of the current study was to examine the whole-brain connectivity pattern of the brainstem nuclei of the ARAS and age differences therein using resting state fMRI data from the Cambridge Centre for Ageing and Neuroscience's (Cam-CAN) population-based cohort. Previous studies examining age differences in functional connectivity of ARAS nuclei have reported a complex

pattern of results, with some connections increasing with age and others decreasing depending on the brain area (Jacobs et al., 2018; Zhang et al., 2016). Thus, we hypothesized that aging would be associated with a diverse set of ARAS-cortical connectivity differences, including both increases and decreases in connectivity to different regions of the brain.

Further, given the essential role of the arousal system in cortical activation and previous findings of disrupted ARAS functioning with age, we hypothesized that age differences in ARAS connectivity relate to concomitant differences in functional network segregation. As already discussed, decreased segregation is characterized by a decrease in within network connectivity and an increase in between network connectivity and is particularly pronounced for the association networks (Chan et al., 2014; Geerligs et al., 2014). Thus, we determined the extent to which age differences in association network connectivity are explained by age-related declines in ARAS-association network connectivity.

Finally, we predicted that the multivariate relationship between ARAS-association network connectivity and cognitive performance will vary with aging (Bethlehem et al., 2020; Tibon et al., 2021; Tsvetanov et al., 2016; Tsvetanov et al., 2021). Since the DMN, FPCN, DAN, and SN have primarily been implicated in memory and attentional control (e.g., (Grady et al., 2016; Sala-Llonch et al., 2015; Shaw et al., 2015; Siman-Tov et al., 2017) , we limited our analyses to tasks from the CamCAN that measure these cognitive functions (including ACE-R, Cattell test of fluid intelligence, Story Recall, Choice Reaction Time, and Visual Short-term Memory). To this end, we ran a canonical correlation analysis relating ARAS-association network connectivity measures to our cognitive variables of interest.

Methods

Participants. A sample of 644 participants (18–88 years old; mean 54.2; SD 18.5; 319 males and 325

females) was taken from the population-derived Stage 2 sample of the Cambridge Centre for Aging and Neuroscience (Cam-CAN) project (Shafto et al., 2014). After excluding participants based on motion correction and cardiovascular health (described further below), a final sample of 535 participants (18–88 years old; mean 53.9; SD 17.5; 272 males and 263 females) approximately equally distributed across the lifespan remained. Demographic information of the current sample is provided in Table 3.1 (divided into age groups for illustrative purposes, but all analyses used age as a continuous variable). Participants were included if they had no contraindications to MRI, no self-reported history of drug or alcohol abuse, no neurological disorders, and no brain abnormalities detected. Participants were native English speakers, had normal or corrected-to-normal vision and hearing, and scored 25 or higher on the mini mental state exam (MMSE). Informed consent was obtained from all participants and the study was approved by the Cambridgeshire 2 Research Ethics Committee, United Kingdom (Shafto et al., 2014).

Table 3.1 - Participant demographics and cognitive scores

Age group	Young	Middle	Older	Total
n	194	178	163	535
Age range (years)	18-45	46-64	65-88	18-88
Sex (male/female)	104/90	85/93	83/80	272/263
Highest education				
University	147 (75.8%)	117 (65.7%)	58 (32.6%)	322 (60.2%)
A' levels	26 (13.4%)	35 (19.7%)	58 (32.6%)	119 (22.2%)
GCSE grade	19 (9.8%)	19 (10.7%)	24 (13.5%)	62 (11.6%)
None over 16	1 (0.5%)	7 (3.9%)	22 (12.4%)	30 (5.6%)
Cognitive Scores				
MMSE	29.32 (1.05)	29.17 (1.05)	28.42 (1.36)	28.99 (1.2)
ACE-R	96.48 (3.42)	96.00 (3.52)	92.76 (5.20)	95.19 (4.38)

Note. Education data missing for two participants. ACE-R and MMSE scores missing for two participants.

Image acquisition. Participants were instructed to rest with eyes closed and to not think of anything in particular during fMRI scanning. Scanning took place at the Medical Research Council Cognition and Brain Sciences Unit (MRC-CBSU) in a 3T Siemens TIM Trio, with a 32-channel head-coil. For resting state, 261 volumes were acquired, each containing 32 axial slices (acquired in descending order), with slice thickness of 3.7mm and interslice gap of 20% (for whole-brain coverage including cerebellum; TR 1970 ms; TE 30 ms; flip angle 78°; FOV 192mm x 192 mm; voxel size 3mm x 3mm x 4.44mm and acquisition time of 8 min and 40 s. Higher-resolution (1mm x 1mm x 1mm) T1 and T2 weighted structural images were also acquired to aid registration across participants (Shafto et al., 2014; Taylor et al., 2017).

Data preprocessing. An overview of the analysis pipeline is shown in Figure 3.1. Using SPM 12 software (http://www.fil.ion.ucl.ac.uk/spm) and the automatic analysis (AA) batching system (http://imaging.mrc-cbu.cam.ac.uk/imaging/), T1 and T2 structural images were coregistered. Unified segmentation was performed on the combined images (Ashburner & Friston, 2005) and

subsequently, the gray matter (GM) and white matter (WM) segments of each participant were used to create a study-specific anatomical template using the DARTEL procedure to optimize inter-participant alignment (Ashburner, 2007), which was subsequently normalized into MNI space. For each participant, field maps were used to undistort the functional EPI T2* images and then the functional images were motion-corrected and slice-time corrected. Subsequently, the EPI images were coregistered to the T1 image and the DARTEL flow fields were applied for MNI normalization (Taylor et al., 2017).

To reduce the effects of motion on our measures of functional connectivity (e.g.,Power et al., 2012; Satterthwaite et al., 2012) additional motion correction procedures were applied. The first step was to apply a wavelet despike method for removing motion artifacts from fMRI data without the need for data scrubbing (Patel et al., 2014). Participants with an average spike percentage of two SDs above the mean were excluded from further analysis (this led to the exclusion of 58 participants). The second step to reduce the effects of motion and other noise confounds was to apply multiple regression of the six original motion parameters as well as average signals from white matter (WM), and cerebrospinal fluid (CSF). We also regressed out the signal of the 4^{th} ventricle due to its proximity to the nuclei of the brainstem (Ngeles Fernández-Gil et al., 2010). Additionally, in order to reduce the confounding effects of head motion and vascular health, for each participant, mean connectivity across all connections was calculated and regressed out of subsequent analyses at the group level (Geerligs et al., 2017). This method has been shown to increase the reliability of both connectivity estimates and effects of age while simultaneously reducing associations between connectivity and vascular health, and between connectivity and head motion (Geerligs et al., 2017).

Next, a high-pass filter of 0.008Hz was implemented. Although band-pass filtering is commonly used to reduce physiological noise, it also leads to less reliable estimates of functional connectivity (Shirer et al., 2015) and research has shown that the effect of age is better identified

when applying high-pass than band-pass filtering (Geerligs et al., 2017).

Age is also associated with changes in cardiovascular health and neurovascular coupling, which is known to affect the BOLD signal and measures of functional connectivity (Abdelkarim et al., 2019; D'Esposito et al., 2003; Hutchison, Lu, et al., 2013; Hutchison, Shokri-Kojori, et al., 2013; Tsvetanov et al., 2020). In order to minimize these effects, participants with cardiovascular disease (65 individuals) were excluded from the current sample and we controlled for vascular function in the rest of the sample by regressing out a composite measure of vascular health(Tsvetanov et al., 2015). This vascular health index was obtained by taking the first principal component from a Principal Components Analysis (PCA) applied to a number of heart rate measures obtained using photoplethysmography / pulseoximeter during scanning. These included: mean heart rate (HR), low-frequency heart rate variability (LF-HRV; 0.05–0.15 Hz), and high-frequency heart rate variability (HF-HRV; 0.15–0.4 Hz). The PCA analysis estimated the first principal component (PC1) to explain 67.96 % of the variance across the three summary measures of HR.

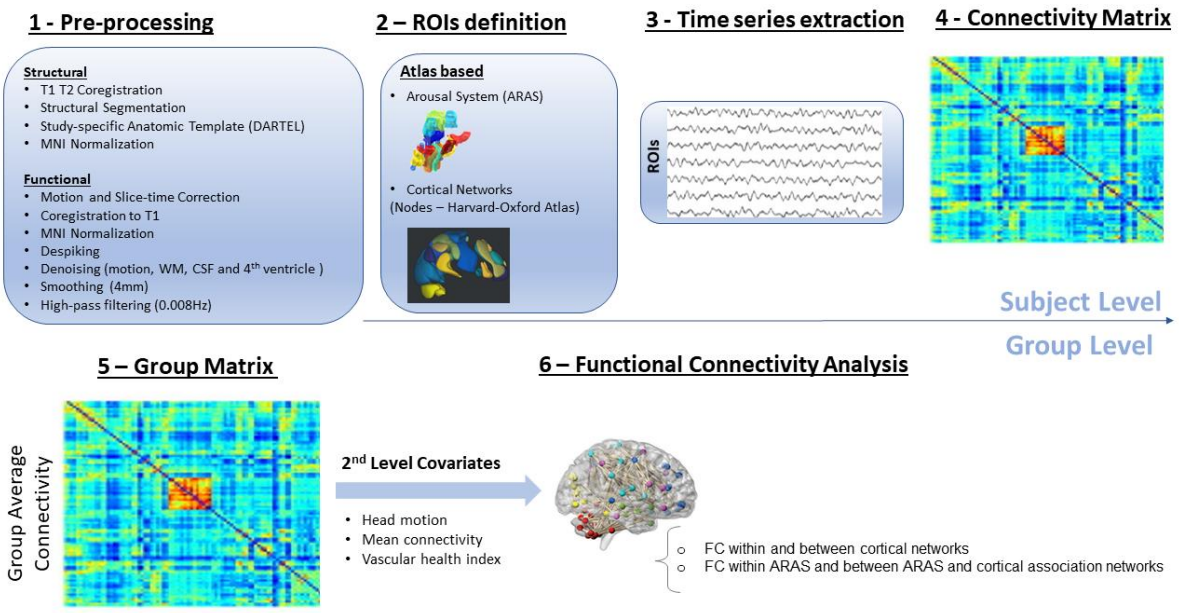

Figure 3.1 - fMRI data preprocessing and analysis pipeline. Nodes of canonical cortical networks (Harvard-Oxford atlas) encompasses the default mode network (DMN), dorsal attention network (DAN), frontoparietal control network (FPCN), and salience network (SN). Additional networks included in the whole-brain connectivity analysis (i.e., canonical cortical networks) included the sensorimotor, visual, language, and cerebellum. The arousal system nuclei included the dorsal raphe nucleus (DR), mesencephalic reticular formation (MRF), median raphe nucleus (MR), periaqueductal gray (PAG), parabrachial complex (PBC), pontine nucleus oralis (PO), pedunculopontine tegmental nucleus (PPN), ventral tegmental area (VTA), and locus coeruleus (LC).

Data analysis – *ARAS and Cortical Network Connectivity*. Regions of interest (ROIs) for our functional connectivity analysis included the ARAS structures from the Harvard Ascending Arousal Network Atlas (Martinos Center for Biomedical Imaging, Charleston, Massachusetts, USA, https://www.martinos.org/resources/aan-atlas) (Edlow et al., 2012): dorsal raphe nucleus (DR), mesencephalic reticular formation (MRF), median raphe nucleus (MR), periaqueductal gray (PAG), parabrachial complex (PBC), pontine nucleus oralis (PO), pedunculopontine tegmental nucleus (PPN), ventral tegmental area (VTA). For the locus coeruleus (LC) ROI, we used a LC probabilistic atlas developed by using ultrahigh field 7T MRI (Ye et al., 2021). ROI masks of nodes from canonical

brain networks (Default Mode [DMN] – four nodes, Salience [SN] – seven nodes, Dorsal Attention [DAN] – four nodes, Frontoparietal Control [FPCN] – four nodes, Sensorimotor [SM] – three nodes, Visual [VIS] – four nodes, Language [LAN] – four nodes, Cerebellar [CEREB] – two nodes) were taken from the FSL Harvard-Oxford atlas available in the Conn Toolbox v.18b (https://web.conn-toolbox.org/). For each subject, the Pearson's correlation coefficients were calculated between the preprocessed fMRI time series of each ROI and the time courses of all other ROIs and transformed to Z-values using the Fisher transformation (Bianciardi et al., 2016) . These Z-values were then used in second-level group analyses to assess 1) mean connectivity within the ARAS, and between the ARAS and other brain networks, 2) mean connectivity within and between cortical networks, and 3) the effect of age on ARAS and cortical network connectivity (False Discovery Rate - FDR corrected two-sided p-value <0.05) (Fig 1). Group level analyses were all performed by controlling for mean connectivity across all ROIs, head motion, vascular health index, and education level (Chan et al., 2018).

Within/Between Network Connectivity Analyses. The association between the arousal system and connectivity within and between cortical networks was assessed specifically for the association networks (i.e., DMN, SN, DAN and FPCN), as age differences in segregation are typically strongest for these networks (Chan et al., 2014; Geerligs et al., 2014). The aim was to evaluate the percentage of age-related variance in functional connectivity of the association networks that is shared with age-related differences in ARAS-cortex connectivity. This was achieved by performing a series of mediation analyses to test the mediating effect of the mean connectivity across all arousal system nuclei and each pair of networks (within network connectivity: DMN, SN, DAN, FPCN [Fig 3.2A]; between network connectivity: DMN x SN, DMN x DAN, DMN x FPCN, SN x DAN, SN x FPCN, DAN x FPCN [Fig 3.2B]).

In this study, we aim to assess the effects of the ARAS as an integrated system, thus, instead

of analyzing the mediation effect of each brainstem nucleus separately, the average connectivity between all ARAS ROIS and the ROIs in a given cortical network was used as a representative metric of the connectivity between the ARAS and that network as a whole. Thus, for each analysis, we aimed to explain the direct effect of age on functional connectivity within a network or between a pair of networks. In the case of within network connectivity, the connectivity between that network and the arousal system (averaged across all ARAS ROIs) was used as a mediator, so only one mediator (see Figure 2A). For between network connectivity, the average connectivity between the ARAS nuclei and both functional networks being analyzed were used as mediators, so two mediators (see Figure 2B). These analyses were run in the Mediation Analysis Toolbox in Matlab using bootstrapping with 10000 samples and FDR was used for the correction of multiple comparisons (Wager et al., 2008).

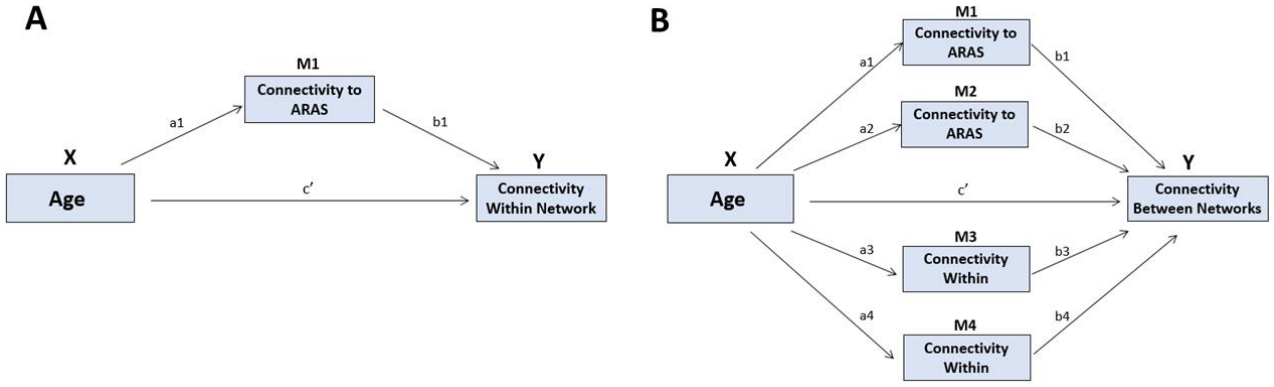

Figure 3.2 – Mediation analyses looking at the effect of ARAS-association network connectivity on the age-related decline in functional connectivity within and between the association networks (averaged across nodes within each network/module). A) Depiction of the within-network connectivity mediation model. B) Depiction of the between-network connectivity mediation model. Mediators M1 and M2 are the connectivity of each module to the arousal system.

Relationship between ARAS-cortical connectivity and cognitive performance.

For the connectivity-behavior analysis, we adopted a two-level approach (Passamonti, et al., 2019; Tibon et al., 2021; Tsvetanov et al., 2016; Tsvetanov et al., 2021). In the first level, to determine which (if any) connections between the ARAS and cortex were important for cognitive performance, we ran a canonical correlation analysis (CCA; Sui et al., 2012; Wang et al., 2020) to identify linear relationships between the two sets of measures (ARAS-association network connectivity, and cognitive performance in our main cognitive variables of interest from Cam-CAN). The set of cognitive variables included the following cognitive tasks: Addenbrooke's Cognitive Examination-revised (ACE-R), Cattell Culture Fair test of fluid intelligence, Story Recall, Choice Reaction Time, and Visual Short-term Memory (full descriptions of the tasks are available in the supplementary material)**.** The first step was to run CCA on both sets of variables (Set 1, ARAS Connectivity; Set2, Cognitive Performance), through which linear combinations within each of the sets were determined in a way that the relationship of the combinations between both sets was maximized. This resulted in a pair of significantly correlated canonical variates (i.e., latent variables), which we refer to as X1 – Connectivity Subject Scores, and Y1 - Cognitive Subject Scores.

Next, we tested whether the relationship between ARAS connectivity and cognitive performance varies with age. To this end, we performed a second-level analysis using moderation analysis. In our model, ARAS connectivity subject scores, age, their interaction term (ARAS connectivity subject scores * age), and covariates of no interest (mean connectivity across all ROIs, head motion, vascular health index, mean connectivity within each of the association networks [i.e., DMN, SN, DAN, and FPCN within-network connectivity], and education level) were used as independent variables and cognitive subject scores as a dependent variable.

Results

ARAS and Cortical Network Connectivity. The ARAS nuclei were all positively correlated with each other (see Figures 3.3A) and widely connected to several cortical networks (Figures 3.3C, 3.3E). Specifically, ARAS nuclei showed several positive connections to the default mode network, insula, and inferior frontal gyrus and negative connections to other regions of the salience network (apart from the insula) and the visual network.

Within the ARAS, age was associated with both increases and decreases in connectivity (see Figures 3.3B). In contrast, ARAS-cortical connectivity was largely characterized by an age-related decrease in the number and strength of positive connections (particularly between the ARAS and some nodes of the default mode and salience networks), but also an increase in the strength of some anti-correlations (Figures 3.3D, 3.3F).

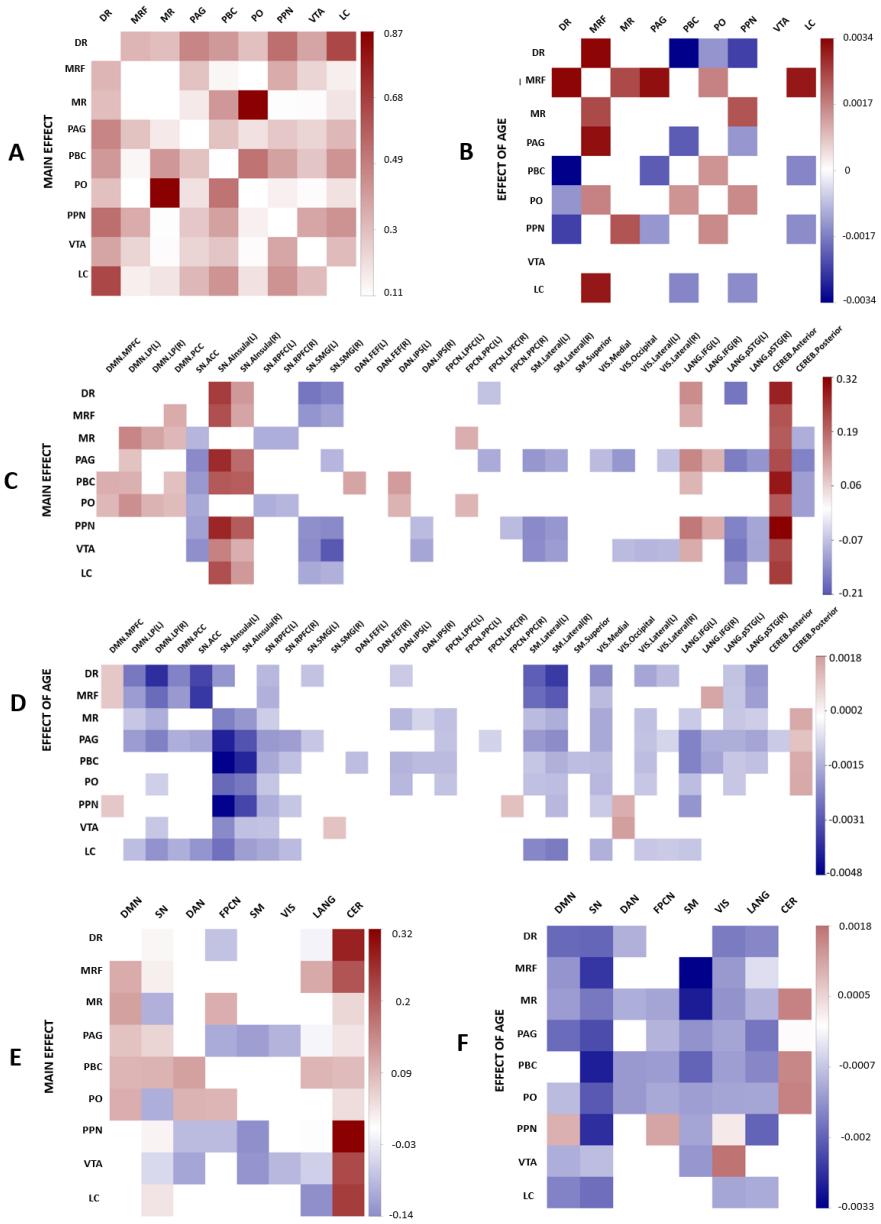

Figure 3.3 – Functional connectivity analysis of the arousal system's nuclei (controlling for mean connectivity across all ROIs, head motion, WM, CSF, 4th ventricle, vascular health index and education level). Correlation matrices of functional connectivity (Pearson r, p-FDR < 0.05) for A) Main effect – Connectivity within ARAS; B) Effect of age - Connectivity within ARAS; C) Main effect – Connectivity between ARAS and cortical networks; D) Effect of age - Connectivity between ARAS and cortical networks; E) Main effect – Connectivity between ARAS and cortical networks (average per network); F) Effect of age - Connectivity between ARAS and cortical networks (average per network). Functional modules included in the analysis: default mode network (DMN), salience network (SN), dorsal attention network (DAN), frontoparietal control network (FPCN), sensorimotor network (SM), visual network (VIS), language network (LAN), cerebellar network (CEREB). The arousal system nuclei included in the analysis are: dorsal raphe nucleus (DR), mesencephalic reticular formation (MRF), median raphe nucleus (MR), periaqueductal gray (PAG), parabrachial complex (PBC), pontine nucleus oralis (PO), pedunculopontine tegmental nucleus (PPN), ventral tegmental area (VTA), and locus coeruleus (LC).

We also examined functional connectivity within/between four cortical association networks previously shown to become less segregated with age (i.e. DMN, SN, DAN, FPCN - see Methods). In line with previous work, nodes from each network clustered together, with most showing higher intrinsic and lower extrinsic connectivity (except for SN to DAN; see Figure S1A). Further, in line with previous findings, age was largely associated with decreased within-network ($r = -0.172$; $p < 0.001$) and increased between-network ($r = 0.155$; $p < 0.001$) functional connectivity (Figure 3.S1B).

Mediation Effects of ARAS-Cortical Connectivity on Age Differences in Cortical Connectivity. To determine whether some of the age-related variance in functional connectivity within and between the association networks is shared with age-related differences in ARAS-cortex connectivity, we performed a series of mediation analyses (see Figure 3.2 and Methods; all analyses FDR corrected for multiple comparisons). Our results show that age is associated with a general decline in connectivity between the ARAS and association networks (Tables 3.S1-3.S2 [a paths]), and that this partly explains some of the observed age-related differences in association network connectivity. Specifically, we found that connectivity between the ARAS and DMN partly explains the age-related decline in connectivity within the DMN ($b = -0.03$, 95% CI [-0.03, -0.02], $t = -2.54$, $p = 0.002$) and the age-related increase in connectivity between the DMN and SN ($b = 0.02$, 95% CI [0.01, 0.03], $t = 2.09$, $p = 0.005$). Additionally, we also found two effects that were significant at $p < .05$, but did not survive FDR correction: ARAS-DMN connectivity was associated with the age-related increase in connectivity between the DMN and DAN ($b = 0.01$, 95% CI [0.01, 0.02], $t = 1.75$, $p = 0.031$), and ARAS-SN connectivity was associated with the age-related decrease in connectivity between the SN and DAN ($b = -0.03$, 95% CI [-0.03, -0.02], $t = -2.03$, $p = 0.024$).Table 2 summarizes the list of models and significant effects (see Tables S1-S2 for complete results of each model; Tables 3.S3-3.S4 show the effects of each nucleus separately for the significant network-level mediation effects).

Table 3.2 – List of mediation models and significant mediation effects

	Model	X	Y	Mediator	p
Within-network connectivity models	1	AGE	DMN	ARAS-DMN	**0.002
	2	AGE	SN	ARAS-SN	0.309
	3	AGE	DAN	ARAS-DAN	0.378
	4	AGE	FPCN	ARAS-FPCN	0.608
Between-network connectivity models	5	AGE	DMN-SN	ARAS-DMN	**0.005
		AGE	DMN-SN	ARAS-SN	0.367
	6	AGE	DMN-DAN	ARAS-DMN	*0.031
		AGE	DMN-DAN	ARAS-DAN	0.455
	7	AGE	DMN-FPCN	ARAS-DMN	0.391
		AGE	DMN-FPCN	ARAS-FPCN	0.296
	8	AGE	SN-DAN	ARAS-SN	*0.024
		AGE	SN-DAN	ARAS-DAN	0.630
	9	AGE	SN-FPCN	ARAS-SN	0.053
		AGE	SN-FPCN	ARAS-FPCN	0.142
	10	AGE	DAN-FPCN	ARAS-DAN	0.769
		AGE	DAN-FPCN	ARAS-FPCN	0.126

Note. ** = significant after FDR correction. * = significant at $p < .05$.

Relationship between ARAS-cortical connectivity and cognitive performance. To determine whether connectivity between the ARAS and association networks relates to cognitive functioning, we ran a canonical correlation analysis to identify relationships between ARAS-association network connectivity and cognitive performance across a range of tasks. The first canonical vector was significant ($r = 0.371$; $p < 0.001$) and identified that higher levels of ARAS-association network connectivity (ARAS-DMN, ARAS-SN, ARAS-DAN, ARAS-FPCN) was associated with better levels of performance in all the cognitive tasks (see Figure 3.4A). To further investigate the relationship between cognitive performance and ARAS connectivity profiles, we conducted a moderation analysis including ARAS connectivity subject scores, age, their interaction term (connectivity subject scores * age), and covariates of no interest (mean connectivity across all ROIs, head motion, vascular health index, mean connectivity within each of the association networks [i.e., DMN, SN, DAN, and FPCN within-network connectivity], and education level) as independent variables and cognitive subject scores as a dependent variable. The results are shown in Table 3.3. The interaction term between connectivity profile and age predicted variance in cognitive performance, ($b = 0.081$, $p = 0.01$), and the direction of the interaction was such that increasing age strengthened the relationship between ARAS connectivity and cognitive performance profiles. It is worth noting that age was a continuous variable in the analysis, although for clarity of illustration in Figure 4B, we divide the cohort into young (18-45 yrs.) middle (45-64 yrs.) and older age groups (65-78 yrs.).

Table 3.3 – Moderation Analysis

Outcome	Predictors	B	Std. Error	t	Sig.
Cognitive Performance Profile	Connectivity Profile	0.123	0.037	3.343	< 0.001
	Age	-0.463	0.045	-10.345	< 0.001
	Connectivity Profile * Age	0.081	0.031	2.593	0.01

Predictors: Connectivity Profile, Age, Cognitive Profile * Age, DMN-DMN, SN-SN, DAN-DAN, FPCN-FPCN, Head Motion, Cardiovascular Health Index, Mean Connectivity

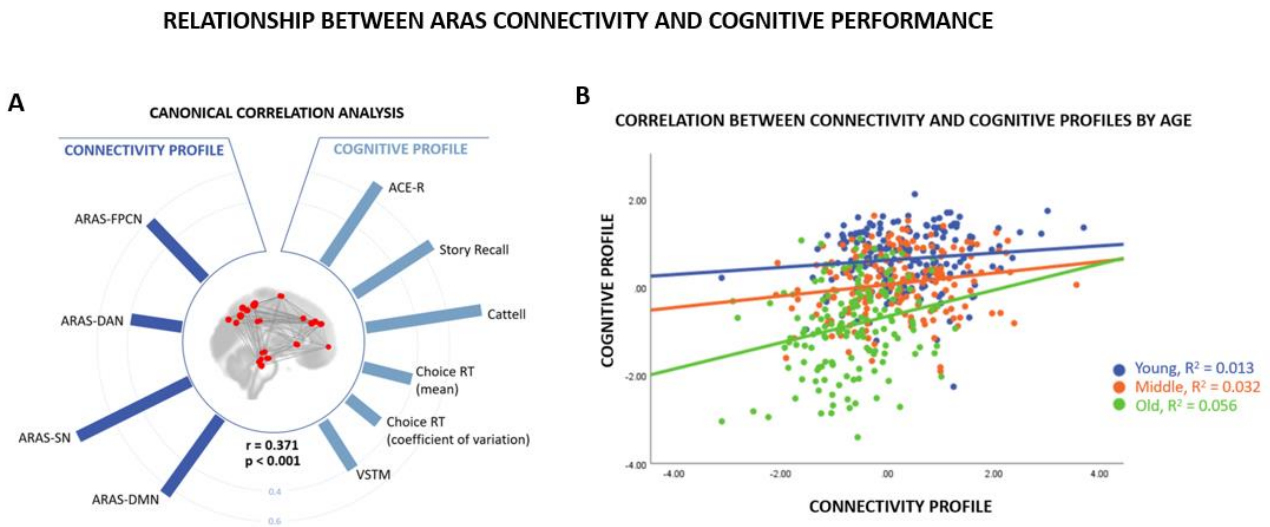

Figure 3.4 – The relationship between ARAS connectivity and cognitive performance. A) Canonical Correlation Analysis (CCA). Heliograph of variate loadings (correlations) for the first canonical variate, where the relative size of the correlations is indicated by the relative length of the bars. The statistical relationship between variables of functional connectivity (connectivity profile) and cognitive performance (cognitive profile) is r = 0.371, p <0.001. The direction of the Choice RT variables is flipped, so that higher scores reflect faster and less variable responding (i.e., better performance). B) The relationship between connectivity and cognitive profiles by age-group. Higher subject loading values indicate stronger expression of the cognitive and connectivity profiles, and the relationship between these is moderated by age (see Table 3.3).

Discussion

The main goals of this study were to 1) characterize functional connectivity patterns of all brainstem arousal system nuclei and age differences therein, 2) test whether age differences in connectivity within and between association networks relate to age differences in ARAS-association network connectivity, and 3) evaluate the relationship between ARAS-cortical connectivity and cognitive performance. Our results show that the ARAS nuclei have positive intrinsic connections, as well as positive and negative connections to the cortex, particularly the default mode and salience networks. In general, aging was associated with reduced ARAS-association network connectivity and, replicating previous work, decreased within-network and increased between-network functional connectivity in the cortex. Additionally, consistent with our predictions, we found that functional connectivity between the arousal system and association networks was significantly associated with age-related differences in connectivity within and between association networks, suggesting that age differences in ARAS functioning may contribute to altered cortical connectivity with age. Finally, we also found that higher connectivity between the ARAS association networks relates to better cognitive performance, and that this relationship is moderate by age.

ARAS Connectivity and the Effects of Aging

Advances in neuroimaging have allowed for the investigation of arousal system functioning in humans and its effects on cortical activity and cognition (Beissner et al., 2014; Sclocco et al., 2018). Previous work has shown that the dopaminergic ventral tegmental area (VTA) and the serotonergic dorsal raphe nucleus (DR) are functionally connected to the default mode network, and that the noradrenergic locus coeruleus is connected to the frontoparietal network (Bär et al., 2016). Here, we characterized functional connectivity of the entire ARAS, showing that ARAS nuclei are positively connected to one another and to nodes of the DMN, SN, DAN, FPCN, language and cerebellar networks. Some ARAS nuclei were negatively correlated with nodes of the SN, DAN, sensorimotor,

visual, language and cerebellar networks. These findings are in line with previous studies showing that ARAS nuclei are widely connected with cortical regions (Bär et al., 2016; Bianciardi et al., 2016; Englot et al., 2017; Parra-Morales et al., 2019). Previous work has shown positive connectivity between the DMN and the ventral tegmental area (VTA), dorsal raphe (DR), media raphe (MR) and periaqueductal grey area (PAG) (Bär et al., 2016; Bianciardi et al., 2016). In addition to these nuclei, we also found positive connectivity between the DMN and the mesencephalic reticular formation (MRF), parabrachial complex (PBC), pontine nucleus oralis (PO), and locus coeruleus (LC). Additionally, our results show positive connectivity between the salience network (SN) and LC and DR, which is similar (though not identical) to previous work showing connectivity between these nuclei and the frontoparietal network (Bär et al., 2016; Bianciardi et al., 2016).

We also examined the effects of age on ARAS connectivity. Within the ARAS itself, we found that some connections increased with age, while others decreased. In contrast, the effect of age on ARAS-cortical connectivity mainly consisted of an increase in negative connections and a reduction in positive connections, which was particularly pronounced for connections to the DMN and SN. Further, the locus coeruleus, periaqueductal gray, and dorsal raphe nucleus appeared to show the strongest age-related decline in connectivity to the cortex, which could reflect age-related physiological disruptions in the noradrenergic and serotonergic neurotransmitter systems (Mather, 2020).

While our aging results largely align with previous work (Bär et al., 2016; Bianciardi et al., 2016b; Englot et al., 2017; Parra-Morales et al., 2019), some differences are apparent. For instance, previous work has found both non-linear and positive effects of age on connectivity between the LC and cortical networks (Jacobs et al., 2018; Zhang et al., 2016), while in our study, we only found a negative effect of age on LC-cortical connectivity. These discrepancies may be due to methodological differences. In our study, we used high-pass filtering and controlled for vascular health, motion, and

mean connectivity across the whole brain. These pre-processing strategies have been shown to lead to more reliable estimates of age-differences in connectivity that are less affected by confounds such as vascular health and head motion (Geerligs et al., 2017), and therefore might be the reason why we found some divergences with previous findings of the literature.

Mediation Effects of the ARAS on Age Differences in Cortical Connectivity

The ARAS plays a critical role in cortical activation (Aston-Jones, 2005; Edlow et al., 2012; Jones, 2003) and shows marked changes with age (Jacobs et al., 2018; Lee et al., 2020; Mather, 2020; Zhang et al., 2016); thus, we hypothesized that age differences in ARAS-association network connectivity may be associated with commonly observed age differences in association network connectivity. We found that decreased ARAS-DMN connectivity with age partly explained the age-related decline in connectivity within the DMN. Age-related declines in DMN connectivity are commonly observed at rest (Grady et al., 2006; Hafkemeijer et al., 2012; Sambataro et al., 2010) and these results suggest that reduced arousal modulation of the DMN may be associated with this decline. Relatedly, several studies have reported that noradrenergic, dopaminergic and serotonergic pharmacological interventions affect DMN connectivity (van den Brink et al., 2019), lending support to the idea that age-related changes in brainstem nuclei functioning may contribute to age differences in DMN connectivity. We also found that decreased ARAS-DMN connectivity with age partly explained age-related differences in DMN-SN connectivity. The salience network is thought to be responsible for processing salient stimuli in the environment and modulating the switch between internally-oriented cognitive processes of the DMN and externally-oriented cognitive processes of the task positive networks (He et al., 2013; Sridharan et al., 2008; Uddin, 2015). Altered connectivity between the ARAS and DMN with age and its impact on DMN-SN connectivity may have knock-on effects, affecting the switch between internally oriented and externally-oriented attention.

Anatomically, the ARAS nuclei have widespread projections to cortical regions, synthesizing

and releasing modulatory neurotransmitters that affect neural activity across the cortex. Many studies have shown that pharmacological interventions on these neurotransmitter systems result in diverse changes in cortical network states, by altering the strength and topography of functional connectivity (van den Brink et al., 2019). Further, dynamic analyses of fMRI data have demonstrated that cortical networks transition between segregated and integrated states within the duration of a typical scan (Shine et al., 2016). Importantly, integrated network states correlate with increases in pupil diameter (a biomarker of arousal), suggesting some role of the ARAS system in cortical connectivity in line with the current results (Shine et al., 2016).

The aging process is associated with structural degeneration and functional disruptions in the arousal system, which is thought to contribute to age differences in circadian and sleep-wake regulation (Mander et al., 2017). However, age-related deterioration of the ARAS is thought to be compensated for by increased levels of some neurotransmitters, which may help older adults maintain sufficient levels of alertness and cognitive functioning (Mather, 2020). As already discussed, pharmacological interventions on these neurotransmitter systems can affect cortical network topology, including measures of network integration (Achard & Bullmore, 2007; Schaefer et al., 2014; Shine et al., 2018; van den Brink et al., 2016). It is possible that age-related compensatory increases in activity of some of the neurotransmitters systems (e.g., noradrenergic and dopaminergic Mather, 2020)) is one of the mechanisms by which aging affects the balance between intra- and inter-network connectivity, though this hypothesis requires further investigation.

Relationship between ARAS-cortical connectivity and cognition

We tested the multivariate association between ARAS-association network connectivity and age-related changes in cognitive performance given that maintaining cortical-wide connectivity is increasingly important for performance in old age (Bethlehem et al., 2020; Tibon et al., 2021; Tsvetanov et al., 2016; Tsvetanov et al., 2021). Overall, higher levels of ARAS-association network

connectivity were associated with better levels of cognition. The ARAS is comprised of a complex set of neurotransmitter pathways that affect brain functioning and influence cognition, and previous research has demonstrated that changes in those neurotransmitter systems impact working and episodic memory, processing of salient stimuli, and executive functions (Briand et al., 2007; Handra et al., 2019; Lobo & Summavielle, 2015). In our study, we found that connectivity between the ARAS and DMN, SN, DAN and FPCN networks is associated with better performance across a range of cognitive tasks largely measuring memory and attention, thereby supporting the hypothesis that in addition to cortical activation, the ARAS might play a role in cognition.

Our findings from the moderation analysis suggested that maintaining youth-like ARAS-association network connectivity becomes progressively more important for maintaining cognitive functioning in old age. This is consistent with previous findings based on neuronal signatures of cortical connectivity from magnetoencephalography data (Bruffaerts et al., 2019; Tibon et al., 2021) or hemodynamic signatures from fMRI BOLD data only after controlling for physiological and vascular confounds (Bethlehem et al., 2020; Geerligs et al., 2017; Tsvetanov et al., 2015). Our study extends findings from previous research by implicating the increasing reliance on ARAS-association network interactivity to sustain cognitive performance with increasing age. We propose that preventative and interventional strategies that target such connectivity, possibly via subcortical neuromodulation systems, will promote the well-being of individuals in old age (e.g., MacInnes et al., 2016).

Final Considerations

In this study we showed the arousal system is functionally connected to widespread cortical regions and mediates age-related differences in cortical networks. However, this study is not without limitations. First, we recognize that our cross-sectional design is not ideal for capturing the true effects of age. Relatedly, significant mediation effects based on cross-sectional data cannot be used to infer causality; thus, our results should be interpreted with caution. Changes in cortical connectivity

associated with age could also be affecting age-related changes in ARAS-cortical connectivity. Another limitation is that the ARAS nuclei are small structures located in regions very susceptible to physiological noise. We included a number of procedures to control for motion and reduce physiological noise, but improved signal definition from these small ARAS nuclei (e.g., by using a high-resolution probabilistic atlas (Ye et al., 2020) may further minimize bias and residual artefacts). Finally, we examined the effects of ARAS connectivity at rest; however, it has been suggested that resting state data provide a very limited picture of age differences in neurocognitive functioning (Campbell & Schacter, 2017). Future studies should evaluate the influence of the ARAS system by integrating data from both resting state and cognitive tasks (Geerligs & Tsvetanov, 2017).

Age differences in cortical connectivity are now well documented, but we still lack a thorough understanding of the mechanisms underlying those differences. Technological and methodological innovations in data acquisition and analysis are allowing for non-invasive studies of ARAS functioning in humans. The results of this study and others suggest that the ARAS might play a critical role in determining age differences in the cortex and cognitive health.

Supplementary Material

Methods

Cognitive tasks used in the canonical correlation analysis relating ARAS-cortical connectivity to cognitive performance.

Addenbrooke's Cognitive Examination-revised (ACE-R): ACE-R (Mioshi et al., 2006) is a brief neuropsychological test that measures general cognitive ability across five domains (attention/orientation, memory, fluency, language, and visuospatial ability). While similar to the Mini-Mental State Exam (MMSE), the ACE-R is more extensive and has been shown to be a more sensitive measure of cognitive ability (Law et al., 2013; Pendlebury et al., 2012; Rittman et al., 2013). In our analysis we used the ACE-R total score, which has a maximum value of 100, and is calculated by the addition of all subtests.

Cattell Culture Fair test of fluid intelligence: Participants completed the standard form of the Cattell Culture Fair, Scale 2 (Cattell, 1971). This paper and pencil test consists of four subtests with different types of nonverbal puzzles: series completion, classification, matrices, and conditions. Before each subtest, instructions and examples are given. Each subtest is timed (3 minutes for the first subtest, 4 minutes for the second, 3 minutes for the third, and 2.5 minutes for the final subtest) although participants are not informed about precise timings beforehand. Correct responses are scored as 1, and the maximum score is 46.

Story Recall: We used the Logical Memory subtest of the Weschler Memory Scale Third UK edition (WMS-III-UK) (Wechsler, 1997). Participants are given an oral presentation of a narrative story followed by a delayed (30 min) recall test. The scoring considers the number of details and general thematic ideas recalled from the story, with a maximum score of 25.

Choice Response Time (RT) Task: The Choice RT task assesses response speed (Trueman et al., 2012). Participants are shown an image of a hand with blank circles above each of the fingers,

while keeping their right hand on a response console with four buttons, one for each finger. When any one of the circles above the fingers becomes black, the participant must press the corresponding finger as quickly as possible (3 seconds RT maximum). On pressing the button (or after 3 seconds), the circle returns to the blank state, and the variable inter-trial interval (ITI) begins. The ITI varies pseudo-randomly (minimum 1.8 seconds, mean 3.7 seconds, and maximum 6.8 seconds). There were 67 trials, and the main outcome is reaction time from stimulus onset to button press. In our study, we used mean RT (averaged across the four fingers - RT values greater than 3 SD from the mean were trimmed) and the coefficient of variation (a common measure of RT variability and one's ability to stay on-task, calculated as SD/mean for each participant) (Hultsch et al., 2008; MacDonald et al., 2008).

Visual Short-term Memory: In this task, participants are shown 1 to 4 colored circular discs to be remembered. After a delay, one of the locations is cued and participants are to report the color of the disc from that location by selecting it from a color wheel with a rainbow of hues (Shafto et al., 2014). On each trial, a central fixation cross and the memory array (set sizes 1 to 4, with the colors chosen at random) were displayed for 250 milliseconds. The locations of the discs on the screen were randomly selected. Following the encoding display, a 900-millisecond blank screen was shown, and then one of the disc locations was highlighted with a border (test display). Participants used a touch screen to indicate the color of the probed item on the color wheel and indicate their confidence in the selected color. Participants had unlimited time to make their response. The task consisted of two blocks of 112 trials each, and estimated parameters include VSTM capacity (K), the accuracy of the reported hues (precision), and the probability of mistakenly reporting an un-cued item. For the current study, we used average capacity (K) across set sizes 3 and 4, as this helped to avoid floor effects in the older group (seen at set size 4) and ceiling effects in the young (seen at set size 3). Set sizes 1 and 2 were too easy and most participants were at ceiling in these conditions.

Results

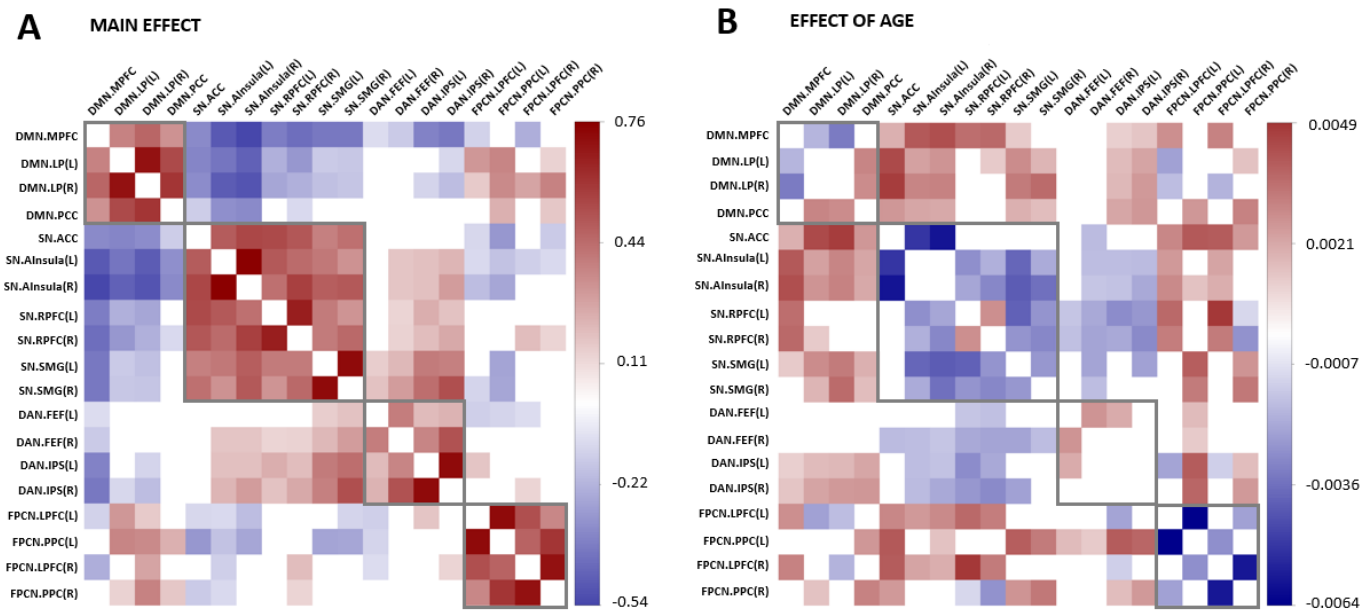

Figure 3.S1 – Functional connectivity of cortical association networks (controlling for mean connectivity across all ROIs, head motion, WM, CSF, 4th ventricle, vascular health index, and education level). Correlation matrices of functional connectivity (Pearson r, p-FDR < 0.05) for A) Main effect and B) Effect of age. Functional modules included in the analysis: default mode network (DMN), salience network (SN), dorsal attention network (DAN), and frontoparietal control network (FPCN).

Table 3.S1 – Results of mediation analysis – Connectivity within networks

MODEL 1		**M1 - ARAS-DMN**						
X	**Y**							
AGE	DMN-DMN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.2	0.05	-3.89	-3.78	-0.24	-0.17	0.000
	Path b1	0.13	0.04	3.33	3.29	0.1	0.15	0.001
	Path c'	0.01	0.05	0.12	0.14	-0.03	0.04	0.886
	Total Effect (c)	-0.02	0.05	-0.38	-0.44	-0.05	0.02	0.662
	Indirect Effect (a1*b1)	-0.03	0.01	-2.54	-3.14	-0.03	-0.02	0.002

MODEL 2		**M1 - ARAS-SN**						
X	**Y**							
AGE	SN-SN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.26	0.05	-5.2	-3.79	-0.29	-0.23	0.000
	Path b1	0.05	0.05	1.15	1.15	0.02	0.09	0.248
	Path c'	-0.29	0.05	-5.62	-3.71	-0.33	-0.26	0.000
	Total Effect (c)	-0.31	0.05	-6.09	-3.7	-0.34	-0.27	0.000
	Indirect Effect (a1*b1)	-0.01	0.01	-1.1	-1.02	-0.02	-0.01	0.309

MODEL 3		**M1 - ARAS-DAN**						
X	**Y**							
AGE	DAN-DAN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.08	0.05	-1.55	-1.52	-0.12	-0.05	0.128
	Path b1	-0.02	0.04	-0.52	-0.47	-0.05	0	0.637
	Path c'	0.12	0.04	2.78	2.76	0.09	0.14	0.006
	Total Effect (c)	0.12	0.04	2.83	2.83	0.09	0.15	0.005
	Indirect Effect (a1*b1)	0	0	0.44	0.88	0	0.01	0.378

MODEL 4		**M1 - ARAS-FPCN**						
X	**Y**							
AGE	FPCN-FPCN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.06	0.05	-1.27	-1.29	-0.1	-0.03	0.196
	Path b1	0.07	0.04	1.52	1.5	0.04	0.09	0.133
	Path c'	-0.29	0.05	-5.82	-3.72	-0.32	-0.25	0.000
	Total Effect (c)	-0.29	0.05	-5.9	-3.7	-0.32	-0.26	0.000
	Indirect Effect (a1*b1)	0	0	-0.85	-0.51	-0.01	0	0.608

Table 3.S2 – Results of mediation analysis – Connectivity between networks

MODEL 5		**M1 - ARAS-DMN**						
X	**Y**	**M2 - ARAS-SN**						
AGE	DMN-SN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.2	0.05	-3.84	-3.76	-0.24	-0.17	0.000
	Path b1	-0.09	0.03	-2.66	-2.76	-0.11	-0.07	0.006
	Path c'	0.24	0.04	5.88	3.63	0.21	0.27	0.000
	Total Effect (c)	0.25	0.04	6.16	3.67	0.22	0.28	0.000
	Indirect Effect (a1*b1)	0.02	0.01	2.09	2.82	0.01	0.03	0.005
	Path a2	-0.26	0.05	-5.23	-3.79	-0.29	-0.23	0.000
	Path b2	0.04	0.04	1.01	1	0.01	0.07	0.317
	Indirect Effect (a2*b2)	-0.01	0.01	-0.97	-0.9	-0.02	0	0.367

MODEL 6		**M1 - ARAS-DMN**						
X	**Y**	**M2 - ARAS-DAN**						
AGE	DMN-DAN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.2	0.05	-3.87	-3.73	-0.24	-0.17	0.000
	Path b1	-0.07	0.03	-2	-1.96	-0.09	-0.04	0.050
	Path c'	0.08	0.04	2.3	2.27	0.06	0.11	0.023
	Total Effect (c)	0.09	0.04	2.63	2.53	0.07	0.12	0.011
	Indirect Effect (a1*b1)	0.01	0.01	1.75	2.16	0.01	0.02	0.031
	Path a2	-0.08	0.05	-1.57	-1.56	-0.12	-0.05	0.118
	Path b2	0.05	0.03	1.47	1.49	0.03	0.07	0.137
	Indirect Effect (a2*b2)	0	0	-0.96	-0.75	-0.01	0	0.455

MODEL 7		**M1 - ARAS-DMN**						
X	**Y**	**M2 - ARAS-FPCN**						
AGE	DMN-FPCN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.21	0.05	-3.89	-3.78	-0.24	-0.17	0.000
	Path b1	-0.04	0.05	-0.79	-0.84	-0.07	0	0.399
	Path c'	0.06	0.05	1.24	1.2	0.03	0.09	0.229
	Total Effect (c)	0.06	0.05	1.23	1.18	0.03	0.09	0.239
	Indirect Effect (a1*b1)	0.01	0.01	0.75	0.86	0	0.02	0.391
	Path a2	-0.06	0.05	-1.25	-1.27	-0.1	-0.03	0.204
	Path b2	0.15	0.05	3.05	2.92	0.11	0.18	0.004
	Indirect Effect (a2*b2)	-0.01	0.01	-1.12	-1.04	-0.02	-0.01	0.296

MODEL 8		M1 - ARAS-SN						
X	Y	M2 - ARAS-DAN						
AGE	SN-DAN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.26	0.05	-5.27	-3.78	-0.29	-0.23	0.000
	Path b1	0.1	0.04	2.29	2.25	0.07	0.13	0.025
	Path c'	-0.18	0.05	-3.53	-3.63	-0.21	-0.14	0.000
	Total Effect (c)	-0.21	0.05	-4.31	-3.86	-0.24	-0.17	0.000
	Indirect Effect (a1*b1)	-0.03	0.01	-2.03	-2.27	-0.03	-0.02	0.024
	Path a2	-0.08	0.05	-1.6	-1.63	-0.12	-0.05	0.103
	Path b2	0.04	0.04	1.07	1.06	0.02	0.07	0.288
	Indirect Effect (a2*b2)	0	0	-0.78	-0.48	-0.01	0	0.630

MODEL 9		M1 - ARAS-SN						
X	Y	M2 - ARAS-FPCN						
AGE	SN-FPCN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.26	0.05	-5.28	-3.8	-0.29	-0.23	0.000
	Path b1	0.09	0.04	2.04	2.07	0.06	0.11	0.038
	Path c'	0.26	0.04	5.92	3.63	0.23	0.29	0.000
	Total Effect (c)	0.24	0.04	5.6	3.65	0.21	0.27	0.000
	Indirect Effect (a1*b1)	-0.02	0.01	-1.89	-1.94	-0.03	-0.02	0.053
	Path a2	-0.06	0.05	-1.24	-1.28	-0.1	-0.03	0.201
	Path b2	-0.08	0.04	-1.95	-1.97	-0.1	-0.05	0.049
	Indirect Effect (a2*b2)	0	0.01	0.98	1.47	0	0.01	0.142

MODEL 10		M1 - ARAS-DAN						
X	Y	M2 - ARAS-FPCN						
AGE	DAN-FPCN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.08	0.05	-1.59	-1.57	-0.12	-0.05	0.117
	Path b1	0.04	0.05	0.9	0.92	0.01	0.08	0.357
	Path c'	0.08	0.05	1.7	1.74	0.05	0.12	0.082
	Total Effect (c)	0.09	0.05	1.76	1.79	0.06	0.12	0.073
	Indirect Effect (a1*b1)	0	0.01	-0.68	-0.29	-0.01	0	0.769
	Path a2	-0.06	0.05	-1.24	-1.21	-0.1	-0.03	0.228
	Path b2	-0.11	0.05	-2.33	-2.31	-0.15	-0.08	0.021
	Indirect Effect (a2*b2)	0.01	0.01	1.02	1.53	0	0.01	0.126

Table 3.S3 – Results of mediation analysis – Connectivity within DMN (Effects of each nucleus)

MODEL 1								
X	**Y**							
AGE	DMN-DMN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
	Path a1	-0.3	0.06	-5.12	-3.75	-0.34	-0.26	0.000
	Path b1	-0.09	0.06	-1.45	-1.49	-0.12	-0.05	0.135
	Path c'	-0.01	0.05	-0.11	-0.14	-0.04	0.03	0.888
	Total Effect (c)	-0.02	0.05	-0.37	-0.38	-0.05	0.02	0.701
	Indirect Effect (a1*b1)	0.03	0.02	1.36	1.56	0.01	0.04	0.118
	Path a2	-0.21	0.05	-4.15	-3.72	-0.24	-0.17	0.000
	Path b2	0.07	0.05	1.38	1.44	0.04	0.11	0.151
	Indirect Effect (a2*b2)	-0.02	0.01	-1.26	-1.19	-0.03	-0.01	0.236
	Path a3	-0.14	0.05	-2.67	-2.69	-0.18	-0.11	0.007
	Path b3	0.03	0.1	0.29	0.3	-0.04	0.1	0.765
	Indirect Effect (a3*b3)	0	0.02	-0.29	-0.16	-0.02	0	0.877
	Path a4	-0.27	0.05	-5.17	-3.71	-0.31	-0.24	0.000
	Path b4	0.02	0.05	0.39	0.33	-0.02	0.05	0.741
	Indirect Effect (a4*b4)	-0.01	0.01	-0.37	-0.42	-0.01	0	0.673
	Path a5	-0.08	0.06	-1.38	-1.38	-0.11	-0.04	0.168
	Path b5	0.02	0.06	0.3	0.31	-0.02	0.06	0.760
	Indirect Effect	0	0.01	-0.24	-0.13	-0.01	0	0.896
	Path a6	-0.1	0.05	-1.84	-1.84	-0.13	-0.06	0.066
	Path b6	0.02	0.11	0.23	0.22	-0.05	0.1	0.822
	Indirect Effect (a6*b6)	0	0.01	-0.16	-0.06	-0.01	0	0.954
	Path a7	0.01	0.05	0.1	0.07	-0.03	0.04	0.941
	Path b7	0	0.05	-0.02	-0.01	-0.04	0.03	0.992
	Indirect Effect (a7*b7)	0	0	0.05	0.07	0	0	0.945
	Path a8	-0.07	0.05	-1.22	-1.21	-0.1	-0.03	0.227
	Path b8	0.08	0.04	1.83	1.84	0.05	0.11	0.066
	Indirect Effect (a8*b8)	-0.01	0.01	-0.92	-0.69	-0.01	0	0.489
	Path a9	-0.18	0.05	-3.4	-3.25	-0.22	-0.15	0.001
	Path b9	0.03	0.05	0.69	0.69	0	0.07	0.492
	Indirect Effect (a9*b9)	-0.01	0.01	-0.65	-0.57	-0.01	0	0.566

Mediators: Connectivity between ARAS nuclei and the Default Mode Network: M1: DR-DMN, M2: MRF-DMN, M3: MR-DMN,M4: PAG-DMN,M5: PBC-DMN,M6: PO-DMN,M7: PPN-DMN,M8: VTA-DMN,M9: LC-DMN. Nuclei of the ARAS: dorsal raphe nucleus (DR), mesencephalic reticular formation (MRF), median raphe nucleus (MR), periaqueductal gray (PAG), parabrachial complex (PBC), pontine nucleus oralis (PO), pedunculopontine tegmental nucleus (PPN), ventral tegmental area (VTA), and locus coeruleus (LC).

Table 3.S4 – Results of mediation analysis – Connectivity between DMN and SN networks (Effects of each nucleus)

MODEL 5								
X	**Y**							
AGE	DMN-SN	**Coeff**	**STE**	**t (~N)**	**Z**	**CI lb**	**CI ub**	**p**
Path a1		-0.3	0.06	-5.19	-3.74	-0.34	-0.26	0.000
Path b1		-0.08	0.05	-1.53	-1.58	-0.11	-0.04	0.115
Path c'		0.21	0.04	4.97	3.72	0.18	0.24	0.000
Total Effect (c)		0.25	0.04	6.16	3.73	0.22	0.28	0.000
Indirect Effect (a1*b1)		0.02	0.02	1.44	1.59	0.01	0.03	0.111
Path a2		-0.21	0.05	-4.14	-3.72	-0.24	-0.18	0.000
Path b2		0.13	0.04	3.06	3.01	0.1	0.16	0.003
Indirect Effect (a2*b2)		-0.03	0.01	-2.45	-2.9	-0.04	-0.02	0.004
Path a3		-0.14	0.05	-2.65	-2.75	-0.18	-0.1	0.006
Path b3		-0.15	0.09	-1.57	-1.54	-0.21	-0.08	0.124
Indirect Effect (a3*b3)		0.02	0.02	1.28	1.85	0.01	0.04	0.064
Path a4		-0.27	0.05	-5.16	-3.74	-0.31	-0.24	0.000
Path b4		-0.13	0.05	-2.83	-2.8	-0.16	-0.1	0.005
Indirect Effect (a4*b4)		0.04	0.01	2.42	3.07	0.03	0.05	0.002
Path a5		-0.08	0.06	-1.38	-1.37	-0.11	-0.04	0.169
Path b5		-0.04	0.05	-0.79	-0.82	-0.08	0	0.414
Indirect Effect (a5*b5)		0	0.01	0.58	1.06	0	0.01	0.287
Path a6		-0.1	0.05	-1.85	-1.85	-0.14	-0.06	0.064
Path b6		0.17	0.1	1.7	1.67	0.1	0.23	0.094
Indirect Effect (a6*b6)		-0.02	0.01	-1.16	-1.06	-0.03	-0.01	0.290
Path a7		0	0.06	0.08	0.1	-0.03	0.04	0.918
Path b7		0.11	0.05	2.03	2.1	0.07	0.14	0.036
Indirect Effect (a7*b7)		0	0.01	0.1	0.2	0	0	0.839
Path a8		-0.07	0.05	-1.24	-1.23	-0.1	-0.03	0.220
Path b8		-0.09	0.04	-2.66	-2.57	-0.12	-0.07	0.010
Indirect Effect (a8*b8)		0.01	0.01	1.06	1.46	0	0.01	0.143
Path a9		-0.18	0.05	-3.48	-3.74	-0.22	-0.15	0.000
Path b9		-0.03	0.05	-0.69	-0.67	-0.07	0	0.505
Indirect Effect (a9*b9)		0.01	0.01	0.65	0.84	0	0.01	0.399
Path a10		-0.26	0.05	-5.24	-3.75	-0.29	-0.23	0.000
Path b10		0.05	0.04	1.1	1.09	0.02	0.08	0.274
Indirect Effect (a10*b10)		-0.01	0.01	-1.06	-1	-0.02	-0.01	0.318

Mediators: Connectivity between ARAS nuclei and the Default Mode Network: M1: DR-DMN, M2: MRF-DMN,M3: MR-DMN,M4: PAG-DMN,M5: PBC-DMN,M6: PO-DMN,M7: PPN-DMN,M8: VTA-DMN,M9: LC-DMN, M10: Connectivity within Salience Network (SN). Nuclei of the ARAS: dorsal raphe nucleus (DR), mesencephalic reticular formation (MRF), median raphe nucleus (MR), periaqueductal gray (PAG), parabrachial complex (PBC), pontine nucleus oralis (PO), pedunculopontine tegmental nucleus (PPN), ventral tegmental area (VTA), and locus coeruleus (LC).

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Chapter 4: Physical activity and sleep quality predict memory function in middle-aged and older adults

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Abstract

Multidomain lifestyle interventions have been shown to preserve cognitive functioning among older adults at increased risk of dementia, nevertheless, more research is still needed to identify the extent to which specific lifestyle factors are associated with brain and cognitive health. In the current study, we investigated the relationship between physical activity, sleep, memory performance, and well-being in middle-aged and older adults (n = 302; age range = 45 - 75 years old). We also assessed the impact of the COVID-19 pandemic on participants' mood and sleep. Our results showed that physical activity was associated with better sleep quality and better working memory performance, whereas sleep quality was associated with working memory and self-perceptions of memory ability. Additionally, we found that the effects of physical activity on working memory were partially mediated by sleep quality, suggesting that physical activity may contribute to improved cognitive performance via improved sleep. The COVID-19 pandemic appeared to affect participants' sleep quality and well-being, and greater stress and sleep disturbances related to the pandemic were negatively associated with physical activity, memory, and mood. In conclusion, our results suggest that lifestyle factors, such as sleep and exercise, are associated with cognitive functioning in healthy middle-aged and older adults. As age-related neurodegenerative diseases become more prevalent within an aging world, multidomain lifestyle interventions may be a cost-effective strategy to delay and/or prevent cognitive impairment in older individuals.

Keywords: *sleep; physical activity; memory; COVID-19 pandemic.*

Introduction

As life expectancy of the world's population increases, neurodegenerative diseases are becoming increasingly widespread, and lifestyle interventions have been explored as key components in preserving brain health and delaying cognitive decline (Toman et al., 2018). Although multidomain lifestyle interventions have been shown to preserve cognitive functioning among older adults, more research is needed to identify the extent to which specific lifestyle factors are associated with brain and cognitive health (Rosenberg et al., 2020).

Sleep is essential for health and well-being throughout the lifespan, and the neural mechanisms involved in sleep-wake regulation are important for optimal cognitive function (Wright et al., 2012). Sleep disturbances and cognitive impairment are common in older adults (Mander et al., 2017). Good sleep health (which is characterized by subjective satisfaction with one's sleep, appropriate timing, adequate duration and high efficiency of sleep, and sustained alertness during waking hours; Buysse, 2014) promotes better cognitive functioning in young and middle-aged adults, serving as a protective factor against subsequent age-related cognitive decline (Scullin and Bliwise, 2015).

Another lifestyle factor that benefits cognition in older adults is physical activity (Gomes-Osman et al., 2018). While previous studies suggest that higher intensity physical activity helps to maintain cognitive function in older age, more information is needed about the relationship between self-reported daily physical activity (including lower intensity activities, such as vacuuming or light yard work) and cognition in older adults (Gomes-Osman et al., 2018). Additionally, physical activity has also been shown to improve sleep quality and well-being in older adults (Bullock et al., 2020), and improved sleep efficiency, which is defined as the percentage of time spent sleeping while in bed, may be one of the pathways by which physical activity benefits neurocognitive function in young and older adults. For instance, Wilckens et al. (2018) showed that sleep efficiency mediated the

relationship between physical activity and executive control tasks, including working memory, in young and older adults (Wilckens, et al., 2018).

Although several studies suggest that good sleep and physical activity relate to better cognitive performance, these effects tend to be most consistent in young adults, and more evidence is needed to support this connection in middle-age and older adults (Scullin & Bliwise, 2015; Stillman et al., 2020). For example, some studies conducted in middle-aged adults linked short sleep duration to poorer executive control, working memory, episodic memory, attention, and frequency of cognitive complaints, while other studies suggest that the association between sleep and cognition weakens as people get older (Scullin & Bliwise, 2015). Further, recent meta-analyses suggest that physical activity in midlife may contribute to the maintenance of cognitive function later in life (Engeroff et al., 2018; Zhidong et al., 2021), including working memory and associative memory which are known to be particularly affected by aging (Matysiak et al., 2019; Nyberg, 2017). Thus, the current study aimed to further investigate the relationship among self-reported physical activity, sleep quality, memory, and well-being in middle-aged and older adults.

We recruited ~300 participants aged 45 to 75 to participate in an online experiment. Working memory was assessed using an operation span task (OSPAN; Oswald et al., 2014; Unsworth et al., 2005) and associative memory was assessed using the Verbal Paired Associates (VPA) subtest from the Wechsler Memory Scale-III (Uttl et al., 2002). Participants also completed the Rapid Assessment of Physical Activity (RAPA) questionnaire (Topolski et al., 2006), the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989), and the Hospital Anxiety and Depression Scale (HADS) to assess levels of anxiety and depression. Finally, since this study was performed in the midst of the COVID-19 pandemic, the impact of the pandemic on participants' mood and sleep was also evaluated.

We hypothesized that higher levels of physical activity would be associated with better sleep quality, better memory performance, and better well-being in middle-aged and older adults. Similarly,

we predicted that better sleep quality would correlate with higher memory performance and well-being. Additionally, we hypothesized that sleep would partially explain the effects of physical activity on cognition. We also expected that increasing age would be associated with poorer sleep quality and lower memory performance. Finally, we anticipated that both middle-aged and older adults would report that the COVID-19 pandemic negatively impacted their mood and sleep quality.

Methods

Participants

Participants were recruited from the online platform Prolific (https://www.prolific.co/). The following eligibility criteria were used: age between 45 and 75 years old, residents of the United Kingdom, English as a first language, and had a Prolific approval rating of 90% or above (meaning that 90% of the time or more they complete experiments will acceptable quality data – i.e., not gibberish or responses that are impossibly fast or slow). Data were collected between December 2020 and February 2021. Of the 317 participants who completed the study, 15 were excluded due to: taking more than twice as long to complete the study than expected (i.e., more than 90 minutes, n = 11) or being outside the specified age range (n = 4). No participants failed the attention check questions, which are described below. Exclusion criteria included self-reported neurological conditions such as epilepsy or head injury, sleep disorders (e.g., sleep apnea, restless legs syndrome), and use of psychoactive medications. The final sample consisted of 302 participants (45–75 years old; mean 59.2; SD 8.3; 150 men and 152 women). This sample size was based on the common heuristic of obtaining at least five observations per variable of interest when performing multiple regression analysis (Hair et al., 2014). The timeslots for participation were posted between 6:00AM-6:00PM GMT. Demographic information of the current sample is provided in Table 4.1. All cognitive tasks and questionnaires were given to participants through the online platform Testable (https://www.testable.org/). Three attention check questions were distributed throughout the tasks to

make sure that participants were paying attention.

Table 4.1 - Participant demographics

Age group	1	2	3	All
n	100	101	101	302
Age range (years)	45-54	55-64	65-75	45-75
Age average	49.7 (2.6)	59.2 (3.0)	68.3 (3.3)	59.2 (8.3)
Sex (male/female)	50/50	50/51	50/51	150/152
Highest education				
Master's / Doctorate	12	16	16	44
Bachelor's Degree	44	36	30	110
High school or equivalent	40	42	50	132
Less than High school	4	7	5	16
Retired (no/yes) *	93/6	69/30	15/86	177/122

*Note. Participants are divided into age groups for descriptive purposes, but all analyses used age as a continuous variable. *Retired data missing for three participants.*

Measures

Physical Activity. The Rapid Assessment of Physical Activity (RAPA) questionnaire was used to determine participants' typical level of physical activity. The RAPA is a self-report questionnaire that has been well validated for use with older adults (Topolski et al., 2006). It assesses one's typical level and intensity (light, moderate and vigorous) of aerobic activity (e.g., "I rarely or never do any physical activities", "I do 20 minutes or more a day of moderate physical activity, etc.), as well as one's typical strength and flexibility activities (e.g., "I do activities to increase muscle strength, such as lifting weights or calisthenics, once a week or more"). In our analyses, we focused on participants' self-reported aerobic activity as previous work has emphasized the importance of aerobic activity in the maintenance of cognitive performance with age (Gomes-Osman et al., 2018). The aerobic RAPA scores range from 1 to 7, and are classified as sedentary (1), under-active (2-3), under-active regular (4-5), and active (6-7).

Sleep Quality. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire (Buysse et al., 1989). The PSQI is a widely used, multidimensional self-report measure

of sleep quality that produces a global sleep quality score, as well as seven components representing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medications, and daytime dysfunction. Participants rate their sleep quality over the past month. We focused on the global sleep score, which is a sum of the seven components. The PSQI global score ranges from 0 to 21, with scores greater than 5 indicative of poor sleep quality.

Paired associate learning. Paired-associate learning (PAL) is often used to assess episodic memory performance, and the Verbal Paired Associates (VPA) subtest from the Wechsler Memory Scale is one of the most widely used tests of PAL (Scorpio et al., 2018). In this task, participants were required to memorize pairs of words (e.g., frog-neck; fruit-apple), which were then tested across three study-test trials. At test, participants were provided with the first word in each pair and asked to recall the response word that went with it. In this study we used the VPA-15, which is an adapted version of the VPA from the Wechsler Memory Scale-III (Uttl et al., 2002). The VPA-15 includes the original eight pairs (four related/easy and four unrelated/difficult) from the VPA- Wechsler Memory Scale-III, plus seven new unrelated/difficult word pairs, making a total of 15 word-pairs in the sequence. In the first encoding phase, each word-pair was presented on screen for 2000ms, followed by a 500ms interstimulus interval (ISI). The test phase immediately followed, in which participants had up to 20 seconds to finish typing their response to each cue word. In the first (PAL1) and second (PAL2) test trials, participants were given another chance to study the word pairs. That is, immediately following the input of their response, the original word-pair was shown again regardless of whether their preceding response was correct or not. The final test trial (PAL3) was given after a ~15 minutes delay (during which participants performed the working memory task, described below). Performance on the PAL task was measured as the total number of correctly recalled responses on each test trial (PAL1, PAL2 and PAL3).

Working Memory. Working memory was assessed using the Operation Span Task (OSPAN,

(Oswald et al., 2014; Unsworth et al., 2005). The OSPAN task is one of the most widely used tasks for measuring working memory capacity and has been shown to have both good reliability and validity (Oswald et al., 2014; Unsworth et al., 2005). In this task, participants were given a series of simple math problems to solve (e.g., (8 / 2) + 9 = ?). Participants pressed a key once they felt they had solved the equation and then a number was shown on the screen. Participants had to indicate whether the number was the correct solution to the math problem or not. After responding to each math problem, participants were given a letter to remember. At the end of each set (which included 4 to 6 math problems to solve and letters to remember), participants were asked to recall the letters in order. A series of boxes were provided on the screen and participants were asked to type the letters in the correct serial position and to leave a blank space if they could not remember the corresponding letter. In total, the task included four trials of set sizes 4 and 6 and two trials of set size 5, making for a total of 50 letters to be recalled. Participants had up to 10 seconds to solve each math problem and up to 3 seconds to answer whether the following number was a correct answer to the operation or not. There was no time limit to answer the sequence of letters. Performance on the OSPAN task was measured by the total number of letters recalled in the correct position. Since the math portion was not speeded, we also took into account percentage correct on the math problems, as well as response time to solve each equation. We computed a composite working memory score by first converting to z-scores the total number of letters recalled, the percentage of math equations correctly solved, and the mean time to solve each math equation, and then averaging these scores for each participant.

Self-perceptions of everyday memory ability. Participants' perceptions of their everyday memory abilities were assessed using the Memory Ability Scale of the Multifactorial Memory Questionnaire (MMQ-Ability) (Troyer & Rich, 2002). The MMQ assesses multiple dimensions of metamemory, and it is focused on memory abilities and strategies that are applicable to everyday life (e.g., remembering names, misplacing belongings) rather than to laboratory situations (e.g.,

remembering word pairs). The MMQ-ability subscale measures one's self-perception of everyday memory ability. Respondents rate how often they experienced 20 common memory mistakes over the previous two weeks (e.g., not recalling the name of someone you just met; forgetting an appointment). Scores range from 0 to 80, and individuals with higher scores on this scale have a better subjective impression of their memory capabilities than those with lower scores.

Mood. The Hospital Anxiety and Depression Scale (HADS) was used to screen for the presence of depression and anxiety (Snaith, 2003). The HADS is a widely used tool for measuring anxiety and depression in both clinical practice and non-clinical research (A. F. Stern, 2014). It includes seven questions related to anxiety and seven related to depression and takes 2–5 min to complete. For both the anxiety and depression scales, scores are classified as 'non-case' (0-7), Mild (8-10), Moderate (11-14), and Severe (15-21).

Impact of COVID-19 on Sleep, Stress, Anxiety and Depression. Finally, we also included a questionnaire to assess the effects of COVID-19 on sleep, stress, anxiety, and depression. For this purpose, we adapted the Stress Symptoms Following September 11th Terrorism Survey (Swenson & Henkel-Johnson, 2003) to assess the impact of the pandemic. It included 5 questions that measure the impact of COVID-19 on: 1) Sleep due to worries related to the pandemic (score range 1-4); 2) Sleep due to bad dreams about the pandemic (score range 1-4); 3) Stress (score range 1-7); 4) Anxiety (score range 1-7); 5) Depression (score range 1-7). As a follow-up analysis, we also compared the sample's PSQI global scores (reflecting sleep quality) with a "normative" (i.e., pre-pandemic) sample from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN - https://www.cam-can.org; Taylor et al., 2017), described further below.

Procedure

Participants first completed a consent form and then a demographics questionnaire in which

they were asked about their age, sex, highest level of education, ethnic origin, marital status, major occupation and if they were retired or not. Then, participants completed the first two trials of the paired associate learning task (PAL1 and PAL2), followed by the operation span task (OSPAN) and finally, the last trial of the paired associate learning task (PAL3). After the cognitive tasks were concluded, participants answered the following sequence of questionnaires: Rapid Assessment of Physical Activity (RAPA), Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS), Impact of COVID-19 on Sleep, Stress, Anxiety and Depression, and the Memory Ability Scale of the Multifactorial Memory Questionnaire (MMQ-Ability).

Data Analysis

Statistical analyses were conducted using IBM SPSS - version 28.0. Pearson correlation analyses were performed to examine the correlations of age, physical activity (RAPA aerobic score), sleep quality (PSQI global score), working memory (composite OSPAN score), associative memory (composite PAL score), and self-perceptions of memory ability (MMQ-Ability score). The level of significance was set at alpha level of $p < 0.05$, and we used the Benjamini–Hochberg correction method for multiple comparisons (Benjamini & Hochberg, 1995)

We followed up on these simple correlations with a series of multiple regression analyses to evaluate the effects of age, physical activity, and sleep quality on working memory, associative learning, and self-perceptions of memory ability. All independent variables were entered into the equation in one step (forced entry). Additionally, we also tested the mediating effect of sleep quality on the relationship between physical activity and memory by using Hayes' Process v3.5 macro in SPSS.

Results

Descriptive Statistics

Means and standard deviations for the physical activity, sleep, and cognitive measures are

provided in Table 4.2, divided by age subgroups for illustrative purposes (age was treated as a continuous variable for all analyses). In terms of physical activity, most participants would be classified as "under-active regular" (M = 4.13 SD = 1.69) according to the metrics of the RAPA (Topolski et al., 2006). Regarding sleep quality, participants' mean global PSQI score was above 5 (M = 6.29 SD = 3.69), indicating that participants were experiencing poor sleep quality on average.

On the OSPAN task, participants remembered an average of 82.94% of the 50 letters in the correct position across trials (M = 41.47, SD = 9.14). Performance on the math portion of the task was also satisfactory, with participants solving 88.17% (SD = 10.61) of the equations correctly in 4.05 seconds (1.26) on average. The mean composite scores per age group are shown in Table 2.

For the paired associate learning task, performance got progressively better across trials (PAL1: M = 5.01, SD = 3.28; PAL2: M = 7.04, SD = 3.61; PAL3: M = 8.43, SD = 3.61). A univariate repeated measures ANOVA using the Greenhouse-Geisser correction indicated there was a significant improvement in PAL scores over trials, $F (1.754, 1021.14) = 318.636$, $p < 0.001$, partial $\eta^2 = .514$. For subsequent analyses, we also created a composite score for the paired associate learning task, as the mean z-score of PAL1 and PAL2 scores (mean composite score per age group is shown in Table 2). PAL3 was not included in the composite score because there was a large degree of variability in the amount of time participants took to complete the OSPAN Task (and hence, a variable delay between PAL2 and PAL3; mean delay = 10.03 minutes, SD = 3.25; MIN = 4.36; MAX = 35.51). Lag time correlated with PAL3 recall ($r = -0.172$, $p = 0.003$) and thus, we decided to exclude this test trial from the PAL composite score (however, it should be noted that including PAL3 in the composite score does not change the conclusions drawn for any of the subsequent analyses).

Finally, on the MMQ – Ability questionnaire, participants' perceptions of their own memory would be classified as "average" (see Table 2) when compared to normative data from the Professional Manual of the Multifactorial Memory Questionnaire (Troyer & Rich, 2002).

Table 4.2 – Mean (SD) physical activity, sleep quality, and cognitive scores

Age group	1 (45-54)	2 (55-64)	3 (65-75)	All
Physical Activity Score (RAPA aerobic)	4.13 (1.77)	4.17 (1.72)	4.08 (1.59)	4.13 (1.69)
Sleep Quality Score (PSQI global)	6.85 (4.04)	6.04 (3.72)	6.00 (3.26)	6.29 (3.69)
Cognitive Scores				
Working Memory - OSPAN	40.16 (10.39)	42.88 (7.32)	41.37 (9.35)	41.47 (9.14)
Working Memory - OSPAN Math - % Correct	88.22 (11.44)	87.82 (11.66)	88.48 (8.56)	88.17 (10.61)
Working Memory - OSPAN RT (seconds per trial)	3.78 (1.17)	4.17 (1.3)	4.19 (1.29)	4.05 (1.26)
Working Memory - OSPAN Composite Score	0.040 (0.695)	-0.005 (0.752)	-0.034 (0.685)	0.000 (0.709)
Episodic Memory - PAL1	4.99 (3.37)	4.99 (3.25)	5.05 (3.24)	5.01 (3.28)
Episodic Memory - PAL2	7.01 (3.82)	6.65 (3.56)	7.47 (3.43)	7.04 (3.61)
Episodic Memory - PAL3	8.64 (3.86)	8.27 (3.62)	8.40 (3.37)	8.43 (3.61)
Episodic Memory - PAL Composite Score	-0.008(0.988)	-0.057 (0.931)	0.065 (0.898)	0.000 (0.938)
Self-perception of memory - MMQ-Ability (Raw Score)	57.39 (15.30)	61.40 (12.03)	59.26 (10.06)	59.35 (12.70)

Note: Standard deviations are provided in parentheses.

Correlation Analysis

Contrary to our predictions, performance on the cognitive measures did not decline significantly with age, though the different metrics of memory were correlated with each other (see Figure 4.1). Also unexpectedly, sleep quality improved with age [r (300) = -0.122, p = 0.034], as indexed by lower scores on the PSQI with increasing age, though it should be noted that this correlation does not survive FDR correction for multiple comparisons. Sleep quality correlated with working memory [r (300) = -0.174, p = 0.002] and self-perceptions of memory ability [r (300) = -0.428, p < 0.001], with poorer sleep quality related to worse working memory performance and poorer perceptions of everyday memory abilities. Physical activity was associated with better sleep quality [r (300) = -0.164, p = 0.004] and better working memory performance [r (300) = 0.188, p = 0.001].

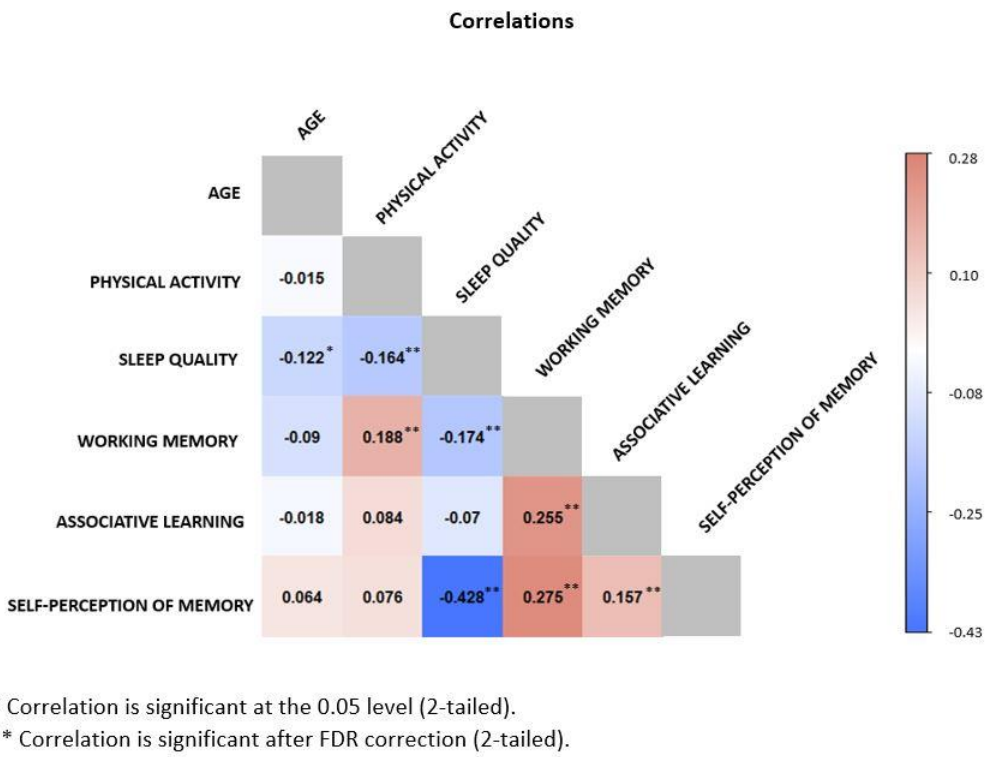


Figure 4.1 – Pearson's correlation coefficients between variables of interest. Physical activity = RAPA Aerobic Score; Sleep Quality = PSQI Global Score; Working Memory = Composite OSPAN Score; Associative Learning – Composite PAL score; Self-perception of memory = MMQ Score-Ability

Regression Analysis

A series of multiple regression analyses were performed to evaluate the predictive effects of age, physical activity, and sleep quality on working memory, associative memory, and self-perceptions of memory (all predictors entered in a single step). We summarize the key findings here (see Table 4.3 for detailed results). The model predicting working memory was significant [R^2 = 0.068, F (3,298) = 7.229, $p < 0.001$]. Physical activity ($\beta = 0.160$, $p = 0.005$) and sleep quality ($\beta = -0.161$, $p = 0.005$) were significant predictors, but age was not ($\beta = -0.107$, $p = 0.161$). The model predicting associative memory was not significant [$R^2 = 0.011$, F (3,298) = 1.104, $p = 0.355$], and there were no significant predictors. The model predicting perceptions of everyday memory ability

(MMQ-Ability) was significant [$R^2 = 0.183$, $F(3,298) = 22.311$, $p < 0.001$], with sleep quality as the only significant predictor ($\beta = -0.425$, $p < 0.001$).

Table 4.3: Regression models on the relationship between age, physical activity, and sleep quality on memory

Model	Outcome	Predictors	Model Summary		Coefficients						
					Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% CI	
			R^2	Sig.	B	Std. Error	Beta			L	U
1	Working Memory	Constant	0.0678	< 0.001	0.460	0.327		1.406	0.161	-0.184	1.104
		Age			-0.009	0.005	-0.107	-1.897	0.059	-0.019	0.000
		Physical Activity			0.067	0.024	0.160	2.825	0.005	0.020	0.114
		Sleep Quality			-0.031	0.011	-0.161	-2.817	0.005	-0.053	-0.009
2	Associative Memory	Constant	0.0108	0.355	0.093	0.446		0.210	0.834	-0.784	0.971
		Age			-0.003	0.007	-0.024	-0.420	0.675	-0.016	0.010
		Physical Activity			0.041	0.032	0.073	1.254	0.211	-0.023	0.104
		Sleep Quality			-0.015	0.015	-0.061	-1.033	0.302	-0.045	0.014
3	Self-Perception of Memory	Constant	0.1834	< 0.001	67.267	5.487		12.260	0.000	56.470	78.065
		Age			0.019	0.081	0.012	0.228	0.820	-0.141	0.178
		Physical Activity			0.050	0.399	0.007	0.125	0.900	-0.735	0.835
		Sleep Quality			-1.464	0.184	-0.425	-7.954	0.000	-1.826	-1.102

Note: The results are the same after controlling for education level

Mediation Analysis

We assessed the mediating effect of sleep on the relationship between physical activity and working memory. Given that working memory was the only significant factor that correlated with both physical activity and sleep, this was the only mediation model evaluated in the study. Our result shows that sleep quality partially mediates the relationship between physical activity and working memory performance (mediation effect: ab = - 0.018, 95% CI [-0.031, -0.040], t = - 2.543, p = 0.012), but the direct effect of physical activity on working memory remains significant after accounting for sleep (c' = - 0.032, 95% CI [-0.002, -0.061], t = - 2.093, p = 0.037).

Impact of the COVID-19 Pandemic

Since this study was run during the COVID-19 pandemic, we conducted some exploratory analyses aimed at assessing the impact of this unprecedented event on sleep quality and levels of stress, anxiety, and depression amongst our participants. Participants' responses to our adapted Stress Symptoms questionnaire are shown in Supplementary Information (Figure 4.SI1; Figure 4.SI2). Some participants reported having trouble sleeping due to worries and bad dreams about the pandemic (46% and 11.3% of participants, respectively, see Figure 4.S1A and 4.SI1B). Moreover, 36.4% and 33.4% of people reported feeling moderate to severe levels of stress and anxiety related to the pandemic (see Figure 4.SI2A and 4.SI2B), while fewer people (25.5%) felt moderate to severely depressed (see Figure 4.SI2C). In terms of differences between age groups, younger participants tended to be more affected than the older ones on all parameters, however, age only played a significant effect on the factor "trouble sleeping because of bad dreams about the pandemic" ($F(2,299) = 7.29$, $p < 0.001$), with this becoming less common with age.

We also found that poor sleep, stress, anxiety, and depression related to the pandemic were associated with poorer performance on our cognitive measures and, as would be expected, worse sleep quality on the PSQI and mood scores on the HADS (see Figure 4.SI3). Interestingly, greater levels of physical activity related to lower levels of pandemic-related stress and sleep disturbances.

Sleep quality relative to a normative sample. As a complementary analysis, we also assessed the impact of the COVID-19 pandemic on sleep quality by contrasting our sample's PSQI global score with that of participants from the Cam-CAN study (Shafto et al., 2014). While we acknowledge that these are different samples, they do share some similarities, in that all participants are from the same country (United Kingdom) and both samples include a similar number of participants within the same age range. The CAM-CAN PSQI data were collected before the pandemic (between 2011-2013), while the current sample was collected during the pandemic (Dec-2020-Feb2021). Comparing

PSQI scores between the two groups, we see that sleep quality was lower in our sample than in the CAM-CAN sample, and that after splitting the sample into corresponding age groups, we observed that this difference is driven by the youngest group (Table 4.4).

Table 4.4: Sleep quality relative to a normative sample

Age Groups	Our sample (During pandemic)			CAM-CAN Sample (Before the pandemic)			t	df	Sig.
	n	Mean	SD	n	Mean	SD			
All	302	6.29	3.69	296	5.08	3.37	-4.20	593.02	< 0.001
Age Group 1 (45-54)	100	6.85	4.04	99	4.58	3.06	-4.48	184.33	< 0.001
Age Group 2 (55-64)	101	6.04	3.72	97	5.24	3.29	-1.61	196.00	0.110
Age Group 3 (65-75)	101	6.00	3.26	100	5.43	3.70	-1.16	199.00	0.248

Since socioeconomic factors, including education level, can be associated with sleep quality (N. P. Patel et al., 2010), it should be noted that the current Prolific sample had slightly higher levels of education (M = 3.46, SD = 0.60) than Cam-CAN participants from the same age range (M = 3.28, SD = 0.97), t (522.2) = 2.68, p = 0.008. Nevertheless, after controlling for education level, we observed the same pattern of results as those shown in Table 4, with the youngest group driving the difference between the two samples.

Discussion

We evaluated the relationships among physical activity, sleep quality, memory, and well-being in middle-aged and older adults, in addition to assessing the impact of the COVID-19 pandemic on participants' well-being and sleep quality. Our results show that participants overall had poor sleep quality and were classified as physically underactive. People who were more active reported better sleep quality and better working memory performance, and better sleep quality was associated with working memory and self-perceptions of memory in everyday life. Additionally, sleep quality partially mediated the relationship between physical activity and working memory performance, suggesting that physical activity may improve cognition via improved sleep. Moreover, the COVID-19 pandemic negatively affected participants' sleep quality and well-being, and greater stress and sleep disturbances related to the pandemic were associated with levels of physical activity, memory, and mood.

As expected, higher levels of physical activity were associated with better sleep quality. This finding corroborates a substantial body of literature that supports the positive relationship between physical activity and sleep (Dolezal et al., 2017). Although our analysis does not allow us to infer causality, several studies have shown that physical activity interventions promote better sleep quality (Dolezal et al., 2017).

Contrary to our predictions, we did not observe an age-related decline in working or

associative memory, but this may have been due to the restricted age range tested here (i.e., we did not include younger adults 18-44) or the relatively high performance of online samples of older adults (Merz et al., 2020). Nevertheless, we found that working memory performance was predicted by both physical activity and sleep quality, and that better self-perceptions of everyday memory abilities were predicted by better sleep quality. Although studies have already demonstrated that better sleepers and more active individuals at middle-age and later life demonstrate better cognitive performance and well-being, this relationship is not as consistent as it is among younger adults (Scullin & Bliwise, 2015). Thus, the current study contributes to the literature by adding evidence of cognitive benefits of being a good sleeper and engaging in physical activity from midlife onwards.

Regarding the effects of physical activity, our findings are in line with recent work with late middle-aged adults showing that those regularly engaged in moderate intensity physical activity demonstrate better working performance than those who only engaged in irregular or low-intensity activities (Chen et al., 2019). Further, several studies show that physical activity increases grey and white matter volume (Koblinsky et al., 2021; Strömmer et al., 2020). Additionally, research also demonstrates that larger volume and higher activation in prefrontal and hippocampal regions are associated with the effects of physical activity on cognitive performance (e.g., executive functions and memory; (Erickson et al., 2011; Stillman et al., 2016). Thus, a growing body of literature suggests that physical activity is beneficially associated with brain and cognitive health.

The positive effects of sleep quality on working memory, executive functions, and episodic memory have also been demonstrated in the literature across the lifespan (Cross et al., 2019; Zavecz et al., 2020). Hence, maintaining good sleep quality may promote better cognitive functioning and protect against age-related cognitive decline.

As predicted, we found that sleep quality mediated the effects of physical activity on working memory. The mediating effect of sleep quality in the relationship between physical activity and

cognitive function had been previously demonstrated (L. Li et al., 2021; Wilckens, Erickson, et al., 2018). Thus, the current results contribute to a growing body of literature suggesting that sleep quality plays an important role in the effects of physical activity on cognitive performance. Preserving the structure and function of the prefrontal cortex is one of the mechanisms by which physical activity is thought to benefit cognitive function (Weinstein et al., 2012). Considering that a healthy prefrontal cortex is essential for the brain to produce efficient slow wave activity (SWA), which in turn, benefits prefrontal functioning itself (and consolidation of hippocampal dependent memory), we speculate that efficient SWA, among other neurological and metabolic processes, is the mechanism by which sleep contributes to the beneficial effects of physical activity on the brain and consequently, cognition.

In our study, we observed no effect of physical activity and sleep on our measure of associative memory. Although physical activity and sleep quality have been positively related to episodic memory in aging (Engeroff et al., 2018; Scullin & Bliwise, 2015), there are inconsistencies across studies. The effects of sleep on cognition tend to be more consistent in young and middle-aged adults and age might be an effect modifier of this association (Scullin & Bliwise, 2015). A period of consolidation between encoding and testing may also be required to see the effects of sleep (Alger et al., 2015; Klinzing et al., 2019; Kurdziel, 2019; Payne et al., 2008). Further, the effects of physical activity vary depending on the nature, intensity, and frequency of the activity (Engeroff et al., 2018). Another potential reason for the lack of such associations in our study is the fact that older adults who participate in online platforms (like Prolific) have been shown to be quite high performing relative to in-lab samples (Merz et al., 2020). Finally, as discussed further below, stress and sleep disturbances caused by the COVID-19 pandemic may have affected the relationship between these factors.

We explored the impact of the COVID-19 pandemic on participants' levels of stress, anxiety, depression, and sleep quality. Overall, some participants reported that the pandemic had some level of impact on these aspects of their lives. Further, our results indicated that poor sleep, stress, anxiety

and depression related to the pandemic were associated with poorer performance on all of our cognitive measures and, worse sleep quality on the PSQI, and poorer mood scores on the HADS. Interestingly, greater levels of physical activity related to lower levels of pandemic-related stress and sleep disturbances. The positive effects of physical exercise on mental health and well-being during the pandemic have also been observed by other researchers, with greater physical activity associated with enhanced happiness, and reduced anxiety, sadness, and depression (Ai et al., 2021).

The negative impact of the COVID-19 pandemic on sleep quality and mental health has also been consistently reported (Jahrami et al., 2021). The prevalence and burden of depressive and anxiety disorders have drastically increased globally (Santomauro et al., 2021). Additionally, longitudinal research has shown that the pandemic has reduced sleep quality in middle-aged and older adults relative to pre-pandemic levels (del Brutto et al., 2021). By contrasting PSQI scores from our sample (collected during the pandemic) with PSQI scores from the Cam-CAN study (collected before the pandemic) we also found that sleep quality was lower in our sample than in the CAM-CAN sample. While comparing two different samples is less ideal than a longitudinal approach, these samples do share some similarities, in that all participants were from the same country and both included a similar number of participants within the same age range (and indeed, our results held up after controlling for group differences in education). Taken together, our results contribute to the growing literature showing that the COVID-19 pandemic has substantially affected sleep quality and well-being worldwide.

Final Considerations

In this study we showed that lifestyle factors, such as sleep and exercise, are associated with cognitive functioning in middle- and older age. However, this study is not without limitations. First, we recognize that our cross-sectional design is not ideal for capturing the effects of causality; thus, our results should be interpreted with caution. Online survey and cognitive task measures might lead to data quality concerns (e.g., lack of attention, "professional" participants who take part in many online studies, etc.). Further, we had to rely on self-report measures of sleep quality and physical activity, which may be less accurate that objective measures taken in person (Wright, 2005). Nevertheless, the current results suggest a link between physical activity, sleep, and cognition in middle-aged and older adults that should be followed up with an in-person, intervention-style study.

As age-related neurodegenerative diseases become more prevalent, multidomain lifestyle interventions could be considered a cost-effective strategy to delay and/or prevent cognitive impairment in older individuals. Future translational studies should evaluate the effects of lifestyle interventions by integrating longitudinal research with clinical services (e.g. Cognitive Behavioral Therapy for insomnia, fitness training programs, etc.) to not only generate scientific knowledge but also potentially bring positive impact in society and people's lives.

Supplementary Information

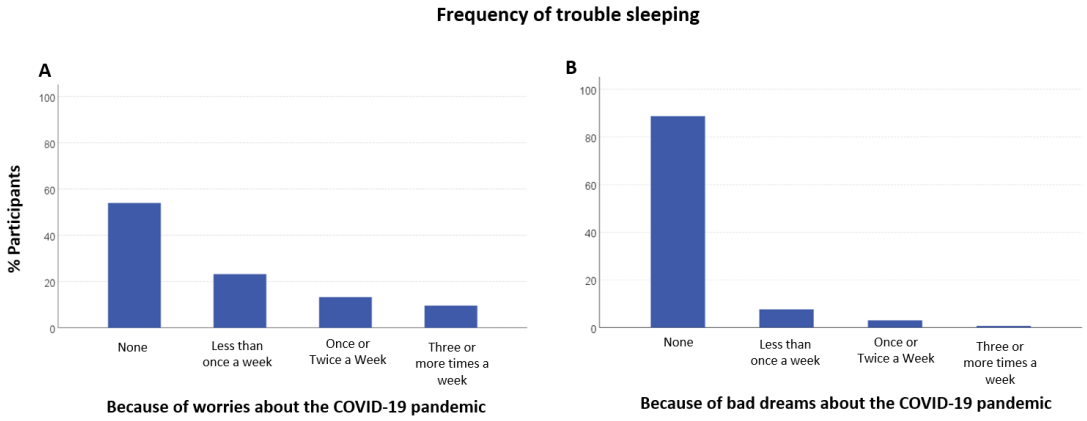


Figure 4.S1 – Percentage of participants reporting frequency of having trouble sleeping because of A) Worries about the COVID-19 pandemic and B) Bad dreams about the COVID-19 pandemic.

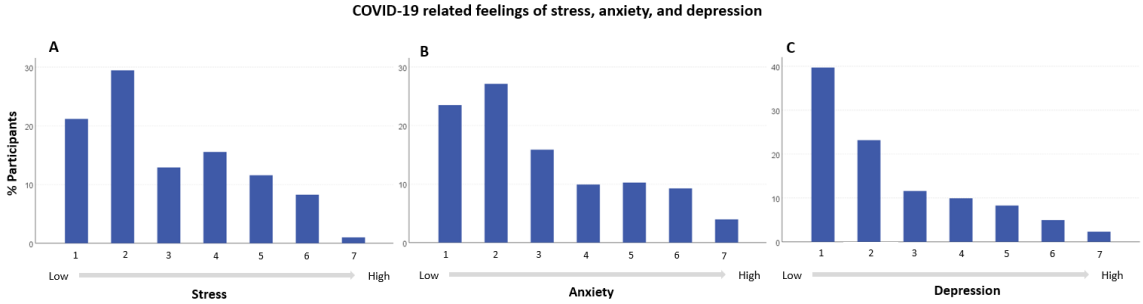
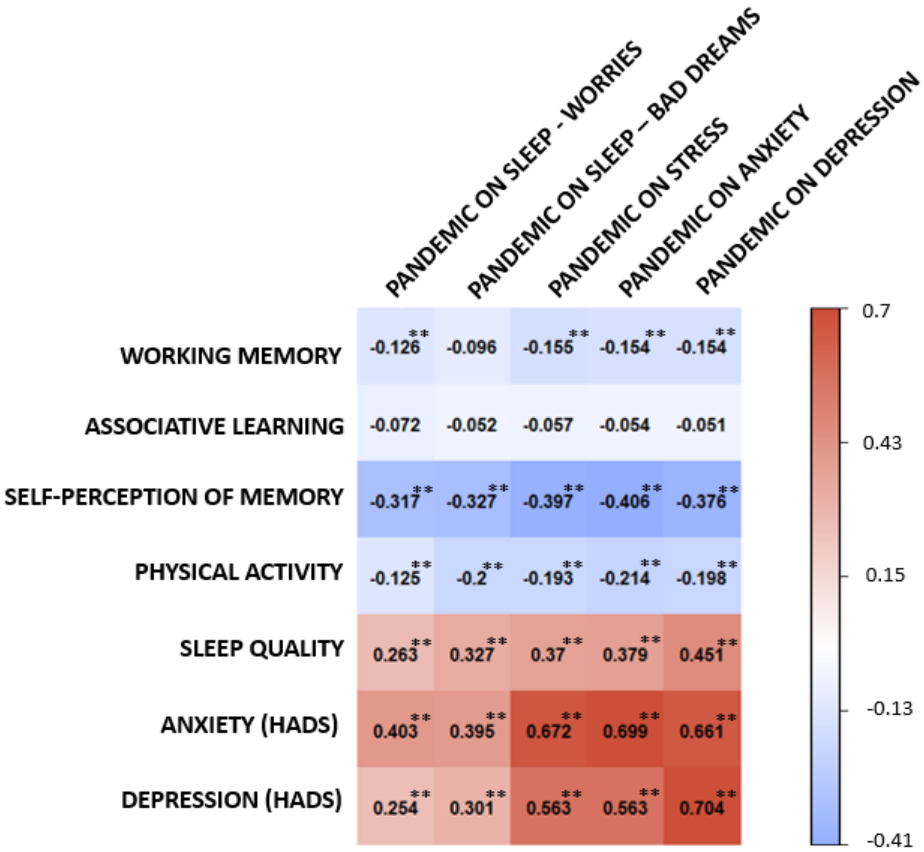


Figure 4.S2 – Percentage of participants reporting each level of A) Stress, B) Anxiety, and C) Depression related to the COVID-19 pandemic.



* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant after FDR correction (2-tailed).

Figure 4.S3 – Pearson's correlation coefficients between variables of interest and impact of COVID-19 pandemic scores. Physical activity = RAPA Aerobic Score; Sleep Quality = PSQI Global Score; Working Memory = Composite score of OSPAN Score, OSPAN Math Percentage Score, and response time of the OSPAN Math Task; Associative Memory – Composite score of PAL1, PAL2 and PAL3; Self-perception of memory = MMQ Score-Ability; HADS = Hospital Anxiety and Depression Scale.

Brock University
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Tel: 905-688-5550 ext. 3035
Email: reb@brocku.ca

Social Science Research Ethics Board

Certificate of Ethics Clearance for Human Participant Research

DATE: 11/24/2020

PRINCIPAL INVESTIGATOR: CAMPBELL, Karen - Psychology

FILE: 20-067 - CAMPBELL

TYPE: Faculty Research STUDENT: Tiago Guardia
SUPERVISOR: Karen Campbell

TITLE: The relationship between physical activity, sleep quality, cognitive performance, and well-being in middle-aged and older adults.

ETHICS CLEARANCE GRANTED

Type of Clearance: NEW Expiry Date: 11/1/2021

The Brock University Social Science Research Ethics Board has reviewed the above named research proposal and considers the procedures, as described by the applicant, to conform to the University's ethical standards and the Tri-Council Policy Statement. Clearance granted from 11/24/2020 to 11/1/2021.

The Tri-Council Policy Statement requires that ongoing research be monitored by, at a minimum, an annual report. Should your project extend beyond the expiry date, you are required to submit a Renewal form before 11/1/2021. Continued clearance is contingent on timely submission of reports.

To comply with the Tri-Council Policy Statement, you must also submit a final report upon completion of your project. All report forms can be found on the Office of Research Ethics web page at: https://brocku.ca/research-at-brock/office-of-research-services/research-ethics-office/#application-forms.

In addition, throughout your research, you must report promptly to the REB:

a) Changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) All adverse and/or unanticipated experiences or events that may have real or potential unfavourable implications for participants;
c) New information that may adversely affect the safety of the participants or the conduct of the study;
d) Any changes in your source of funding or new funding to a previously unfunded project.

We wish you success with your research.

Approved:

Angela Book, Chair
Social Science Research Ethics Board

Dipanjan Chatterjee, Chair
Social Science Research Ethics Board

Note: Brock University is accountable for the research carried out in its own jurisdiction or under its auspices and may refuse certain research even though the REB has found it ethically acceptable.

If research participants are in the care of a health facility, at a school, or other institution or community organization, it is the responsibility of the Principal Investigator to ensure that the ethical guidelines and clearance of those facilities or institutions are obtained and filed with the REB prior to the initiation of research at that site.

Brock University
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Social Science Research Ethics Board

Certificate of Ethics Clearance for Human Participant Research

DATE: January 8, 2021

PRINCIPAL INVESTIGATOR: CAMPBELL, Karen - Psychology

FILE: 20-067 - CAMPBELL

STUDENT: Tiago Guardia

TYPE: Faculty Research SUPERVISOR: Karen Campbell

TITLE: The relationship between physical activity, sleep quality, cognitive performance, and well-being in middle-aged and older adults.

ETHICS CLEARANCE GRANTED

Type of Clearance: MODIFICATION Expiry Date: 11/1/2021

The Brock University Social Sciences Research Ethics Board has reviewed the above named research proposal and considers the procedures, as described by the applicant, to conform to the University's ethical standards and the Tri-Council Policy Statement.

Modification:

e) New recruitment pool (SONA) and compensation (academic credit) added

The Tri-Council Policy Statement requires that ongoing research be monitored by, at a minimum, an annual report. Should your project extend beyond the expiry date, you are required to submit a Renewal form before **11/1/2021**. Continued clearance is contingent on timely submission of reports.

To comply with the Tri-Council Policy Statement, you must also submit a final report upon completion of your project. All report forms can be found on the Office of Research Ethics web page at: https://brocku.ca/research-at-brock/office-of-research-services/research-ethics-office/#application-forms

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d) Any changes in your source of funding or new funding to a previously unfunded project.

We wish you success with your research.

Approved: 

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Social Science Research Ethics Board

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Social Science Research Ethics Board

Certificate of Ethics Clearance for Human Participant Research

DATE: 9/19/2022

PRINCIPAL INVESTIGATOR: CAMPBELL, Karen - Psychology

FILE: 20-067 - CAMPBELL

TYPE: Faculty Research

TITLE: The relationship between physical activity, sleep quality, cognitive performance, and well- being in middle-aged and older adults.

ETHICS CLEARANCE GRANTED

Initial Clearance Date: 11/24/2020

Type of Clearance: RENEWAL

Expiry Date: 9/1/2023

The Brock University Social Science Research Ethics Board has reviewed the above named research proposal and considers the procedures, as described by the applicant, to conform to the University's ethical standards and the Tri-Council Policy Statement.

Renewed certificate valid from **9/19/2022 to 9/1/2023**.

The Tri-Council Policy Statement requires that ongoing research be monitored by, at a minimum, an annual report. Should your project extend beyond the expiry date, you are required to submit a Renewal form before **9/1/2023**. Continued clearance is contingent on timely submission of reports.

To comply with the Tri-Council Policy Statement, you must also submit a final report upon completion of your project. All report forms can be found on the Office of Research Ethics web page at: https://brocku.ca/research-at-brock/office-of-research-services/research-ethics-office/#application-forms

In addition, throughout your research, you must report promptly to the REB:

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b) All adverse and/or unanticipated experiences or events that may have real or potential unfavourable implications for participants;
c) New information that may adversely affect the safety of the participants or the conduct of the study;
d) Any changes in your source of funding or new funding to a previously unfunded project. We

wish you success with yourresearch.

Approved:

Nicole Luke, Chair
Social Science Research Ethics Board

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Chapter 5: General Discussion

The overall goal of this thesis was to evaluate age-related differences in brain structure and functional connectivity to further our understanding of the neural mechanisms involved in age-related declines in cognition. This thesis also aimed to investigate the influence of lifestyle factors on age differences in cognition, and in that regard, I focused on the effects of sleep quality and physical activity on memory. Across three studies, I found that aging is associated with decreased grey matter volume and alterations in whole-brain functional connectivity, which in turn are associated with reduced cognitive performance. Moreover, I showed that better sleep quality and higher levels of physical activity are associated with better memory performance in middle-age and older adults.

In Study 1, I assessed the impact of aging on grey matter volume of the MTL and PFC, and my findings emphasize the critical role of the frontal lobes, and the control processes they subserve, in determining the detrimental effects of age on memory. I showed that aging is associated with grey matter volume loss in substructures of both the MTL and PFC, and that structures of the PFC alone predicted memory performance better than either structures of the MTL alone or PFC and MTL combined. Additionally, I observed that the relationship between frontal grey matter volume and memory was not moderated by age or sex, suggesting that greater volume in PFC structures relates to better memory performance across the lifespan and in both sexes.

In Study 2, I assessed the effects of age on functional brain networks. Given the essential role of the arousal system (ARAS) in cortical activation and previous findings of disrupted ARAS functioning with age, I investigated the hypothesis that age-related changes in ARAS-cortical functional connectivity may contribute to commonly observed age-related differences in cortical connectivity. Our findings showed that the arousal system is functionally connected to widespread cortical regions and that it mediates age-related differences in connectivity within and between cortical networks. Moreover, connectivity between the ARAS and cortical association networks

predicted cognitive performance across several tasks over and above the effects of age and connectivity within the cortical networks themselves. These findings suggest that age differences in functional connectivity within the cortex may be driven by age-related changes in the brainstem and these altered connectivity patterns have important implications for cognitive health.

In Study 3, I investigated the relationship between sleep quality, physical activity, and memory in middle-age and older adults, in addition to assessing the impact of the COVID-19 pandemic on participants' mood and sleep quality. Our results showed that people who were more active reported better sleep quality and showed better working memory performance, and better sleep quality was associated with working memory and self-perceptions of memory in everyday life. Moreover, our findings also showed that some of the beneficial effects of physical activity on cognition are partially mediated by improved sleep. Additionally, this study indicated that the COVID-19 pandemic had a deleterious effect on people's sleep quality and overall well-being.

Taken together, these studies suggest that aging is associated with disruptive effects on brain structure and function, and that these changes are associated with age-related cognitive decline. Additionally, our study supported the association between lifestyle factors, more specifically, sleep quality and physical activity, and cognitive performance during aging.

Age-related episodic memory decline is predicted by grey matter volume in the PFC

The association between aging and brain volume loss has been consistently demonstrated in the literature through a large body of cross-sectional and longitudinal studies (Lockhart & DeCarli, 2014; Raz et al., 2010). Global shrinkage of grey and white matter volume is one of the main hallmarks of an aging brain, with the frontal lobes showing the greatest declines, followed by the temporal lobes, and the parietal and occipital lobes (Lockhart & DeCarli, 2014; Raz et al., 2005, 2010). Healthy aging is also commonly accompanied by impairments in multiple cognitive functions (Glisky, 2007; Grady, 2012; Park & Reuter-Lorenz, 2009), and among them, episodic memory is, in

general, the ability that shows the largest degree of age-related decline (Nyberg et al., 2012; Wang & Cabeza, 2016). Although age-related grey-matter volume loss has been associated with both age-related decline and inter-individual differences in episodic memory, most structural studies have focused on the relationship between a small number of brain regions (e.g., hippocampus, entorhinal cortex) and memory (Becker et al., 2015; Carr et al., 2017; DeMaster et al., 2014; Grady & Ryan, 2017; Nilssen et al., 2019; Poppenk & Moscovitch, 2011; Rajah et al., 2010; Schlichting et al., 2017; Yeung et al., 2019).

In Study 1, I assessed the joint contributions of several subregions within the MTL and PFC to episodic memory performance across the lifespan. Our findings demonstrated that grey matter volume of the PFC alone predicted memory performance better than either volume of the MTL alone or the PFC and MTL combined. This result is supported by recent publications showing that grey matter volume in the PFC is a better predictor of individual differences in associative memory functioning than grey-matter volume in MTL regions (Becker et al., 2015; Brehmer et al., 2020), though these studies were based on older adults alone, rather than a lifespan sample. Our findings and those of these previous studies, which emphasized the role of the lateral PFC in associative memory in older adults (Becker et al., 2015; Brehmer et al., 2020), support the idea that age differences in cognitive control are a primary contributor to impairments in episodic memory (Campbell et al., 2010; Cohn et al., 2008). Age-related loss of grey matter volume in the PFC, along with functional changes, likely contributes to impaired cognitive control with age, including selective attention and inhibitory control, which in turn may affect long-term memory (Zanto & Gazzaley, 2019).

A second goal of Study 1 was to examine sex differences in the effects of age on memory, brain structure, and the relationship between them. As expected, age was largely associated with a

decrease in episodic memory performance in both men and women (Duarte & Dulas, 2020). However, our results showed that the age-related decline in associative memory was steeper in men. This result is supported by the literature on sex differences in episodic memory, which indicates that women usually outperform men on tasks that require verbal processing (Asperholm et al., 2019). Sex differences in the rate of age-related decline in episodic memory have also been attributed to sex difference in hippocampal volume (Zheng et al., 2017); however, in our study, we did not observe sex differences in either the relationship between age and grey matter volume or the relationship between grey matter volume and memory performance. Perhaps our finding of an age x sex interaction in predicting associative memory was due to some other factor, such as functional and hormonal differences between men and women (J. Li et al., 2022; Subramaniapillai et al., 2022). Clearly more work is needed to determine how neurocognitive aging differs between the sexes.

The mediating effect of the ascending reticular activating system on age-related differences in cortical functional connectivity and cognitive performance

Across the lifespan, several changes are observed in the brain´s global functional network organization, including alterations to connectivity within cortical brain networks, as well as in the dynamic interactions between them (Damoiseaux, 2017; Edde et al., 2021; Geerligs et al., 2014; Liem et al., 2019; Spreng & Turner, 2019). Middle age is considered a turning point at which the developmental trajectory becomes inverted, with a decrease in network segregation and an increase in between network connectivity with increasing age. This results in a more diffuse connectivity pattern, in which brain networks become less specific and more integrated with one another (Chan et al., 2014; Edde et al., 2021; Geerligs et al., 2014). This age-related decline in network segregation is particularly pronounced amongst association networks, and although this effect has been well documented by the literature, there is still a lack of thorough understanding of the mechanisms underlying this shifting balance between intra- and inter-network connections.

In Study 2, I demonstrated that the arousal system is functionally connected to widespread cortical regions and that age-related differences in ARAS-cortical connectivity mediated some of the age-related decline in cortical network segregation. Additionally, our results show that connectivity between the ARAS and association networks predicted cognitive performance across several tasks over and above the effects of age and connectivity within the cortical networks themselves. The ARAS is composed of a complex set of neurotransmitter pathways that continuously interact with and modulate one another on route to the cortex, affecting brain functioning and influencing many aspects of cognition (Briand et al., 2007; Handra et al., 2019; Lobo & Summavielle, 2015). Recent functional neuroimaging studies have also started to characterize the connectivity of brainstem nuclei and to investigate age differences therein (Jacobs et al., 2018; Serra et al., 2018; Zhang et al., 2016). Our results are in line with previous studies showing that ARAS nuclei are widely connected with cortical regions (Bär et al., 2016; Bianciardi et al., 2016b; Englot et al., 2017; Parra-Morales et al., 2019); however, no study to date had examined age differences in functional connectivity across the entire ARAS and determined its relationship to cortical connectivity. Thus, our findings contribute to the neuroscience of aging literature by suggesting that age differences in cortical connectivity may be driven, at least in part, by altered arousal signals from the brainstem and that ARAS-cortical connectivity relates to cognitive performance with age.

Sleep quality, physical activity, and cognitive performance during aging

Over the last few decades, lifestyle interventions have been increasingly explored as key components in preserving brain health and delaying cognitive decline (Toman et al., 2018). Although multidomain lifestyle interventions have been shown to preserve cognitive functioning among older adults, more research is needed to identify the extent to which specific lifestyle factors are associated with brain and cognitive health (Rosenberg et al., 2020). In Study 3, I investigated the relationship between physical activity, sleep, memory performance, and well-being in middle-aged and older

adults.

We found that participants who were more physically active reported better sleep quality and better working memory performance, and better sleep quality was associated with working memory and self-perceptions of memory in everyday life. Our findings are supported by and corroborate a substantial body of literature that indicates the positive relationship between physical activity and sleep (Dolezal et al., 2017). Although our cross-sectional analysis does not allow us to infer causality, several studies have shown that physical activity interventions promote better sleep quality (Dolezal et al., 2017). The bidirectional relationship between sleep quality and physical activity has been investigated, and although good sleep is also considered a key factor in whether people initiate and/or maintain physical activity, more research is still required to support the effects of sleep quality on levels on physical activity (Kline, 2014). As stated above, our results showed that working memory performance was predicted by both physical activity and sleep quality, and that better self-perceptions of everyday memory abilities were also predicted by better sleep quality. Previous studies have already demonstrated that better sleep quality and an active lifestyle tend to be associated with better cognitive performance and well-being in middle aged and older adults; nevertheless, this relationship in older adults is not as consistent as it is in younger adults (Scullin & Bliwise, 2015). Thus, the results from Study 3 contribute to the literature by providing evidence of the cognitive benefits of being a good sleeper and engaging in physical activity from midlife onwards.

Study 3 also demonstrated that sleep quality partially mediates the effects of physical activity on working memory. The mediating effect of sleep quality in the relationship between physical activity and cognitive function has been shown previously (Li et al., 2021; Wilckens, et al., 2018), and our results contribute to this growing body of literature suggesting that sleep quality may serve as a mechanism through which physical activity improves cognitive performance. Preserving the structure and function of the prefrontal cortex is also one of the mechanisms by which physical

activity is thought to benefit cognitive function (Weinstein et al., 2012), and this may also contribute to improved sleep since the prefrontal cortex plays an essential role in the production of slow wave activity (SWA) (Mander et al., 2013). I speculate that supporting efficient SWA, among other neurological and metabolic processes, is the mechanism by which physical activity contributes to improved sleep and consequently, cognitive performance.

The impact of the COVID-19 pandemic

Study 3 was conducted in the middle of the COVID-19 pandemic, and in an exploratory analysis, I investigated the impact of this global health challenge on participants' levels of stress, anxiety, depression, and sleep quality. Overall, our results are in line with the growing body of work showing that the COVID-19 pandemic has had deleterious effects on sleep quality and well-being worldwide (Jahrami et al., 2021; Santomauro et al., 2021). For instance, the prevalence and burden of sleep problems, and depressive and anxiety disorders have drastically increased around the world since the start of the COVID-19 pandemic, as indexed by studies with pre- and post-pandemic measures of sleep quality and mental health (Jahrami et al., 2021; Santomauro et al., 2021). Our results indicated that poor sleep, stress, anxiety, and depression related to the pandemic were also associated with poorer performance on both subjective and objective memory measures, in line with both people's perceptions of pandemic-related "brain fog" that have also been supported by empirical findings (e.g., Brusaferri et al., 2022). Moreover, greater levels of physical activity related to lower levels of pandemic-related stress and sleep disturbances. Interestingly, the positive effects of physical exercise on mental health and well-being during the pandemic have also been observed by other researchers, with greater physical activity associated with enhanced happiness, and reduced anxiety, sadness, and depression (Ai et al., 2021).

Future directions

It is becoming increasingly important to link scientific research to pressing societal issues,

and to maximize the impact of research findings through effective application of translational science, knowledge mobilization, and implementation practices (Randall, 2020). As life expectancy of the world's population increases, age-related cognitive decline will affect more people worldwide, and neurodegenerative diseases will become more widespread. Science-based strategies to prevent or minimize the negative effects of age on brain health and cognition are becoming increasingly necessary (Giovannoni et al., 2019). In response to this massive need for solutions to age-related cognitive decline and dementia, recent large-scale longitudinal studies are currently underway to deepen our understanding of how modifiable lifestyle factors can be applied to reduce cognitive decline and minimize the risk of dementia (Rosenberg et al., 2020). Despite very promising results demonstrating lifestyle interventions that support brain health and delay cognitive decline, the development of specific recommendations and therapeutic protocols to prevent, slow, or even reverse cognitive decline in older adults still requires further research (Giovannoni et al., 2019; Olanrewaju et al., 2015; Rakesh et al., 2017; Rosenberg et al., 2020). Future longitudinal studies dedicated to finding non-pharmacological solutions to age-related cognitive decline should consider several main guiding principles including feasibility, potential for widespread implementation at individual, household, and community levels, and sustainability, in addition to using multi-intervention approaches (Olanrewaju et al., 2015).

Obviously, experimental neurocognitive studies remain critical for understanding the mechanisms underlying any successful interventions, and these will no doubt evolve as new technologies become available. Portable wireless neuroimaging equipment and biomarker wearable devices (e.g., wrist bands, head bands, smart watches, skin patches, etc.) are becoming more precise and affordable, thus allowing new research designs to investigate the effects of aging on human neurocognitive functions and the impact of behavioral, lifestyle or cognitive interventions as they occur in natural settings (Arvan et al., 2020; Clark et al., 2020; Dunås et al., 2021; Elenko et al., 2015;

Huppert et al., 2017; Saikia, 2019; Soto et al., 2018; Yaqub et al., 2020). Further, as knowledge mobilization practices become a standard in the field of scientific research, the number of collaborations between basic and applied researchers will hopefully increase, thus accelerating the translation of scientific findings into evidence-based approaches to support cognitive longevity during the aging process (Alnajjar et al., 2019; Callahan et al., 2014; Hertzog et al., 2021; Randall, 2020; Turin et al., 2020). As it is not enough to show which factors contribute to healthy neurocognitive aging – this information needs to be disseminated to the public so theory can be put into practice in support of improving life.

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