Understanding cognitive ageing

From unraveling inter-individual variability in cognitive functioning to advancing research

Michelle G. Jansen

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Understanding cognitive ageing

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by

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in Arnhem

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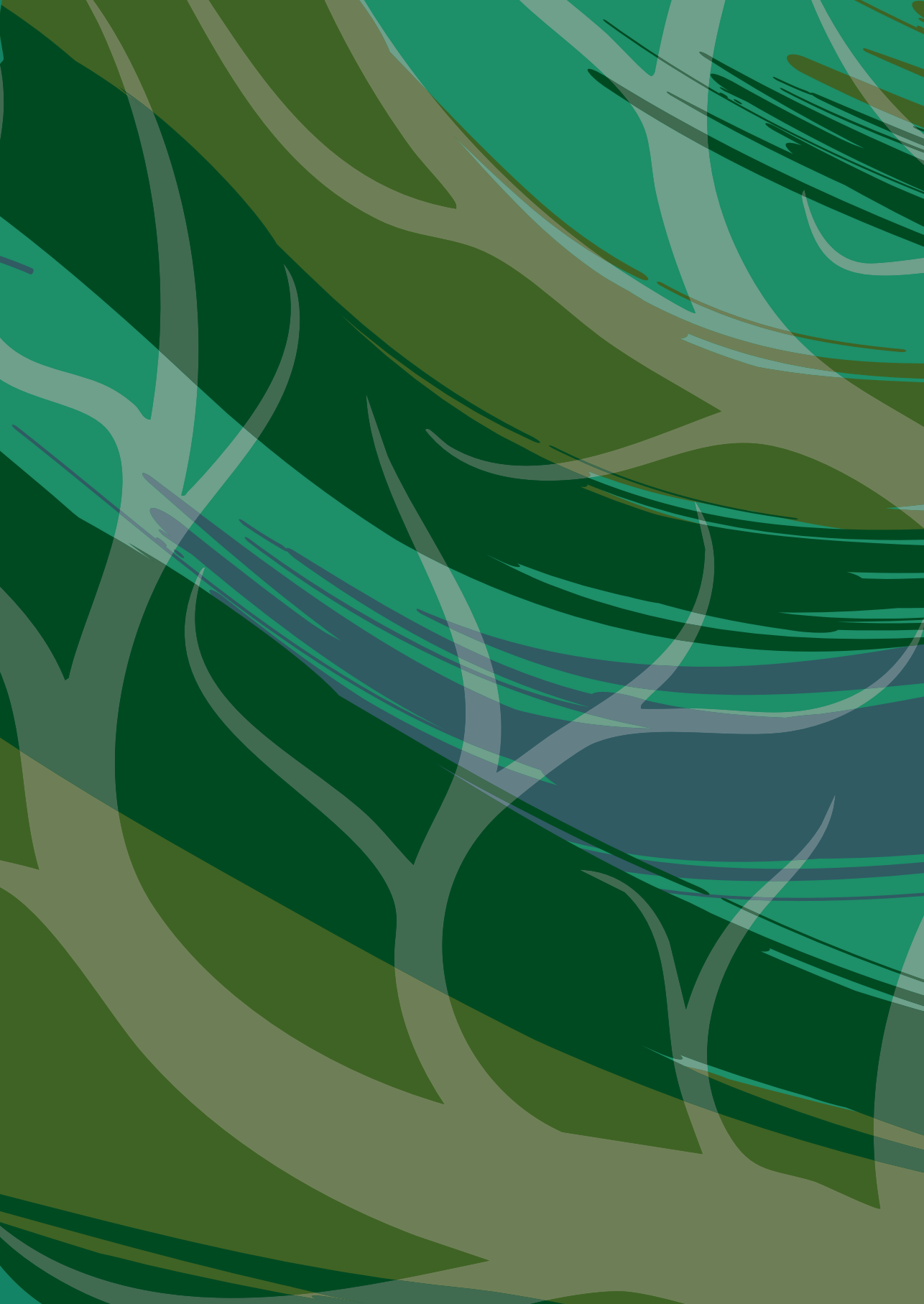
"In nature, nothing is perfect and everything is perfect.
Trees can be contorted, bent in weird ways, and they're still beautiful."

- Alice Walker



Introduction

Chapter 1

General introduction

When you think of healthy ageing, what comes to mind? Perhaps you envision your 83-year-old neighbour, who cycles to the nearby village every day to collect groceries, chatting with every person along the way. Or maybe you recall the 79-year-old bed-and-breakfast owner you once met, who not only had a successful business but also continued to make her garden flourish every year. The World Health Organization defines healthy ageing as: "the process of developing and maintaining the functional ability that enables well-being in older age" (World Health Organization [WHO], 2015, p. 28). This definition highlights healthy ageing as an active process that is more than merely the absence of disease. It is about the capacities that enable us to engage with life in a meaningful and fulfilling way – from spending quality time with your loved ones to enjoying your favourite meal or simply remaining curious about the world around you.

The ageing population is increasing globally (Crimmins, 2015; Lutz et al., 2008). This is not only due to the increased life expectancy, resulting from healthcare advancements and improved living conditions, but also because of a demographic shift in many countries where the proportion of elderly individuals within the total population is growing. According to Statistics Netherlands (CBS, 2024), the proportion of individuals with the age of 65 or older in the Netherlands, relative to those of working age, is predicted to rise from 34.9% in 2024 to 44.4% in 2050. Additionally, within this older population, the number of individuals with the age of 80 or older is expected to further increase, also referred to as double ageing. However, the extent to which our lives are spent in good health has not kept pace with these developments (Crimmins, 2015). The prevalence of ageing-related conditions will continue to rise, as well as its corresponding socioeconomic burden (Partridge et al., 2018; Rudnicka et al., 2020; Sander et al., 2015). These developments emphasize the need to unravel the building blocks of healthy ageing.

Variability in cognitive functions as a window of opportunity

An important facet of healthy ageing involves the maintenance of cognitive functions, as this is crucial for sustaining functional independence and a good quality of life (Depp & Jeste, 2006; Martin et al., 2014; Rowe & Kahn, 1997). Therefore, it is not surprising that cognitive functioning is often the most important outcome measure in interventions and prevention strategies aimed at promoting healthy ageing, as well as in clinical trials targeting

neurodegenerative diseases such as Alzheimer's disease (Christian Haass & Dennis Selkoe, 2022; Kivipelto et al., 2020; Kozauer & Katz, 2013).

The severity of cognitive decline occurs on a continuum, ranging from normal ageing-related changes to subjective cognitive decline and cognitive impairments associated with pathological ageing (Jack et al., 2018). Normal ageing is typically accompanied by a decline in several cognitive domains, predominantly processing speed, as well as executive functions and episodic memory (Harada et al., 2013; Salthouse, 2010; Salthouse, 2019). While there is no clear consensus on when ageing-related decline precisely starts for each of these domains, it is generally recognized that this process accelerates after approximately the age of 60 (Eikelboom et al., 2020). In contrast, other cognitive abilities, such as vocabulary and general knowledge, are relatively preserved in older age (Harada et al., 2013; Nyberg et al., 2020; Salthouse, 2019).

Experiencing cognitive impairments is one of the most expressed fears of older age, particularly the loss of memory (Laditka et al., 2011; Werner et al., 2021). From a clinical perspective, cognitive impairments are reflected by cognitive performance falling below the age- and education-expected norm, ranging from mild cognitive impairment (MCI) to dementia (Jack et al., 2018). While both MCI and dementia are characterized by cognitive deficits, in dementia these impairments substantially hinder day-to-day functioning, typically progressively worsen over time, and often span multiple cognitive domains (Arvanitakis et al., 2019; McKhann et al., 2011). The most frequent causes of dementia include Alzheimer's disease and cerebrovascular disease, with older age being the primary risk factor of these conditions (Arvanitakis et al., 2019; Kapasi et al., 2017; Schneider et al., 2009). Notably, subjective cognitive decline (SCD), which refers to the self-perceived decline of cognitive abilities despite having no objective cognitive impairments, also profoundly affects quality of life (Jessen et al., 2014; Mol et al., 2007), and is a risk factor for further cognitive decline and dementia (Kang et al., 2024; Koppara et al., 2015; Slot et al., 2019).

However, there is a large heterogeneity in cognitive functioning across the whole continuum of cognitive decline (Baker et al., 2017; Mungas et al., 2010; Nyberg et al., 2020). Individuals vary in their overall cognitive abilities across the lifespan (Figure 1A), the rate at which cognitive decline progresses (Figure 1B), or both (Tucker-Drob, 2019; Walhovd et al., 2023). This first source of variability, where individuals vary in their overall cognitive ability, results in different intercepts and is also referred to as *preserved differentiation,* whereas

the second source, the rate at which cognitive decline progresses, corresponds to differences in slopes and is termed as *differential preservation* (Salthouse, 2006). The extent to which specific cognitive domains are affected markedly differs from person to person, including better-than-expected performance in some cases (MacAulay et al., 2018; Salthouse & Soubelet, 2014). For example, the term "*superagers*" describes individuals of 80 years and older with episodic memory performance comparable to – or even better than – 50 to 65-year-olds (de Godoy et al., 2021; Harrison et al., 2012). Similarly, individuals of 60 years and older with processing speed that closely aligns to that of young adults have been referred to as "*resilient-agers*" (Bott et al., 2017). These observations not only underscore the heterogeneous nature of cognitive performance, but also illustrate that high levels of cognitive functioning can be preserved in old age.

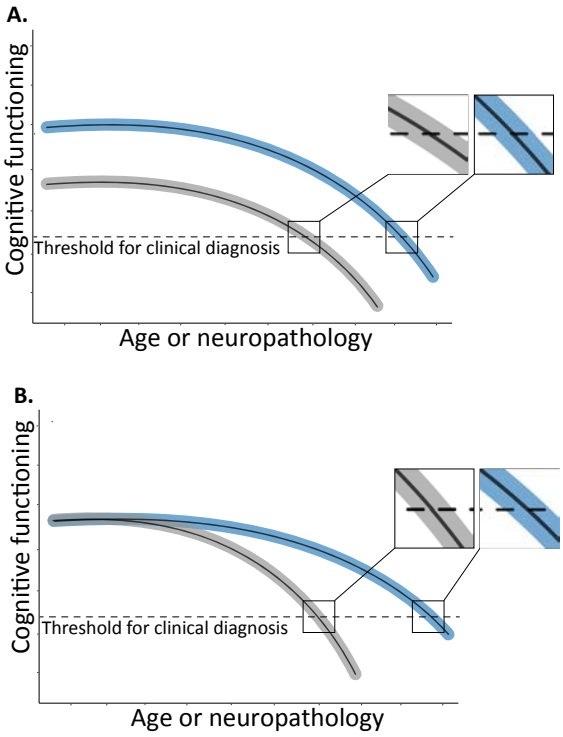


Figure 1. Variability in cognitive performance across the lifespan. **A.** Individuals vary in their overall cognitive abilities throughout the lifespan, also referred to as preserved differentiation, reflected by different intercepts. **B.** Individuals differ in their trajectories of cognitive decline, termed differential preservation, where differences are observed in slopes. Different factors may contribute to preserved differentiation and differential preservation, and these processes are not mutually exclusive. The differently coloured lines illustrate potential trajectories of cognitive functioning across the lifespan.

This heterogeneity in cognitive functioning provides a window of opportunity to increase our knowledge of the building blocks that contribute to optimizing cognitive ageing (Cabeza et al., 2018; Dohm-Hansen et al., 2024). By investigating the underlying mechanisms of this variability, we can identify factors that contribute to either risk or resilience in ageing. In this thesis, risk refers to the increased likelihood of cognitive impairments or decline (Livingston et al., 2020), whereas resilience comprises the relative maintenance of cognitive functions at a certain age and/or degree of neuropathology (Stern et al., 2020). Which factors contribute to overall increased cognitive performance over time (Figure 1A) and which to slower rates of cognitive decline (Figure 1B)? This knowledge can be utilized for the development of interventions that promote healthy ageing, especially if this involves the identification of potentially modifiable factors (Livingston et al., 2020; Tucker-Drob, 2019; Walhovd et al., 2023).

The ageing brain

One source of variability in cognitive functioning across the lifespan comes from the brain (Cabeza et al., 2018; Lindenberger, 2014; Turrini et al., 2023). Magnetic resonance imaging (MRI) allows us to characterize many different properties of the brain in a non-invasive manner. Since the first MRI image of the brain was captured in 1978, further technological advancements and extensive neuroimaging research have increased our understanding of how the brain's structural and functional architecture changes in normal and pathological ageing, and subsequently affects cognitive functioning (Viard et al., 2021). Below, I briefly summarize some key insights obtained from these studies. Notably, the impact of brain alterations on cognitive functions largely depends on which brain regions are affected, the underlying pathology, and the extent of these changes (Boyle et al., 2018; Turrini et al., 2023; Wilson et al., 2023).

Normal ageing is accompanied by several changes in brain morphology, which can be characterized with structural MRI. Grey matter volume loss occurs in most brain regions throughout the adult lifespan (Bethlehem et al., 2022; MacDonald & Pike, 2021). Brain regions mostly affected by ageing-related atrophy include the frontal and temporal regions, which are important for executive functioning and episodic memory, respectively (D'Esposito & Postle, 2015; Jurado & Rosselli, 2007). Particularly the hippocampus, which is situated in the temporal lobe, demonstrates accelerated decline after the

age of 60 (Fjell et al., 2014; Fjell & Walhovd, 2010; Raz et al., 2005). White matter volume gradually declines after the age of 30, with accelerated decline occurring after the age of 50 (Bethlehem et al., 2022), especially in the frontal areas (Bennett & Madden, 2014). Measures of white matter integrity can be derived from diffusion-weighted imaging (DWI), such as fractional anisotropy (FA) and mean diffusivity (MD). White matter microstructures (e.g., myelin, axonal membranes, and microtubules) restrict diffusion along the length of the axon, which increases the directionality of diffusion (FA) and reduces its overall magnitude (MD) (Alexander et al., 2007; Beaulieu, 2002). In older age, white matter integrity is compromised by several microstructural alterations, such as demyelination and axonal damage, resulting in overall lower FA and higher MD (Cox et al., 2016; Madden et al., 2012). These ageing-related changes in white matter have been linked to reduced cognitive performance, predominantly processing speed and executive functioning (Bennett & Madden, 2014; MacDonald & Pike, 2021).

Functional MRI (fMRI) allows for the measurement of brain activity, for example, while an individual performs a cognitive task or is at rest. Previous studies have often reported increases in brain activity and bilateral recruitment during task performance in older adults relatively to younger adults, particularly in the prefrontal regions (Cabeza et al., 2002; Davis et al., 2008; Park & Reuter-Lorenz, 2009). However, the extent to which these changes in activity patterns benefit or hinder cognitive performance remains unclear (Grady, 2012). It is also possible to study the functional connectivity within and between networks of brain regions by focusing on the co-activation of these areas over time (Power et al., 2011; Yeo et al., 2011). With advancing age, connectivity within brain networks typically decreases, whereas connectivity between networks increases, suggesting that these functional networks may become less distinct from each other (Geerligs et al., 2015; Liem et al., 2021). Older adults also showed a reduced ability to effectively recruit task-relevant functional networks and suppress those that are task-irrelevant, which is associated with lower cognitive performance (Grady et al., 2009; Raichle, 2015; Samu et al., 2017).

Looking into the brain characteristics underlying successful cognitive performance in older adults, the importance of brain health is further emphasized. For example, compared to normal ageing individuals, *superagers* exhibit less atrophy in the hippocampus and overall grey matter, as well as higher white matter integrity (Garo-Pascual et al., 2023; Harrison et al.,

2012). Similarly, if we use many structural brain properties (e.g., regional brain volumes, cortical thickness, white matter microstructure) to predict an individual's chronological age, those with a relatively younger predicted age compared to their chronological age show better cognitive performance (Cole et al., 2019; Wrigglesworth et al., 2022), even in the context of dementia (Lee et al., 2022). Additionally, older adults whose activity patterns more closely resemble those of younger adults exhibit better performance (Cabeza et al., 2018; de Godoy et al., 2021).

In the context of pathological ageing, changes in the brain are far more substantial, as well as their implications for cognition (Boyle et al., 2018; Wilson et al., 2023). Dementia most often concurs with neuropathological damage caused by both Alzheimer's disease and cerebrovascular disease, whereas other degenerative conditions, such as Lewy Body disease, are less common (Arvanitakis et al., 2019). Importantly, several potentially modifiable lifestyle-related risk factors, including hypertension, type 2 diabetes, obesity, smoking, and physical inactivity, have been associated with an increased risk of brain disease and corresponding cognitive decline (Iadecola et al., 2016; Livingston et al., 2020; Norton et al., 2014; Yaffe et al., 2020).

Alzheimer's disease is predominantly marked by progressive neurodegeneration and pathological accumulation of the proteins amyloid beta (Aβ) and tau, ultimately leading to dementia (Jack et al., 2018). The medial temporal lobes are often affected in its initial stages, which is related to the presence of episodic memory deficits, whereas other cognitive impairments typically arise in more advanced stages (Jagust, 2018; Serrano-Pozo et al., 2011). Cerebrovascular disease refers to any condition that affects the vasculature of the brain (Portegies et al., 2016). A highly prevalent example in the ageing population is cerebral small vessel disease (SVD). This condition is one of the most important underlying causes of dementia (Cannistraro et al., 2019; Wardlaw et al., 2013), and involves several pathological processes that affect the deep perforating arteries of the brain, thereby damaging the white matter and deep grey matter structures (Pantoni, 2010; Wardlaw et al., 2013). MRI features indicative of SVD, such as white matter hyperintensities, are commonly associated with impairments in executive functioning and processing speed, but other domains can also be affected (ter Telgte et al., 2018). Neuropathology and cerebrovascular injury together explain up to 43% of the variance in cognitive decline among community-based cohort studies (Boyle et al., 2018; Dawe et al., 2020). Measures of medial temporal

lobe atrophy have been shown to be more strongly related to global cognitive decline, explaining approximately 5-9% more variance (Dawe et al., 2020; Woodworth et al., 2022).

From a theoretical perspective, it has been suggested that brain health in late life is facilitated through higher levels of *brain maintenance* and/or *brain reserve* (Stern et al., 2023). Brain maintenance refers relative absence of ageing-related brain changes or neuropathology in older age (Nyberg et al., 2012). For example, less cortical atrophy over time has been associated with slower rates of cognitive decline (e.g., Johansson et al., 2022; Figure 1B). In contrast, brain reserve involves advantages in brain characteristics that are present throughout the lifespan (Katzman et al., 1988; Stern, 2009). In line with this, for instance, higher cortical surface area in early age has been linked to increased cognitive functioning throughout the lifespan (Walhovd et al., 2016). Additionally, higher intracranial volume – which is often considered as measure of premorbid brain size – has been related to better cognitive performance after adjusting for neuropathology (van Loenhoud et al., 2018). Following this line of reasoning, if neurodegenerative processes become evident, the onset of cognitive impairments will be delayed because more performance decline is required to reach the clinical threshold of an 'impaired' performance. As this buffer is inherently present, brain reserve is also referred to as a form of passive reserve (Barulli & Stern, 2013; Stern, 2009).

Other contributors to sustaining cognitive functions

There is more to sustaining cognitive functions in older age than our brain's health. Variability in cognitive performance is only partially explained by measures of brain structure, function and neuropathological damage (Boyle et al., 2018; Dawe et al., 2020; Finn et al., 2015). At similar degrees of neuropathological severity, some individuals show profound cognitive deficits, whereas others may still show normal cognitive performance (Bennett et al., 2006; O'Brien et al., 2009). To explain this discrepancy, the theoretical construct of cognitive reserve was introduced (Stern, 2002, 2009). The Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging defines cognitive reserve as follows: "a property of the brain that allows for cognitive performance that is better than expected given the degree of life-course related brain changes and brain injury or disease" (Stern et al., 2023). Higher levels of cognitive reserve would indicate that an individual is able to

counteract the effects of ageing- related brain changes or neuropathology through compensatory processes, including the recruitment of alternative brain networks and/or strengthening existing ones (Oosterhuis et al., 2022; Stern et al., 2020). Variations in cognitive reserve across individuals would therefore contribute to *differential preservation* as displayed in Figure 1B (i.e., differences in slope). Note that although brain maintenance also would contribute to different cognitive decline rates, the mechanisms as to why this is the case are markedly different (i.e., absence of ageing- related brain changes in brain maintenance vs. actively compensating for their effects in cognitive reserve).

The precise definition and optimal operationalization of cognitive reserve has been a topic of ongoing debate (Cabeza et al., 2018; Kremen et al., 2022; Nilsson & Lövdén, 2018; Pettigrew & Soldan, 2019; Pinto et al., 2024; Stern et al., 2020). In practice, researchers frequently use socio-behavioural factors as proxy measures of cognitive reserve, with the assumption that these enhance the neural capacities of an individual to counteract ageing-related brain changes or neuropathology (Pappalettera et al., 2024; Stern et al., 2020). This includes factors such as educational attainment, verbal intelligence, occupational complexity, and engaging in mentally stimulating activities, as well as composites of these variables (Harrison et al., 2015; Opdebeeck et al., 2016; Pinto et al., 2024). These socio-behavioural factors relate to reduced risk of cognitive impairments and dementia (Nelson et al., 2021; Xu et al., 2019). Higher levels of these measures are also linked to better cognitive performance in older age (Opdebeeck et al., 2016), even in individuals aged over 85 (Lavrencic et al., 2017; Martin et al., 2023), as well as among individuals with neurodegenerative disease (Staekenborg et al., 2020). Notably, the number of individuals in these population groups is especially expected to increase in the next decades (CBS, 2024). Therefore, these socio-behavioural factors might be viable targets for prevention or intervention strategies (Livingston et al., 2020).

To demonstrate that certain socio-behavioural factors contribute to cognitive reserve, it has been suggested that they should ideally moderate the association between age or neuropathology and cognitive functions (Stern et al., 2023; Stern et al., 2020). For example, prior research showed that higher educational attainment, the most common used proxy measure of cognitive reserve (Pinto et al., 2024), mitigated the adverse impact of Aβ accumulation on episodic memory (Bennett et al., 2003; Joannette et al., 2019). However,

educational attainment and other socio-behavioural factors have not been consistently related to reduced negative effects of brain changes or neuropathology on cognitive functions, nor with slower rates of cognitive decline (Boyle et al., 2021; Lane et al., 2017; Pettigrew & Soldan, 2019). It has been hypothesized that neuropathological burden eventually becomes too severe for compensation to occur (Barulli & Stern, 2013). Several studies indeed observed that the positive effects of educational attainment diminished as a function of neuropathological burden (Mungas et al., 2018; Zahodne et al., 2019), or clinical symptomatology (Groot et al., 2018). Therefore, inconsistent study findings might be partially explained by the differences in underlying disease severity of the studied populations.

It should be noted that higher educational attainment is one of the main predictors of cognitive performance (as opposed to decline), as evidenced by neuropsychological normative data that adjust for this factor (e.g., Lezak et al., 2012). Furthermore, accumulating evidence suggests that the positive effects of education on cognitive functions result from early life advantages in brain structure and cognitive performance (i.e., passive reserve), rather than cognitive reserve (Lövdén et al., 2020; Nyberg et al., 2021; Seblova et al., 2020). Similarly, higher levels of intelligence have been related to structural brain advantages in early life as well as better brain maintenance, independent of educational attainment (Walhovd et al., 2022). Although a lot is still unclear about the interplay between different socio-behavioural factors, brain health and cognitive functioning, it is undisputed that these socio-behavioural factors have positive effects on cognitive functions in both normal and pathological ageing (Chan et al., 2018; Vemuri et al., 2014).

Another influential cognitive ageing theory that addresses why some individuals may better cope with the effects of ageing-related brain changes or neuropathology is the revised Scaffolding Theory of Aging and Cognition (STAC-r; Reuter-Lorenz & Park, 2014; Reuter-Lorenz & Park, 2024). In this context, variability arises from individual differences in scaffolding or "the forging of new neural pathways or circuitry that relies on the brain's inherent neuroplasticity in the face of cognitive challenge across the entire lifespan" (Reuter-Lorenz & Park, 2024, p. 1). A detailed comparison of STAC-r and cognitive reserve is provided in Oosterhuis et al. (2022). Similarly to cognitive reserve, STAC-r suggests that compensation is facilitated by the recruitment of alternative brain areas or strengthening of brain networks. However, STAC-r additionally emphasizes the recruitment of bilateral or frontal regions as well

as the synthesis of new neurons as compensatory processes (Oosterhuis et al., 2022; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). Nevertheless, disentangling compensatory mechanisms in the brain has proven to be challenging. As outlined previously, for example, the observation of increased frontal recruitment in older adults has been linked to both superior and inferior levels of cognitive performance (Cabeza et al., 2002; Grady, 2012; Park & Reuter-Lorenz, 2009). While compensation theoretically does not have to concur with better performance (Festini et al., 2018), other findings suggest that this overactivation in frontal regions more likely reflects decreased neural specificity (Grady, 2012; Morcom & Henson, 2018), possibly due to the differentially perceived task demands by older participants (Ryan & Campbell, 2021).

One potential explanation for these discrepancies in findings across fMRI studies may be provided by the notion of many-to-one mapping or brain degeneracy (Westlin et al., 2023), which suggests that multiple neural systems may underlie task performance (Edelman & Gally, 2001; Price & Friston, 2002). In line with this, prior studies identified subgroups of participants characterized by different neural activity patterns during task engagement (Kherif et al., 2009; Noppeney et al., 2005), yet equal task performance (Noppeney et al., 2006). Conversely, similar brain characteristics have been related to different cognitive outcomes (Lövdén et al., 2018; Patel et al., 2022). However, most studies have overlooked this inter-individual variability and assume that similar brain regions are recruited during task engagement across most individuals (i.e., one-to-one mapping). As specific brain-cognition associations may be present only in subgroups, the identified brain-cognition associations could depend on the study population used (Seghier & Price, 2018; Westlin et al., 2023). Therefore, the notion of brain degeneracy could provide a complementary perspective to increase our understanding of the underlying mechanisms of to sustain cognitive functions throughout the lifespan.

Promoting healthy cognitive ageing

In the previous sections, several building blocks of healthy ageing have been introduced, based on their role in explaining variability in cognitive functions across the lifespan. This also included several potentially modifiable factors contributing to risk (e.g., hypertension or physical inactivity) or resilience (e.g., educational attainment or verbal intelligence). Consequently, one route

to optimize cognitive ageing involves addressing these lifestyle- related factors in interventions (Livingston et al., 2024; Livingston et al., 2020; Norton et al., 2014). Another useful route involves the use of cognitive rehabilitation approaches, which more directly target cognitive functions (Andrieu et al., 2015; Gates et al., 2011). Typically, these interventions consist of cognitive training through repetitive exercise or other paradigms (i.e., restorative approach), or strategy training where compensatory strategies are taught (i.e., compensatory approach) (Eikelboom et al., 2020).

Several large-scale multi-domain lifestyle interventions that included cognitive rehabilitation techniques demonstrated improved cognitive outcomes in older adults with increased risk of dementia (Chhetri et al., 2018; Kivipelto et al., 2018; Ngandu et al., 2015). Conversely, cognitive rehabilitation approaches have shown beneficial effects across the whole continuum of cognitive decline; however, these effects are generally small, vary considerably across studies, and do not generalize well to untrained cognitive domains (i.e., far transfer, especially if a restorative approach was adopted) (Eikelboom et al., 2020; Gavelin et al., 2020; Kane et al., 2017). The success of these interventions might vary due to differences in intervention-specific factors (e.g., training duration, applied setting; e.g., Lampit et al., 2014) and individual-specific factors (e.g., demographic variables, baseline performance metrics; e.g., Roheger, Meyer, et al., 2020). However, heterogeneity in intervention paradigms and insufficient reporting of study designs have made it difficult for systematic reviews and meta-analyses to determine which intervention components are most effective and for whom (Lauenroth et al., 2016; Roheger, Folkerts, et al., 2020; Traut et al., 2021; Zhu et al., 2016). Although intervention approaches aimed at supporting cognitive functioning in normal and pathological ageing are promising, there is a need for more standardized reporting to fully evaluate and optimize their potential.

Thesis outline

The present thesis aims to further increase our understanding of cognitive ageing by 1) utilizing the heterogeneity in cognitive functioning across both normal and pathological ageing, particularly focusing on the dynamics between the brain, cognitive functioning, and potentially modifiable factors (e.g., socio-behavioural or lifestyle-related factors) to understand why we all age differently; and 2) advancing the study of cognitive ageing by taking

a broader perspective, directly facilitating research on this topic, challenging common assumptions, and supporting standardized reporting. In turn, this knowledge could aid in the development of potential strategies to optimize cognitive ageing.

Part I. Understanding heterogeneity in cognitive ageing

Part I (**chapter 2-4**) focuses on the dynamics between cognitive functions, brain health and/or other factors contributing to risk and resilience in ageing, including socio-behavioural and vascular risk factors. In **chapter 2**, we investigate whether cognitive reserve mitigates the relationship between age and cognitive functioning among the old-old (71-94 years old). Identifying mechanisms of cognitive ageing is especially of interest in this age group due to the substantial increase of this age group in the context of the worldwide ageing of the population (i.e., double ageing). To capture the theoretical construct of cognitive reserve, a composite measure of verbal intelligence and educational attainment is used. Cognitive functioning is assessed using various neuropsychological tests for episodic memory, processing speed, and executive functioning. This approach enables us to understand whether compensatory mechanisms may still occur in the old-old.

In **chapter 3**, the effects of educational attainment on cognitive functioning are examined in more detail. Although protective effects of educational attainment are widely recognized, it is unclear how this relationship is affected by disease severity. Therefore, this study examines whether the relationship between educational attainment and cognitive functioning differs across various (pre-)clinical syndromes, including SCD, MCI, and Alzheimer's dementia. Additionally, the role of neuropathological burden within a particular diagnosis is considered, specifically the severity of global atrophy, medial temporal lobe atrophy, and white matter hyperintensities. This knowledge could increase our understanding of the precise conditions under which educational attainment contributes to cognitive functioning. In turn, this helps to explain why findings may differ across studies.

Chapter 4 investigates cerebral small vessel disease (SVD) burden in a sample of community- dwelling older adults. Specifically, total SVD burden is linked to other measures of structural brain health, and retrospectively related to vascular risk and cognitive functions. MRI scans are acquired at the age of 70 (i.e., late life), whereas measures on vascular risk and cognitive functions are available from up to 25 years prior to the MRI scan at intervals of five years (i.e., from

mid-to-late life). Total SVD burden scores are based on several MRI features of the disease, including white matter hyperintensities, cerebral microbleeds, lacunes and perivascular spaces. Structural brain health is characterized with grey matter volumes and indices of white matter integrity. The associations between SVD burden in late life with trajectories of vascular risk and cognitive decline from mid-to-late life could provide insights into the optimal stage in life for intervention that promote healthy ageing.

Part II. Advancing research on cognitive ageing

In part II (**chapters 5-7**), we broaden our perspective to improve the study on cognitive ageing itself. To facilitate research on the underlying mechanisms of neurocognitive ageing, **chapter 5** introduces the Advanced BRain Imaging on Aging and Memory (ABRIM) study. Specifically, ABRIM aims to complement previously released openly available datasets by including a detailed behavioural and MRI examination among a cross-sectional adult lifespan sample (18- 80 years old). This study particularly focuses on the assessment of variables related to risk and resilience, cognitive functioning, and advanced imaging parameters, such as those derived from quantitative MRI. This comprehensive characterization enables researchers to study how these variables change with age (e.g., in the context of normative models) and to further elucidate the factors that promote cognitive functioning throughout life.

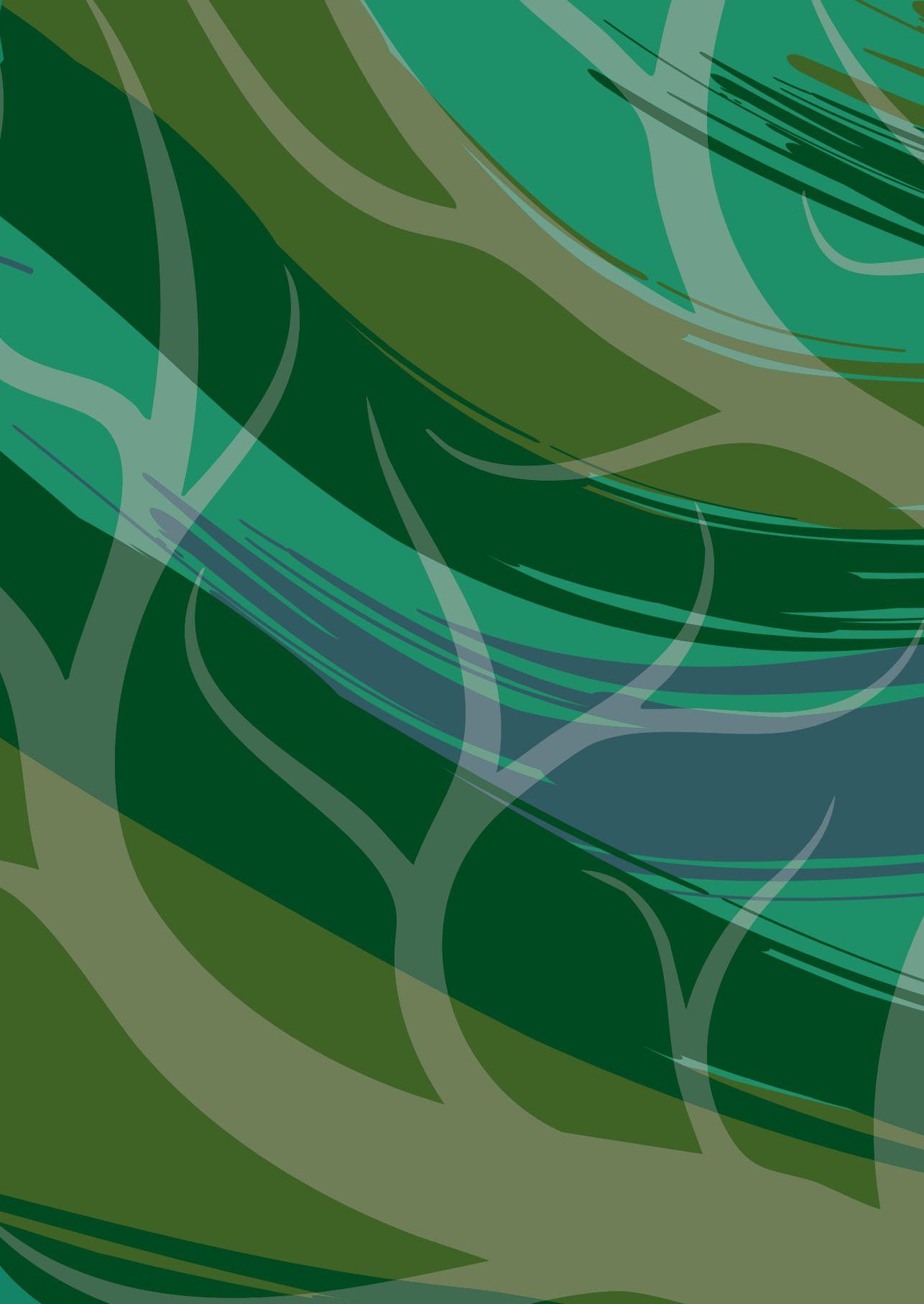
Chapter 6 explores the possibility multiple neural pathways could underlie cognitive performance, also referred to as brain degeneracy. Although research typically assumes that cognitive performance is supported by the same neural systems in most individuals, brain degeneracy is increasingly recognized for its potential to enhance our understanding of variability in brain-cognition associations across individuals and studies. The presented study utilizes an innovative method to identify subgroups of participants with different brain activity patterns during a visual short-term memory task. Subsequently, these differential recruitment patterns are related to participants demographics, brain structural characteristics, and task performance. This not only provides a more comprehensive picture of the individual-specific factors that explain variability in brain activity but also identifies which activity patterns are adaptive or maladaptive for cognitive performance and how this might vary across individuals.

Chapter 7 introduces a novel tool to facilitate the standard reporting of memory interventions to increase our understanding of the efficacy of these

approaches. There is a large heterogeneity in memory intervention protocols, and previous studies often have not sufficiently described the designs of these approaches. This lack of detailed reporting has hindered systematic reviews and meta-analyses in determining which memory intervention components are most effective and for whom. This chapter tackles this issue by its roots, adopting several qualitative methods to create an online tool that eases the systematic description and comparison of memory interventions.

General discussion

In the final part, the summary and discussion in **chapter 8**, the multifaceted aspects of cognitive ageing are synthesized from the previous chapters, together with an outlook for cognitive ageing research in the future. **Chapter 9** provides a Dutch summary of the thesis.



Part I.

Understanding heterogeneity in cognitive ageing

Chapter 2

Cognitive reserve relates to executive functioning in the old-old

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Abstract

Cognitive reserve (CR) is known to reduce or even protect against the negative effects of aging on cognitive functioning. Nonetheless, little is known about how CR influences the relationship between different cognitive abilities and age in the old-old. The goal of the present study was, therefore, to test the hypothesis whether, in the old-old, CR still modifies the relationship between age and cognitive functioning. Eighty-three adults (aged 71-94) without mild cognitive impairment or dementia residing in residential care facilities completed a detailed neuropsychological test battery. CR was estimated using a combination of educational attainment and an estimation of verbal intelligence. Moderation analyses revealed a significant effect for fluency and a trend for flexibility, showing that the negative relationship between age and cognitive performance is reduced as the level of CR increases. These results demonstrate that CR still influences the relationship between age and executive functions in adults of advanced age.

Introduction

Cognitive reserve (CR) has become one of the most studied constructs in understanding the major variability in aging-related cognitive decline across individuals (Stern et al., 2020). It has been hypothesized that CR increases the adaptability of cognitive or functional brain processes, thus acting as a buffer against the negative effects of aging-related brain pathology on cognition (Stern et al., 2020). Although there are currently no established methods to capture CR directly, proxy measures of CR involve sociodemographic variables reflective of experiences that may promote CR (e.g., educational attainment and verbal intelligence) (Seblova et al., 2020; Stern et al., 2020). Studies have indeed shown that higher levels of CR are associated with diminished cognitive decline in healthy aging (Seblova et al., 2020; Stern et al., 2020). However, what remains less understood is the potential protective effect of CR at advanced ages (e.g., mean age over 80).

Previous studies that examined CR in the old–old have several limitations. First, although executive functions are considered the core functions underlying the compensatory mechanisms of CR (Tucker & Stern, 2011), an intensive evaluation of diverse executive control processes in relation to CR in very old individuals is lacking. Most studies in the old–old examined CR in relation to global cognitive functioning or only a limited number of cognitive functions such as memory and processing speed (Lavrencic et al., 2018; Seblova et al., 2020). Second, studies that did examine multiple cognitive domains, including executive functions, mostly examined simple associations between CR and cognition (Kaplan et al., 2009; Lindenberger & Baltes, 1997). Therefore, it is unclear to what extent these findings may not merely represent main effects of, for instance, educational attainment (Stern et al., 2020). Moreover, simple associations such as zero-order correlations cannot disentangle how CR attenuates the negative effects of aging and aging-related brain changes on cognition (Stern et al., 2020).

The present study aims to overcome these limitations and gain further insight into the effects of CR on cognition in the old–old. We examined how CR relates to cognitive test performance, primarily focusing on the different executive functions. Moreover, we examined how CR moderates the relationship between age and cognition. Due to the importance of executive functions in compensating for aging-related cognitive decline (Tucker & Stern, 2011), we hypothesized that CR particularly influences the relationship between age and executive functions.

Methods

Participants

Eighty-three participants (mean age = 84.9, SD = 5.2, range 71–94; 29 men) were recruited in cooperation with four different homes for the elderly in Amsterdam, the Netherlands (see Oosterman et al., 2007 for more details). We screened medical records of residents admitted to somatic wards for the following inclusion criteria: no neurological disease (e.g., dementia, Parkinson's disease, stroke), no psychiatric disorder (e.g., schizophrenia, major depression), and no substance use disorder. To exclude individuals with potential cognitive impairments, the Mini Mental State Examination (MMSE) (Lezak, 2004) was administered with a score of ≥ 24 as a requisite for participation (see Table 1 for descriptives).

Neuropsychological assessment

A comprehensive battery of tests tapping memory, speed and attention, and executive functioning was administered, including the following tests (see Lezak, 2004; Oosterman et al. 2007).

Episodic memory tests

The Rey Auditory Verbal Learning Test (RAVLT) was used as a measure of verbal episodic memory (immediate and delayed recall) and the Pattern Recognition Test (PRM; total correct) of the Cambridge Neuropsychological Test Automated Battery (CANTAB) as a measure of visual episodic memory.

Executive function tests

To fully grasp the complexity of executive functioning, we administered a wide array of tests to measure the following domains: flexibility, working memory, inhibition, fluency and planning. For flexibility, the Trail Making Test (TMT, using the TMT-B/TMT-A ratio score) and the Intra-Extradimensional Set Shift (IED, number of stages completed) task of the CANTAB were used. Working memory was assessed using the Digit Span (DS, forward and backward total correct) and CANTAB Spatial Working Memory (SWM, total between-search errors). Inhibition was measured with the 45 s version of the Stroop Colour-Word test. The interference score was used as primary outcome, which is based on the total correctly named words/colours on the Word (W), Colour (C) and Colour-Word (CW) cards, and calculated using the following formula: interference = $CW - [(W \times C) / (W + C)]$. Fluency was assessed using category and letter fluency (for both total number correct productions). Finally,

planning was assessed with CANTAB Stockings of Cambridge (SOC) (number of problems solved in minimal moves).

Table 1. Characteristics of the study sample

Variable	*N*	Value
Age	83	84.9 (5.2)
Education level	83	
< Primary education	1	1.2%
Primary education	21	25.3%
Incomplete lower secondary education	13	15.7%
Lower secondary education	16	19.3%
Vocational education	19	22.9%
Higher secondary/professional education	7	8.4%
University degree	6	7.2%
NART IQ	80	98.7 (12.4)
MMSE	83	27.0 (1.7)
Memory		
RAVLT immediate recall	78	32.0 (9.4)
RAVLT delayed recall	78	5.7 (3.0)
Pattern recognition memory	76	18.9 (3.0)
Psychomotor speed		
TMT-A	81	98.4 (60.1)
Stroop Color-Word test W card	79	72.1 (19.3)
Stroop Color-Word test C card	79	59.6 (13.8)
Executive function		
Letter fluency	83	26.6 (10.9)
Category fluency	82	25.7 (9.5)
TMT-B	68	236.0 (125.6)
Stroop Color-Word test CW card	79	25.7 (12.3)
Digit Span total	83	10.8 (2.4)
SWM no. of between-search errors	75	66.1 (18.8)
IED no. stages completed	75	7.0 (2.4)
SOC no. of problems solved	68	6.2 (1.9)

Abbreviations: C = Color; CW = Color Word; IED = Intra-Extradimensional Set Shift; MMSE = Mini Mental State Examination; NART = National Adult Reading Test; RAVLT = Rey Auditory Verbal Learning Task; SOC Stockings of Cambridge; SWM Spatial Working Memory; TMT = Trail Making Test; W = Word. All values represent means ± standard deviations, with the exception of education, which represents percentages. Stroop scores represent the number of correct responses within 45 s for a certain condition.

Information processing speed tests

We used the TMT part A (completion time) and the W and C cards (number of word/colours correctly named) of the Stroop test to measure processing speed.

Cognitive reserve

Whereas previous studies mostly only used educational attainment to capture CR (Seblova et al., 2020), we combined the level of educational attainment with verbal intelligence to obtain a more comprehensive and reliable proxy measure of CR (Caffò et al., 2016). For this, educational attainment was assessed with an ordinal rating scale based on the Dutch educational system that distinguishes between levels of education (rather than years of education): 1 = less than primary education, 2 = primary education, 3 = incomplete lower secondary education, 4 = lower secondary education, 5 = vocational education, 6 = higher secondary and professional education, 7 = university degree. The Dutch version of the National Adult Reading Test (NART) was used to estimate verbal intelligence.

Analyses

All CR and neuropsychological test scores were z standardized. As we used two outcome measures of the RAVLT for episodic memory (immediate and delayed recall), z scores of immediate and delayed recall were first averaged into one score. A similar procedure was used for the two outcomes of the Stroop Colour-Word test for processing speed (C and W cards). Next, we used the z-standardized scores to calculate cognitive domain scores that covered flexibility (TMT-B/TMT-A, IED), working memory (DS, SWM), fluency (letter, category), information processing speed (TMT-A, Stroop Colour-Word) and episodic memory (RAVLT, PRM), as well as a CR score (education, NART). For inhibition and planning, the single test score was used. In case of missing data, we used the available scores to calculate the domain. If necessary, test scores were multiplied by – 1 such that a higher score indicates better performance.

Moderation analyses (5000 Bootstraps; Hayes, 2007) were performed to determine if CR moderates the relationship between age and the cognitive domain scores. The domain scores were used as dependent variable, age as main predictor, CR as moderator, and sex as covariate. We report both uncorrected and false discovery rate (FDR)-corrected p values to account for multiple comparisons. To estimate the effect sizes, we reported R^2 and calculated Cohen's f^2 statistics using the following formula: Cohen's $f^2 = R^2 / (1 - R^2)$. We interpreted 0.02 as a small effect size, 0.15 as a medium effect size and 0.35 as a large effect size.

Results

Occasional missing data were present, most pronouncedly for the computerized CANTAB tests and the TMT-B, primarily due to the observed inability to complete or comprehend the (display of the computerized) test.

Results from the moderation analyses (see Table 2), after applying FDR corrections, showed main effects of CR for fluency, information processing speed, and working memory, indicating that a higher CR is associated with better cognitive performance. Furthermore, CR moderated the relationship of age with fluency performance (corrected $p = 0.02$, R^2 change = 0.08), whereas a trend (uncorrected $p = 0.06$, R^2 change = 0.04) was observed for flexibility. To further explore these effects, the relationship between age and these cognitive scores was plotted as a function of lower (– 1 SD), average (0 SD), and higher (+ 1 SD) CR (see Table for the slope statistics). For both fluency and flexibility, a significant negative association with age was found only in individuals with a lower CR (all corrected $p < 0.05$), but not in individuals with an average or high CR (Figure 1).

The effect sizes (see Table 2) for the entire model ranged from small (planning, inhibition) to medium (episodic memory, working memory, flexibility, information processing speed) and large (fluency) effect sizes. A sensitivity analysis showed that, given a sample size of 83 with $\alpha = 0.05$, the study was sufficiently powered ($1 - \beta = 0.80$) to detect a medium effect size ($f^2 = 0.16$).

Table 2. Interactions between age and CR for different cognitive domains

Cognitive domain	Episodic memory	Working memory	Fluency
Age	– 0.06 (– 0.09– – 0.02)*** *†	– 0.01 (– 0.04– 0.02)	– 0.02 (– 0.05– 0.02)
CR	0.09 (– 0.10– 0.28)	0.32 (0.13– 0.50)****†	0.55 (0.36– 0.74)****†
Sex	0.36 (0.01– 0.71)**	0.12 (– 0.21– 0.46)	0.15 (– 0.20– 0.50)
Age*CR	0.02 (– 0.02– 0.05)	0.02 (- 0.01–0.06)	0.05 (0.02– 0.09)***†
Finteraction	$F(1,76) = 1.06$	$F(1,78) = 1.93$	$F(1,78) = 8.86$
ΔR^2 *interaction*	0.01	0.02	0.08
R^2 *total*	0.22	0.15	0.32
Cohen's f^2	0.28	0.17	0.47

Abbreviations: CR = cognitive reserve (compound score of educational attainment and verbal intelligence estimate). B values are reported, together with lower and upper borders of the 95% confidence interval. Higher cognitive domain scores indicate better performance. Cohen's f^2 calculations are based on the unrounded R^2 values. *Uncorrected $p < 0.07$; **Uncorrected $p < 0.05$; ***Uncorrected $p < 0.01$; ****Uncorrected $p < 0.001$; †Survived FDR-corrections

Table 3. Slopes of the relationship between age and the cognitive domains as a function of CR

Cognitive domain	Fluency	Flexibility
Slopes		
Low CR	– 0.07 (– 0.11– – 0.02)*†	– 0.07 (– 0.13–-0.02)*†
Average CR	– 0.01 (– 0.05–0.02)	– 0.03 (– 0.07–0.00)
High CR	0.03 (– 0.01–0.07)	0.00 (– 0.05–0.05)

Abbreviations: CR = cognitive reserve (compound score of educational attainment and verbal intelligence estimate). *B* values are reported, together with lower and upper borders of the 95% confidence interval. Slopes represent the relation between age and the cognitive domain score at a lower (– 1 SD), average (0 SD) and higher (+ 1 SD) level of cognitive reserve (CR). *$p < 0.01$; †Survived FDR corrections

Flexibility	Planning	Inhibition	Processing speed
– 0.04 (– 0.07– 0.00)*	– 0.05 (– 0.15– 0.04)	– 0.31 (– 0.69– 0.07)	– 0.04 (– 0.08– – 0.01)**
0.15 (– 0.07– 0.38)	0.14 (– 0.42– 0.70)	0.38 (- 1.87–2.63)	0.32 (0.12– 0.52)***†
0.41 (0.00– 0.83)*	0.05 (– 0.98– 1.08)	1.55 (– 2.62– 5.71)	0.10 (– 0.27– 0.47)
0.04 (0.00– 0.08)*	0.02 (– 0.08– 0.12)	0.16 (– 0.25– 0.56)	0.01 (– 0.03– 0.05)
F(1,75) = 3. 55	*F*(1,63) = 0. 14	*F*(1,73) = 0 .58	*F*(1,76) = 0. 24
0.04	0.00	0.01	0.00
0.16	0.02	0.06	0.19
0.19	0.03	0.06	0.23

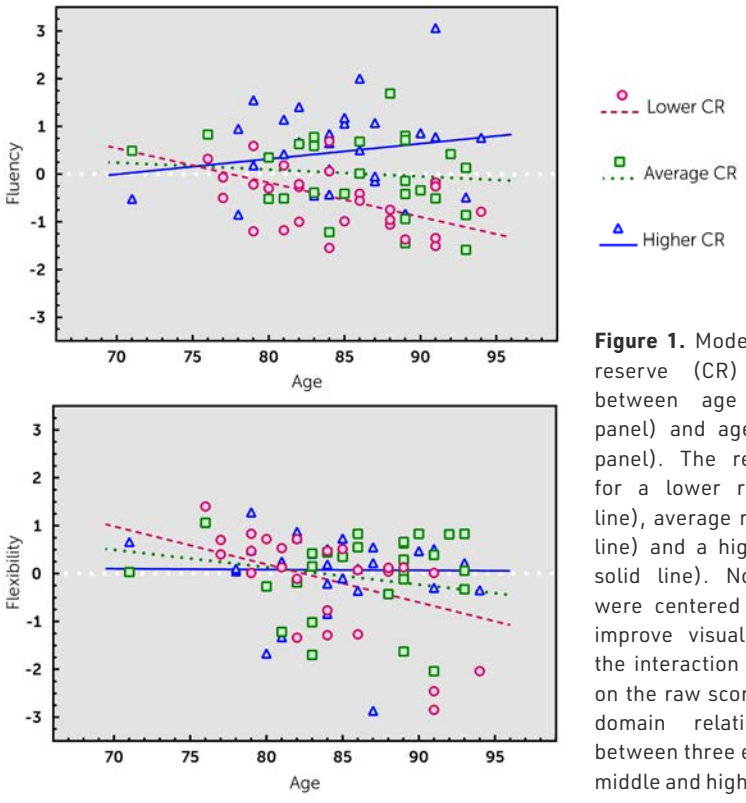

Figure 1. Moderating role of cognitive reserve (CR) on the relationship between age and fluency (upper panel) and age and flexibility (lower panel). The relationship is depicted for a lower reserve (circles/dashed line), average reserve (squares/dotted line) and a higher reserve (triangles/solid line). Note that the variables were centered for these analyses; to improve visualization of the effects, the interaction lines are superimposed on the raw scores of the age–cognitive domain relationship, distinguishing between three equal groups of CR (low, middle and high CR).

Discussion

The goal of the present study was to examine whether CR influences the relationship between age and cognitive performance, with a particular focus on executive functioning, in the old-old. The results show that CR moderates the relationship of age with performance on fluency and, potentially, flexibility tasks. Corresponding to the notion that CR reflects one's ability to alleviate the cognitive effects of aging-related brain pathology (Stern et al., 2020), these findings revealed that the negative correlation between age and cognitive performance levels is less pronounced as the level of CR increases. This study, therefore, clearly illustrates that even in a very old population, CR attenuates cognitive test performance. As cognitive, and particularly executive, functions play a profound role in functional independence in geriatric populations (Overdorp et al., 2016), these findings are of clinical relevance.

Our findings corroborate and extend previous studies showing that CR relates to cognitive functions in very old populations (Kaplan et al., 2009; Lindenberger & Baltes, 1997; Seblova et al., 2020). Our study provides new insights as we tested this for multiple executive functions, and analysed how CR modulates the relationship between age and cognition to focus on the hypothesized CR effects rather than the main effects of education (Stern et al., 2020). Very little is known about how CR relates to the negative relationship between age and cognition in the old-old. From a theoretical point of view, one could hypothesize that CR may protect across the full life span, that is, as long as the aging-associated cognitive decline continues. Our study results corroborate this, by showing that even in very old individuals, CR still attenuates the negative age–cognition relationship for two executive function domains, although the moderation effect of CR on flexibility requires replication in larger studies.

The current study findings contrast those from a recent longitudinal study showing that education (as a proxy for CR) did not influence cognitive decline in these old populations (Wilson et al., 2019). As the current study relied on cross-sectional data, our findings may be confounded by cohort effects (Salthouse, 2019), although it has been reported that cross-sectional data may actually provide a very accurate indication of the true cognitive aging that occurs across the adult lifespan (Salthouse, 2019). Moreover, previous work confirmed the interaction between CR and age, suggesting that the effects of CR actually increase with advancing age (Opdebeeck et al., 2016). Likewise,

the current study indeed revealed that with increasing age, the effect of CR becomes more pronounced (see Figure 1).

The precise mechanisms via which CR exerts its protective role is still a topic of debate. According to one of the most prevailing theories, part of the protective role of CR may be exerted via increased capacity, efficiency or flexibility of existing neural networks (Stern et al., 2020). From this perspective, CR may have a general effect on diverse cognitive functions that is supported by the already involved networks of brain regions. On the other hand, CR may work via compensatory mechanisms that are supported by alternative neural networks (Stern et al., 2020), mostly via increased involvement of prefrontal cortex processes and associated executive control processes (Tucker & Stern, 2011). However, a very recent study in unilateral frontal and non-frontal stroke patients failed to support this notion, showing that CR similarly influences cognitive performance in both patient groups (MacPherson et al., 2020). The extent to which existing versus compensatory mechanisms are involved in the current study findings as well as in maintaining cognition in aging in general, requires further investigation.

To conclude, the current study suggests that CR attenuates the effects of age on executive functioning in old to very old adults. Considering the current worldwide double aging of the population, future studies are needed that examine the complex dynamics between age, neurodegenerative processes, and CR, as well as the functional and cognitive mechanisms in these old-old individuals that allow them to compensate for the effects of aging-related pathologies.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics statement

The study was approved by the local ethics committee of the Vrije Universiteit Amsterdam, and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Chapter 3

Positive effects of education on cognitive functioning depend on clinical status and neuropathological severity

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Abstract

Background: Variability in cognitive functions in healthy and pathological aging is often explained by educational attainment. However, it remains unclear to which extent different disease states alter protective effects of education. We aimed to investigate whether protective effects of education on cognition depend on 1) clinical diagnosis severity, and 2) the neuropathological burden within a diagnosis in a memory clinic setting.

Methods: In this cross-sectional study, we included 108 patients with subjective cognitive decline (SCD, median age 71, IQR [66-78], 43% men), 190 with mild cognitive impairment (MCI, median age 78, IQR [73-82], 44% men), and 245 with Alzheimer's disease dementia (AD) (median age 80, IQR [76-84], 35% men). We combined visual ratings of hippocampal atrophy, global atrophy, and white matter hyperintensities on MRI into a single neuropathology score. To investigate whether the contribution of education to cognitive performance differed across SCD, MCI, and AD, we employed several multiple linear regression models, stratified by diagnosis and adjusted for age, sex, and neurodegeneration. We re-ran each model with an additional interaction term to investigate whether these effects were influenced by neuropathological burden for each diagnostic group separately. False discovery rate (FDR) corrections for multiple comparisons were applied.

Results: We observed significant positive associations between education and performance for global cognition and executive functions (all adjusted p-values < 0.05). As diagnosis became more severe, however, the strength of these associations decreased (all adjusted p- values < 0.05). Education related to episodic memory only at lower levels of neuropathology in SCD (β = -0.23, uncorrected p = 0.02), whereas education related to episodic memory in those with higher levels of neuropathology in MCI (β = 0.15, uncorrected p = 0.04). However, these interaction effects did not survive FDR-corrections.

Conclusions: Altogether, our results demonstrated that positive effects of education on cognitive functioning reduce with diagnosis severity, but the role of neuropathological burden within a particular diagnosis was small and warrant further investigation. Future studies may further unravel the extent to which different dimensions of an individual's disease severity contribute to the waxing and waning of protective effects in cognitive aging.

Introduction

The process of aging is accompanied by alterations in cognitive functions, ranging in severity from normal aging-related changes, to subjective cognitive decline (SCD), mild cognitive impairment (MCI) and, ultimately, dementia (Jack et al., 2018; Salthouse, 2019). Within each diagnostic group, however, there is considerable inter-individual variability in the extent to which cognitive decline manifest itself (Cabeza et al., 2018; Soldan et al., 2020). Educational attainment is a major contributor to this heterogeneity, where individuals with higher levels of education are not only at a lower risk of developing cognitive impairments (Livingston et al., 2020), but also demonstrate better cognitive performance than those with lower educational attainment, sometimes even in advanced stages of pathological aging (Lövdén et al., 2020; Seblova et al., 2020; Stern et al., 2020). The extent to which the positive effects of education are sustained across SCD, MCI, and Alzheimer's disease dementia (AD) remains poorly understood. It has been suggested that disease state may attenuate such effects (Gregory et al., 2017; Mungas et al., 2021; Stern, 2012) and previous studies have demonstrated that the benefits of higher education become less pronounced or disappear entirely as disease severity increases (Groot et al., 2018; Soldan et al., 2015; Ye et al., 2013). In contrast, recent findings revealed stronger education-cognition associations in AD relatively to SCD and MCI (Staekenborg et al., 2020). Furthermore, neuropathological burden varies greatly within each diagnostic group (Mehta & Schneider, 2021), and the protective effects of education may consequently vary as a function of neuropathological severity (Mungas et al., 2021; Mungas et al., 2018; Perneczky et al., 2009).

In this cross-sectional study, we therefore investigated how different syndromal states that differ in neuropathological severity may alter the positive effects of education on cognitive functions in a memory clinic population. More specifically, we investigated whether this relationship differed 1) *across* diagnostic categories with varying levels of clinical severity (SCD, MCI, and AD), and 2) *within* each diagnostic category based on the severity of neuropathological features.

Methods

Study population

For this retrospective study, we included a total of 543 participants; 108 with SCD, 190 with MCI, and 245 with dementia due to AD. Data from this study

sample were extracted from a database containing data of patients who were referred for memory complaints to the memory clinic at Gelre Hospital in Zutphen, the Netherlands, between November 2004 and February 2015. All participants underwent a comprehensive clinical and neurological evaluation, neuropsychological assessment, blood screening, electroencephalogram, and magnetic resonance imaging (MRI) (Overdorp et al., 2014). Patients were excluded from the present study if MRI data were missing and/or of too poor quality for assessment.

Each clinical diagnosis was established within multidisciplinary consensus meetings and in accordance with the established criteria. Diagnosis of MCI was based on the Petersen et al. (2001) criteria. Diagnosis of probable AD was based on the DSM-IV-TR criteria for dementia of the Alzheimer's type (APA, 2000). Although assessment of cerebrospinal fluid (CSF) biomarkers is not part of the standard diagnostic work-up in the Netherlands for diagnosing AD, CSF biomarkers were additionally obtained as supportive evidence in case no consensus was reached. Those patients who neither demonstrated any cognitive impairments after neuropsychological assessment using age- and education adjusted normative data, nor suffered from a psychiatric or neurological disorder, were classified as having SCD.

Education

Educational attainment was measured using the Dutch education classification system, which distinguishes different edactional *levels*, rather than using the *years* of education that are typically used in the Anglosaxon world. This educational classification is comparable with the International Standard Classification of Education (UNESCO, 2011), and results in a score between 1-7: 1) unfinished primary school, 2) finished primary school, 3) unfinished low-level secondary education, 4) lower vocational training, 5) advanced vocational training or lower professional education, 6) finished higher professional education or senior general secondary education and 7) obtained a university degree (Verhage, 1964). Considering the low prevalence of individuals with unfinished primary school (n = 7) and a university degree (n = 31), we made the categorical distinction between low (Verhage scores 1-3), average (4-5), and high education level (6-7; Zhou et al., 2019).

Cognitive functioning

All neuropsychological tests were administered and subsequently analyzed by two experienced neuropsychologists, that were blinded to all medical records

at the time. A detailed overview of the assessment protocol and tests has been described previously (Overdorp et al., 2014). For the present study, we only included tests with available normative data. Briefly, we incorporated the total score of the Mini-Mental State Examination (MMSE; Folstein et al., 1975), the total score of the Visual Association Test (VAT; Lindeboom et al., 2002), immediate and delayed recall of the 8-Word Test of the Amsterdam Dementia Screening (Krijgsveldt et al., 1994), total number correct in the Semantic Fluency Test (1-min animal/profession naming), the total score of the Frontal Assessment Battery (FAB; Dubois et al., 2000), the time to complete part A of the Trail Making Test (TMT; Reitan, 1958), and the TMT ratio score (time to complete B/A).

We generated compound scores for three cognitive domains: global cognition, episodic memory, and executive functioning. First, raw test scores were z-standardized using the mean and standard deviation of the whole study sample. We inverted the z-scores of the TMT, so that higher z-scores are always indicative of better cognitive performance. Compound scores were then calculated for each cognitive domain by taking the average of the z-scores from the available (sub-) tasks of an individual corresponding to that domain. Global cognition was based on scores of the MMSE, VAT, 8-Word Test, |Verbal Fluency, FAB, TMT A, and TMT ratio; episodic memory on the VAT and 8-Word test; executive functioning on verbal fluency, FAB, and TMT ratio. If participants were unable to complete part B of the TMT (n = 112), which primarily occurred in patients with MCI (n = 40) and AD (n = 65), the lowest possible z-score of the sample was assigned. Participant characteristics for the individual (sub-)test scores, including an overview of missing data, are displayed in Supplementary table A.

MRI

All MRI scans were obtained using a 1.5 Tesla GE-Signa Horizon LX scanner. Briefly, the MRI protocol included the following sequences: whole brain axial and coronal fluid-attenuated inversion recovery (FLAIR) sequences (TR/TE 10.000/160 ms); a sagittal T1-weighted sequence (TR/TE 300/4 ms); and an axial T2-weighted sequence (TR/TE 6500/105 ms).

Measures of neuropathology

Three experienced independent observers (EJO, JAHRC, JMO), blinded to the clinical diagnoses and neuropsychological test scores, visually rated white matter hyperintensities (WMH), medial temporal lobe atrophy (MTA), and global atrophy (GA). In this study, we employed qualitative visual rating scales as these are easily applicable in clinical practice and, relatively to volumetric

measures, provide comparable or even more reliable assessments of neuropathology (Gouw et al., 2006; Persson et al., 2018; Topiwala et al., 2019). WMH were rated on axial FLAIR and T2-weighted images using the Fazekas scale, providing a score between 0-3 based on the deep and periventricular areas of the brain (Fazekas et al., 1987). MTA was rated on coronal T1-weighted images with a 5-point (0-4) scale, considering the height of the hippocampus as well as the width of the choroid fissure and temporal horn of the left and right MTA (Scheltens et al., 1992). GA was rated on a 4-point (0-3) rating scale using all available MRI sequences, and represented the mean score for cortical atrophy based on the width of gyri and sulci across the whole cerebrum (Scheltens et al., 1997).

As we were interested in capturing the accumulation of neuropathological damage rather than the effects of a particular type of neuropathology, we combined the effects of MTA, GA, and WMH to obtain a single measure indicative of neuropathology per patient in relation to each separate cognitive domain. To accomplish this, first, separate multiple linear regression models were performed using the cognitive domain scores as dependent variables and the measures of neuropathology as predictors. As sample sizes differed across the diagnostic groups, with substantially less cases of SCD, we wanted to make sure that our neuropathology metric was not biased by the number of patients per group. To this end, a bootstrap scheme was adopted. Across 100 replications, we randomly selected 75 cases from each diagnosis group. Within each bootstrap, leave one out cross validation (LOOCV) was applied to retrieve optimal model parameters. The resulting intercepts and regression weights were averaged to obtain the final parameters, and were subsequently inverted to retrieve the final measure of neuropathological burden (the higher this score, the more neurodegeneration was present that was relevant to a particular cognitive domain). These final burden scores allowed us to identify whether cognitive-domain specific neuropathology scores affect the relationship between education and cognitive functioning.

Statistical analysis

Demographics, vascular risk factors, cognitive performance and measures of brain degeneration were compared between groups using univariate tests (analysis of variance, ANOVA; Chi-squared test; Mann-Whitney U test; and Kruskall-Wallis test, where appropriate). Post-hoc pairwise comparisons (SCD vs. MCI; SCD vs. AD; MCI vs. AD) were corrected for multiple comparisons using false discovery rate (FDR) adjustments.

First, to investigate whether the contribution of education to cognitive performance differed *across* the different clinical diagnoses (SCD, MCI, and AD), we applied Analysis of Covariance (ANCOVA) models. The cognitive domain scores functioned as outcome variables and education level, diagnostic group, and the interaction between education level and diagnostic group as predictors. Subsequently, to further investigate the direction of significant interactions, several multiple linear regression models were performed stratified by diagnostic group, and the resulting slopes of education were compared pairwise using Welch T-tests (SCD vs. MCI, SCD vs. AD). All analyses were corrected for age, sex, and neuropathology scores.

Second, we investigated whether the effects of education differed as a function of neuropathology *within* each diagnosis group. We performed another set of multiple linear regression models, but now separately for each diagnosis group, and education level, neuropathology, and the interaction between education and neuropathology functioned as predictors. This model allowed to test whether the relationship between education and cognitive performance was moderated by current degree of neuropathology. Significant interactions were further examined using simple slope analysis from the *interactions* package in R (Bauer & Curran, 2005). Briefly, the relationship between education and cognitive performance was plotted as a function of different degrees of relative neuropathological burden: lower levels of neuropathology (-1 standard deviation [SD]), average neuropathology (0 SD), and higher levels of neuropathology (+1 SD).

Furthermore, we performed sensitivity analyses to investigate whether our results were influenced by using standardized norm scores to calculate the cognitive domain scores, as norm scores provide an indication of cognitive performance relatively to an individual's age, sex and/or educational level. Norm scores were computed using a large Dutch normative database from the Advanced Neuropsychological Diagnostics Infrastructure (ANDI; de Vent et al., 2016). As normative data for the FAB were unavailable in ANDI, these norm scores were generated using another normative database (Coen et al., 2016). Moreover, given that floor performance on the TMT ratio scores and delayed recall of the 8-Wordt Test occurred more frequently in AD and MCI relatively to SCD (see Supplementary Table A, p 3 in Supplemental Material), we also repeated our analyses while deriving the compound scores without these particular (sub-)tests. In addition, we investigated whether the effects of the neuropathological compound score were driven by a particular MRI rating

(MTA, GA, or WMH). Therefore, we repeated our analysis using either MTA, GA, or WMH in the interaction term and corrected for the other neuropathological features (e.g., interaction between education and MTA, additionally correcting for GA and WMH).

For each linear regression model, all variables were scaled (i.e. z-normalized) prior to the analysis. Assumptions were checked using regression diagnostic plots and the *gvlma* package in R (Pena & Slate, 2006). None of the assumptions were violated (e.g., linearity, distribution of residuals, homoscedasticity).

All analyses were performed using R (version 3.6.1; https://www.R-project.org). Two-tailed *p*-values of < 0.05 were considered statistically significant. We report uncorrected *p*-values and FDR-corrected *p*-values to account for multiple comparisons across diagnoses and cognitive domains. We calculated Cohen's f^2 to indicate the effect sizes for our effects of interest (0.02 = small, 0.15 = medium, 0.35 = large; Cohen, 2013). Data visualization was performed using the *raincloudplots* and *sjPlot* packages in R (Allen et al., 2021; Lüdecke, 2021).

Results

An overview of participant characteristics for participants with SCD, MCI, and AD is provided in Table 1. The variability in cognitive performance across each cognitive domain and diagnosis group is visualized in Figure 1. We did not observe any differences between diagnosic groups regarding sex (p = 0.11), diabetes (p = 0.80), hypertension (p = 0.56), cardiac disease (p = 0.06), and history of stroke (p = 0.91). After FDR-adjustments for multiple comparisons, age, education, cognitive performance and visual MRI ratings differed significantly between groups (all corrected *p*-values < 0.01). Post-hoc tests revealed that individuals with SCD were relatively younger than those with MCI or AD, and those with MCI were younger than with AD (all corrected *p*-values < 0.05). Educational attainment was relatively higher in SCD, followed by MCI and AD (all corrected *p's* < 0.05). MTA, GA and WMH were less pronounced in individuals with SCD when compared to both MCI and AD; and both MTA and GA were less severe in MCI relatively to AD (all corrected *p*-values < 0.05).

Table 1. Overview of participant characteristics

	SCD	MCI	AD	
N	**108**	**190**	**245**	**p-value**
Demographics				
Age, median (IQR)	71 (66-78)	78 (73-82)	80 (76-84)	<.001a,b,c,d
Sex, N (%)	61 (57%)	106 (56%)	159 (65%)	.110
Education level, median (IQR)	5 (3-5)	4 (4-5)	4 (3-5)	.006a,c,d
High education, N(%)	26 (24%)	46 (24%)	45 (18%)	
Average education, N(%)	54 (50%)	102 (54%)	114 (47%)	
Low education, N(%)	28 (26%)	42 (22%)	86 (36%)	
Vascular risk factors				
Diabetes mellitus, N(%)	20 (19%)	30 (16%)	39 (16%)	.800
Hypertension, N(%)	46 (43%)	88 (46%)	101 (41%)	.561
History of stroke/TIA, N(%)	16 (15%)	30 (16%)	35 (14%)	.915
Cardiac disease, N(%)	26 (24%)	67 (35%)	66 (27%)	.063
Cognitive functions				
MMSE, mean (SD)	28.06 (2.02)	26.25 (2.49)	22.34 (3.84)	<.001a,b,c,d
Global cognition, mean (SD)	0.74 (0.49)	0.13 (0.47)	-0.56 (0.58)	<.001a,b,c,d
Episodic memory, mean (SD)	1.13 (0.58)	0.10 (0.63)	-0.52 (0.58)	<.001a,b,c,d
Executive functions, mean (SD)	0.56 (0.69)	0.12 (0.63)	-0.51 (0.72)	<.001a,b,c,d
Neuropathological measures				
MTA, median (IQR)	0 (0-1)	1 (1-2)	2 (1-2)	<.001a,b,c,d
WMH, median (IQR)	1 (0-2)	2 (1-3)	2 (1-3)	<.001a,b,c
GA, median (IQR)	1 (0-1)	1 (1-2)	1 (1-2)	<.001a,b,c,d

Abbreviations: SCD = subjective cognitive decline; MCI = mild cognitive impairment; AD = Alzheimer's disease dementia; TIA = transient ischemic attack; MTA = medial temporal lobe atrophy; WMH = white matter hyperintensities; GA = global atrophy. Information was missing for history of stroke/TIA in 1 (0.18%), cardiac disease in 1 (0.18%), episodic memory in 2 (0.37%), executive functions in 1 (0.18%). P-values displayed are uncorrected. [a]Group contrast, surviving FDR-correction for multiple comparisons; [b]Significant SCD vs. MCI comparison after FDR-corrections; [c]Significant SCD vs. AD comparison after FDR-corrections; [d]Significant MCI vs. AD comparison after FDR-corrections

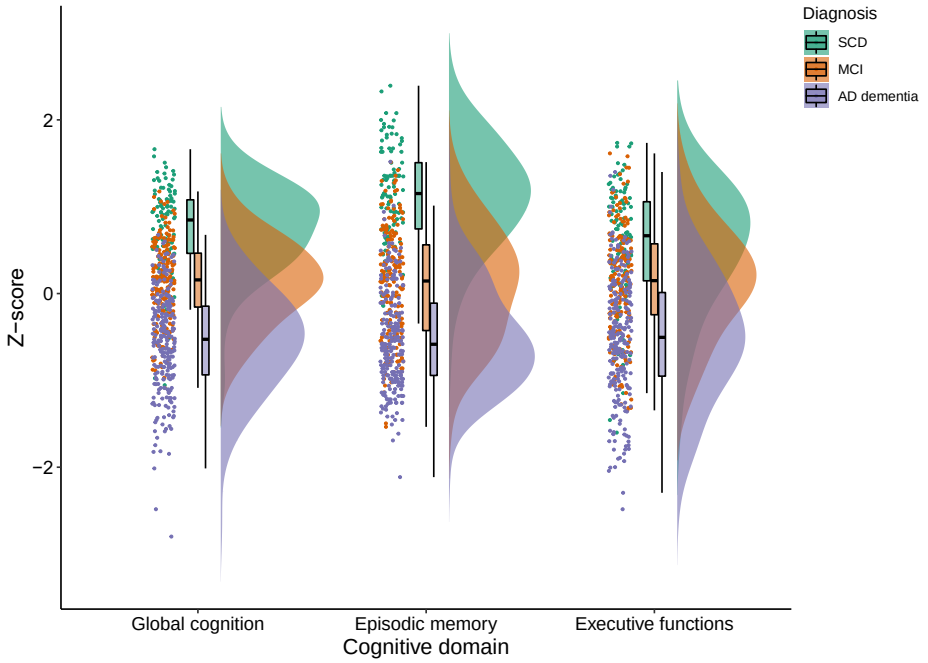


Figure 1. Variability in cognitive performance in subjective cognitive decline (SCD), mild cognitive impairment (MCI), and Alzheimer's disease dementia

We noted significant interactions between education and clinical diagnosis on global cognition ($F_{2,534}$ = 4.48, p = 0.01), episodic memory ($F_{2,532}$ = 3.84, p = 0.01), and executive functions ($F_{2,533}$ = 5.09, p = 0.006). Forest plots of the subsequent stratified multiple linear regression models, by diagnostic group, corrected for age, sex, and neuropathological burden, is displayed in Figure 2. These analyses revealed that education independently contributed to cognitive performance on global cognition and executive functions across each diagnosis group (all corrected *p-values* < 0.05), but not on episodic memory in MCI and AD (all corrected *p*-values > 0.05). Statistical comparison of the corresponding slopes showed that the associations between education and global cognition were stronger in those with SCD relatively to both MCI and AD (uncorrected p = 0.04 and p = 0.002, respectively). However, the slope difference between SCD and MCI did not survive FDR-corrections (corrected p > 0.05). For executive functions, we found that the effects of education were stronger in the SCD group as compared to both MCI and AD (all corrected *p-values* < 0.05).

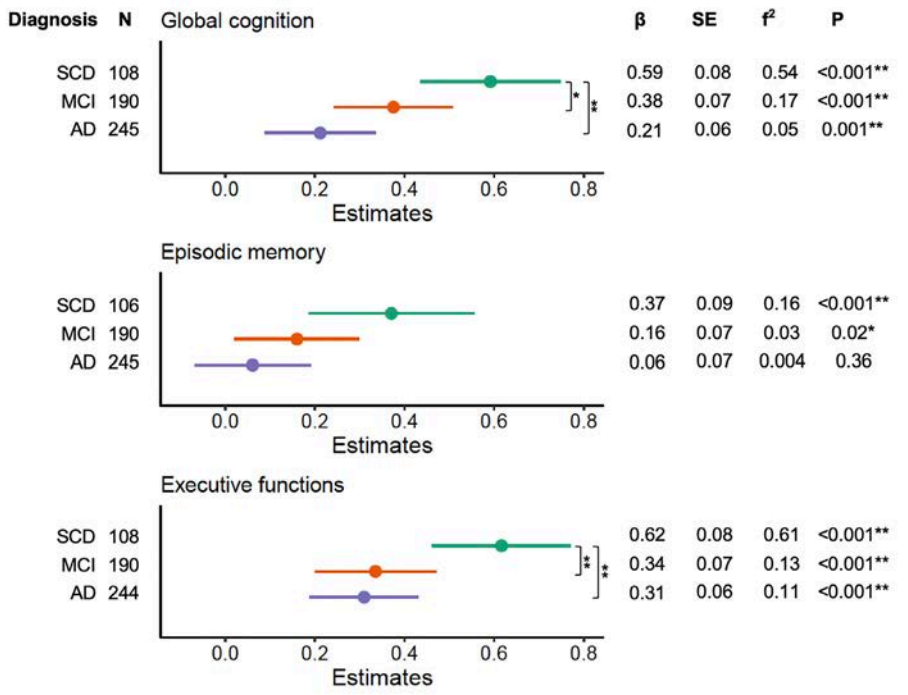


Figure 2. Effects of education on cognitive performance across diagnosis severity. Forest plots indicating the role of education in predicting cognitive performance across diagnosis groups, corrected for age, sex, and neuropathological burden. Effect sizes for the contribution of education were calculated with Cohen's f^2. P-values displayed are uncorrected. Differences in slopes (β) between diagnosis groups were compared using Welch's t-tests (SCD vs. MCI, SCD vs. AD, MCI vs. AD). Abbreviations: SCD = subjective cognitive decline; MCI = mild cognitive impairment; AD = Alzheimer's disease dementia. *Uncorrected $p < 0.05$; **FDR-corrected $p < 0.05$

The second set of linear regression models, modeling the interaction between education and neuropathological burden, revealed significant interactions in the domain of episodic memory only. These were found among those individuals with SCD (β = -0.23, 95% CI = [-0.42; -0.04], uncorrected $p = 0.02$), and MCI (β = 0.15, 95% CI = [0.01; 0.30], uncorrected $p = 0.04$; Figure 3). However, these associations did not survive FDR-corrections. In the SCD group, subsequent simple slope analyses revealed significant effects of education on episodic memory only in those with average or relatively lower levels of neuropathology (β = 0.36, uncorrected $p < 0.001$; β = 0.59, uncorrected $p < 0.001$). In contrast, among patients with MCI, simple slope analyses revealed that education only significantly contributed to episodic memory performance in those with average or relatively higher levels of neuropathology (β = 0.17, uncorrected

p = 0.02; β = 0.33, uncorrected p = 0.003). Results from the multiple linear regression models, including and excluding the interaction terms, are provided in Supplementary Table B.

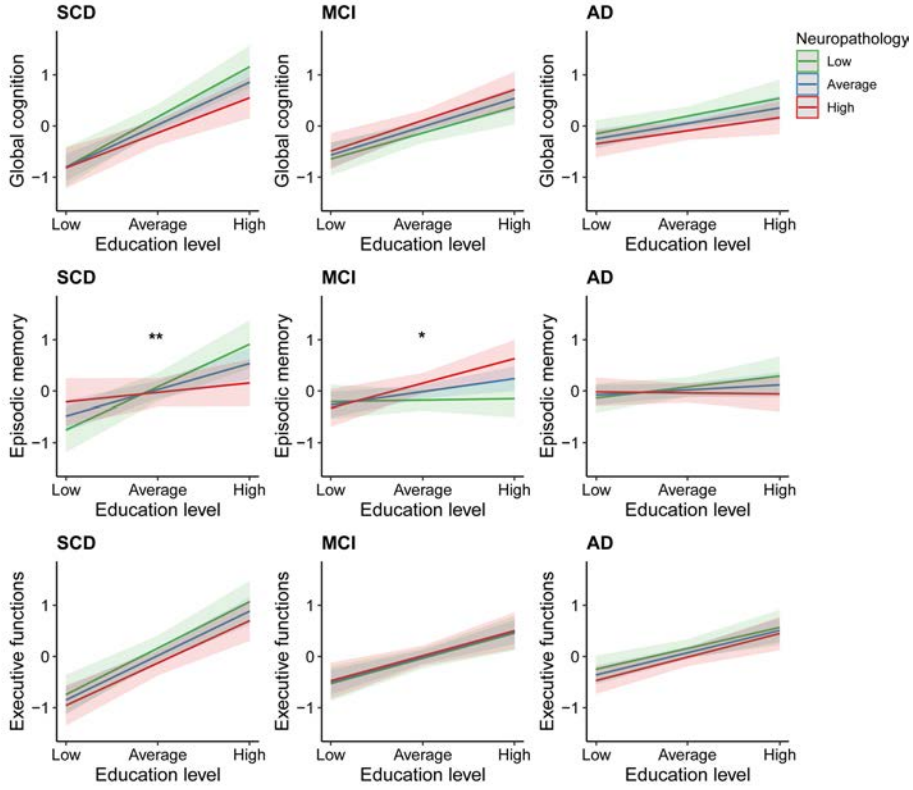


Figure 3. Effects of education on cognitive performance across different degrees of neuropathological burden. Abbreviations: SCD = subjective cognitive decline; MCI = mild cognitive impairment; AD = Alzheimer's disease dementia. *Uncorrected p = 0.04 for interaction between education and neuropathological burden; **Uncorrected p = 0.02 for interaction between education and neuropathological burden

The sensitivity analyses showed that the use of standardized norm scores rather than whole population z-scores to calculate the cognitive domain scores concurred with weaker effects of education on cognitive performance across the different diagnoses. However, the direction of results remained similar (i.e. effect of education on cognition decreased with diagnosis severity). Moreover, the interaction between education and neuropathology on episodic memory in MCI was no longer significant (see Supplementary Table C and Figure A). After calculating the compound scores without the TMT ratio and 8-Word Test

delayed recall, our results remained largely similar, however the interaction between education and neuropathology on episodic memory was no longer significant in MCI (see Supplementary Table D). When using the separate visual MRI ratings in our models, our results were also largely unaffected. We observed that MTA was the main driver of the interaction effect in SCD, whereas GA was the main driver of the interaction in MCI. A complete overview of these results is shown in Supplementary Tables E, F, and G.

Discussion

In this study, we characterized the effects of education on cognitive functions across the different syndromes that differ in the severity of neuropathology and cognitive dysfunction. First, we focused on the different clinical diagnoses as observed in a memory clinic population, comparing patients with SCD, MCI and AD. We demonstrated that the contribution of education in explaining variability in cognitive performance decreased with diagnosis severity, independent of age, sex, and neuropathological burden. Second, we concentrated on the severity of neuropathological burden within these diagnostic groups. We found that the role of education differed as a function of neuropathology in the domain of episodic memory. In SCD, the effects of education on cognition were only found in those individuals with lower levels of neuropathology. In contrast, among those with MCI, the role of education was merely present in individuals with relatively more severe neuropathological burden.

The observed positive effects of education on cognitive functioning throughout SCD, MCI, and AD are in line with previous studies (Groot et al., 2018; Ossenkoppele et al., 2020; Perneczky et al., 2009). Although positive effects of education on global cognition and executive functioning were present across all clinical diagnoses, these effects were less pronounced with increasing diagnosis severity. With regard to episodic memory, positive associations with education were merely present in SCD. These results corroborate previous findings among AD-biomarker positive memory clinic patients, where education level was more strongly associated with measures of attention and executive functioning in SCD and MCI when compared to AD, while no associations were found between education and episodic memory (Groot et al., 2018). It has been suggested that clinical deterioration may become too severe at some point in time, accompanied by a subsequent decline of protective mechanisms including the positive effects of education (Mungas

et al., 2018; Soldan et al., 2020; Stern, 2012; van Loenhoud et al., 2019). This may also explain why education was not related to episodic memory in MCI and AD patients, as episodic memory loss is considered to be the most pronounced clinical hallmark of these diagnoses and the underlying pathological processes (Albert et al., 2011; McKhann et al., 2011; Veitch et al., 2019).

Although pathological processes overall exacerbate with clinical severity, neuropathological burden remains highly variable within a particular clinical diagnosis (Boyle et al., 2017; Mehta & Schneider, 2021). Previous studies among individuals with normal cognitive functions, MCI, and AD demonstrated that positive effects of education on cognitive performance declined with increased neuropathological burden, sometimes even provoking worse cognitive outcomes (Mungas et al., 2021; Mungas et al., 2018; Perneczky et al., 2009; Zahodne et al., 2019). Our findings add to these prior studies by showing that neuropathological burden may differentially alter the association between education and cognition in SCD and MCI. More specifically, we only observed positive effects of education on cognition in those with relatively lower levels of neuropathology in SCD, while in MCI these associations were found in individuals with relatively higher levels of neuropathology. As our results did not survive corrections for multiple comparisons and did not remain significant in several sensitivity analyses, however, cautious interpretation is warranted. Interestingly, similar changes in the direction of effects were observed in a recent study that compared the effects of a composite measure of education and verbal intelligence on episodic memory at different degrees of grey matter atrophy between young-old and old-old participants in a normal elderly cohort (Kwak et al., 2020). Differences in neuropathological burden across seemingly similar populations thus may influence the observed education-cognition associations, conversely contributing to discrepancies in findings across studies (Ewers et al., 2020; Soldan et al., 2020). More specifically, it has been suggested that the positive effects of education initially emerge as a function of neuropathology, plateau, and subsequently decline (Gregory et al., 2017; Staekenborg et al., 2020). For example, contrarily to our study results and prior findings (de Groot et al., 2019), another recent study demonstrated that education more strongly related to cognitive performance in AD relative to SCD and MCI, although these effects diminished in the most severely affected AD patients (Staekenborg et al., 2020).

Several mechanisms have been proposed to explain the benefits of education in both healthy and pathological ageing (Fratiglioni et al., 2020). It has

been suggested that education contributes to an increased resistance for neurodegenerative processes (i.e. brain maintenance; Noble et al., 2012; Chen et al., 2019; Steffener, 2021). However, this does not explain why individuals with higher levels of education show better cognitive performance at similar levels of neuropathology or demonstrate relatively more neuropathological burden in clinical samples (Soldan et al., 2020; Stern, 2012). Furthermore, a recent large-scale longitudinal study found that education related to an initial advantage in structural properties of the brain instead, and not to different rates in neural decline (Nyberg et al., 2021). Education may thus contribute to a stable advantage, where relatively more neurodegeneration is required before the threshold is reached where cognitive dysfunctions start to emerge (i.e. brain reserve; Stern et al., 2020; Cabeza et al., 2018). In line with this, previous studies associated education with better cognitive functions in healthy ageing (Seblova et al., 2020; Lövdén et al., 2020) as well as in SCD, MCI, and AD (Groot et al., 2018; Staekenborg et al., 2020). Moreover, it has been hypothesized that education facilitates cognitive functions by promoting cognitive reserve (CR; Stern, 2012; Stern et al., 2020). CR refers to the ability to compensate for the deteriorative effects of neuropathological processes through the recruitment of existing neural networks and/or compensatory processes via alternative networks (Cabeza et al., 2018; Soldan et al., 2020; Stern, 2012; Stern et al., 2020). However, the contribution of education to CR is under debate, as previous longitudinal and cross-sectional studies have not consistently demonstrated that higher levels of education concur with relatively decreased rates of age- or pathology-related cognitive decline over time (Ewers, 2020; Lövdén et al., 2020; Seblova et al., 2020; Wilson et al., 2019). Lastly, it has to be noted that higher levels of cognitive functioning themselves could facilitate the likelihood of an individual completing higher levels of education (Peng & Kievit, 2020). Therefore, the precise underlying mechanisms and direction of effects between education and cognitive performance remain to be elucidated.

The present study has several strengths and limitations. While earlier studies mostly focused on a single marker of neuropathology (Kwak et al., 2020; Mortamais et al., 2014; Perneczky et al., 2009; Soldan et al., 2015; Teipel et al., 2009), we combined multiple visual MRI ratings into a single measure reflective of brain-wide pathology. Nevertheless, these approaches are restricted in terms of the spatial characterisation of neurodegenerative processes (Jagust, 2018). Voxel-wise analyses (Ledig et al., 2018), connectivity-based approaches (Berron et al., 2020), or data-driven techniques could help to further delineate neuropathological patterns that may better explain individual

variations in cognitive performance (Verdi et al., 2021). Furthermore, although we examined a representative sample of patients referred to a memory clinic in the Netherlands, increasing the external validity of our results, causal inference is impossible due to the lack of longitudinal data, and our cross-sectional design did not allow the investigation of the effects of education on disease progression across the different syndromes. Lastly, we emphasize that our findings require replication in larger cohort studies, given that the neuropathology-dependent effects of education did not survive corrections for multiple comparisons. An increased understanding of such dynamics is not only critical to understand healthy cognitive aging (Cabeza et al., 2018; Stern et al., 2020), but may also aid in the development of individualized prevention or intervention strategies and prognostic models of cognitive decline (Livingston et al., 2020; Fratiglioni et al., 2020; Soldan et al., 2020; Anatürk et al., 2021). Future research should ideally incorporate longitudinal, multi-modal MRI measures to determine how education-cognition associations vary as a function of neuropathology in SCD, MCI, and AD.

In conclusion, we further characterized the extent to which education continues to benefit cognitive performance depending on different disease stages: across and within SCD, MCI, and AD. Generally, the positive effects of education were most strongly pronounced in individuals with SCD and diminished with diagnosis severity. Within a particular diagnosis, however, an increased degree of neuropathological burden does not necessarily imply a reduction of effects. Altogether, our findings highlight the complex dynamics between education and its protective effects on cognitive functions, and the importance of taking into account the diverse dimensions of an individual's disease severity to understand such associations.

Data availability statement

The datasets analyzed for this study are available upon reasonable request. Requests to access these datasets should be directed to JO, joukje.oosterman@donders.ru.nl.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was not provided because all data were collected as part of routine clinical assessments between 2004 and 2015 and were stored in an in-house clinical database in a pseudononymous manner,

compliant with the then-current EU Data Protection Directive 95/46/EC. Data extraction from that database for this study was done by EJO, in compliance with the EU General Data Protection Regulation 2016/679, resulting in a fully anonymous database for further analysis.

Supplements

Supplementary Table A. Characteristics for the individual (sub-)test scores

	SCD (*n* = 108)		MCI (*n* = 190)		AD (*n* = 245)		p-value
Neuropsychological test score	**Mean (SD) or median (IQR)**	***N***	**Mean (SD) or median (IQR)**	***N***	**Mean (SD) or median (IQR)**	***N***	
MMSE, total score, median (IQR)	28 (27-29.25)	108	27 (25-28)	190	23 (20-25)	245	<.001a,b,c,d
VAT, total score, median (IQR)	12 (11-12)	96	7 (4-10)	182	3 (1-7)	229	<.001a,b,c,d
8-word test, immediate recall, mean (SD)	27.83 (5.44)	94	22.88 (4.92)	189	19.51 (6.08)	242	<.001a,b,c,d
8-word test, delayed recall, median (IQR)	4 (2-6)	94	1 (0-2)	187	0 (0-1)	242	<.001a,b,c,d
Fluency, total score occupations, mean (SD)	12.82 (4.72)	106	10.28 (4.15)	189	7.24 (3.85)	244	<.001a,b,c,d
Fluency, total score animals, mean (SD)	17.16 (4.90)	106	14.09 (4.68)	189	11.31 (4.51)	243	<.001a,b,c,d
FAB, total score, median (IQR)	16 (14-17)	99	14 (12-16)	160	11 9-13	207	<.001a,b,c,d
TMT A, seconds, median (IQR)	50 (38.50-59)	91	58 (48-79.50)	135	70 (56.50-101)	111	<.001a,b,c,d
TMT ratio (B/A), seconds, median (IQR)	2.39 (2.02-3.10)	91	3.10 (2.24-4.01)	135	3.78 (2.66-5.52)	111	<.001a,b,c,d

Abbreviations: SCD = subjective cognitive decline; MCI = mild cognitive impairment; AD = Alzheimer's disease dementia; MMSE = Mini Mental State Exam; VAT = Visual Association Test; FAB = Frontal Assessment Battery; TMT = Trail Making Test; IQR = interquartile range; SD = standard deviation. P-values displayed are uncorrected. Univariate tests were used to investigate whether the scores differed per diagnostic group, using analysis of variance (ANOVA), Mann-Whitney U test, and Kruskall-Wallis test, where appropriate. [a]Group contrast, surviving FDR-correction for multiple comparisons; [b]Significant SCD vs. MCI comparison after FDR-corrections; [c]Significant SCD vs. AD comparison after FDR-corrections; [d]Significant MCI vs. AD comparison after FDR-corrections

Supplementary Table B. Effects of education on cognitive performance in SCD, MCI, and AD

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Global cognition						
Constant	0.00 (-0.15, 0.15)	0.01 (-0.14, 0.16)	0.00 (-0.13, 0.13)	-0.001 (-0.13, 0.13)	0.00 (-0.12, 0.12)	0.001 (-0.12, 0.12)
Age	-0.06 (-0.25, 0.13)	-0.05 (-0.25, 0.14)	-0.24*** (-0.38, -0.10)	-0.24*** (-0.38, -0.10)	-0.07 (-0.20, 0.05)	-0.07 (-0.20, 0.06)
Sex	-0.05 (-0.20, 0.11)	-0.04 (-0.20, 0.11)	0.06 (-0.07, 0.20)	0.07 (-0.07, 0.20)	-0.07 (-0.20, 0.05)	-0.07 (-0.20, 0.05)
Neuropathology	-0.15 (-0.34, 0.04)	-0.15 (-0.34, 0.04)	0.12* (-0.02, 0.26)	0.12* (-0.02, 0.27)	-0.13** (-0.26, -0.005)	-0.14** (-0.26, -0.01)
Education	0.59*** (0.44, 0.75)	0.59*** (0.44, 0.75)	0.38*** (0.24, 0.51)	0.38*** (0.25, 0.51)	0.21*** (0.09, 0.34)	0.22*** (0.09, 0.34)
Education* Neuropathology		-0.11 (-0.27, 0.06)		0.03 (-0.11, 0.17)		-0.03 (-0.16, 0.09)
Observations	108	108	190	190	245	245
R^2	0.38	0.39	0.18	0.18	0.09	0.09
Adjusted R^2	0.36	0.36	0.17	0.16	0.07	0.07
Episodic memory						
Constant	0.005 (-0.17, 0.18)	0.02 (-0.15, 0.20)	0.00 (-0.14, 0.14)	-0.01 (-0.14, 0.13)	-0.00 (-0.13, 0.13)	0.004 (-0.12, 0.13)
Age	-0.12 (-0.35, 0.11)	-0.11 (-0.33, 0.12)	-0.20*** (-0.34, -0.05)	-0.20*** (-0.34, -0.05)	-0.05 (-0.18, 0.09)	-0.04 (-0.18, 0.09)
Sex	-0.04 (-0.23, 0.14)	-0.02 (-0.20, 0.16)	-0.14* (-0.28, -0.001)	-0.13* (-0.27, 0.01)	-0.05 (-0.18, 0.08)	-0.05 (-0.17, 0.08)
Neuropathology	-0.04 (-0.26, 0.18)	-0.05 (-0.26, 0.17)	0.15* (0.0003, 0.29)	0.17** (0.02, 0.32)	-0.03 (-0.17, 0.10)	-0.04 (-0.17, 0.10)
Education	0.37*** (0.19, 0.55)	0.37*** (0.19, 0.54)	0.16** (0.02, 0.30)	0.17** (0.04, 0.31)	0.06 (-0.07, 0.19)	0.07 (-0.06, 0.20)
Education* Neuropathology		-0.23** (-0.42, -0.04)		0.15** (0.01, 0.30)		-0.08 (-0.21, 0.05)
Observations	106	106	190	190	245	245
R^2	0.15	0.20	0.10	0.12	0.01	0.02
Adjusted R^2	0.12	0.16	0.08	0.10	-0.005	-0.003

Supplementary Table B. Continued

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Executive functions						
Constant	0.00 (-0.15, 0.15)	0.002 (-0.15, 0.15)	0.00 (-0.13, 0.13)	-0.0000 (-0.13, 0.13)	0.002 (-0.12, 0.12)	0.002 (-0.12, 0.12)
Age	-0.05 (-0.24, 0.14)	-0.05 (-0.24, 0.15)	-0.18** (-0.32, -0.03)	-0.18** (-0.32, -0.03)	-0.11* (-0.24, 0.01)	-0.12* (-0.24, 0.01)
Sex	-0.01 (-0.16, 0.14)	-0.01 (-0.16, 0.15)	0.19*** (0.06, 0.33)	0.19*** (0.06, 0.33)	-0.02 (-0.14, 0.10)	-0.02 (-0.14, 0.10)
Neuropathology	-0.14 (-0.34, 0.05)	-0.14 (-0.34, 0.05)	0.03 (-0.12, 0.17)	0.03 (-0.12, 0.17)	-0.09 (-0.22, 0.04)	-0.09 (-0.22, 0.04)
Education	0.62*** (0.46, 0.77)	0.62*** (0.46, 0.77)	0.34*** (0.20, 0.47)	0.34*** (0.20, 0.47)	0.31*** (0.19, 0.43)	0.31*** (0.19, 0.43)
Education* Neuropathology		-0.03 (-0.19, 0.13)		-0.002 (-0.14, 0.14)		0.02 (-0.10, 0.14)
Observations	108	108	190	190	244	244
R^2	0.40	0.40	0.15	0.15	0.13	0.13
Adjusted R^2	0.37	0.37	0.13	0.13	0.12	0.11

Abbreviations: SCD = subjective cognitive decline; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease dementia. Values represent standardized coefficients (β) and corresponding 95% confidence interval (CI). *p<0.1; **p<.05; ***p<0.01.

Supplementary Table C. Sensitivity analysis with norm scores

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Global cognition						
Constant	0.00 (-0.17, 0.17)	0.01 (-0.16, 0.17)	0.00 (-0.14, 0.14)	-0.001 (-0.14, 0.14)	0.00 (-0.12, 0.12)	0.0004 (-0.12, 0.12)
Age	0.11 (-0.10, 0.32)	0.12 (-0.09, 0.33)	0.03 (-0.12, 0.19)	0.03 (-0.12, 0.19)	0.19*** (0.06, 0.32)	0.19*** (0.06, 0.32)
Sex	-0.05 (-0.22, 0.12)	-0.04 (-0.21, 0.13)	0.04 (-0.10, 0.19)	0.04 (-0.10, 0.19)	-0.05 (-0.18, 0.08)	-0.05 (-0.18, 0.08)
Neuropathology	-0.15 (-0.35, 0.06)	-0.15 (-0.36, 0.06)	0.08 (-0.07, 0.23)	0.09 (-0.07, 0.24)	-0.08 (-0.22, 0.05)	-0.08 (-0.22, 0.05)
Education	0.48*** (0.31, 0.65)	0.48*** (0.31, 0.65)	0.16** (0.02, 0.30)	0.16** (0.02, 0.31)	0.01 (-0.12, 0.14)	0.01 (-0.12, 0.14)
Education* Neuropathology		-0.13 (-0.30, 0.05)		0.02 (-0.13, 0.17)		-0.01 (-0.14, 0.12)
Observations	108	108	190	190	245	245
R^2	0.25	0.27	0.04	0.04	0.03	0.03
Adjusted R^2	0.23	0.23	0.02	0.01	0.02	0.01
Episodic memory						
Constant	-0.01 (-0.19, 0.18)	0.01 (-0.17, 0.19)	0.00 (-0.14, 0.14)	-0.01 (-0.15, 0.13)	0.00 (-0.11, 0.11)	0.01 (-0.11, 0.12)
Age	0.18 (-0.05, 0.41)	0.19* (-0.03, 0.42)	0.15** (0.004, 0.30)	0.15** (0.004, 0.30)	0.44*** (0.32, 0.56)	0.44*** (0.32, 0.56)
Sex	-0.06 (-0.25, 0.13)	-0.04 (-0.23, 0.15)	-0.16** (-0.30, -0.02)	-0.15** (-0.30, -0.01)	0.03 (-0.08, 0.15)	0.03 (-0.08, 0.15)
Neuropathology	-0.0001 (-0.22, 0.22)	-0.01 (-0.22, 0.21)	0.06 (-0.09, 0.21)	0.08 (-0.07, 0.23)	-0.03 (-0.15, 0.09)	-0.04 (-0.16, 0.08)
Education	0.22** (0.03, 0.40)	0.21** (0.03, 0.39)	0.01 (-0.13, 0.16)	0.02 (-0.12, 0.16)	-0.02 (-0.14, 0.09)	-0.01 (-0.13, 0.11)
Education* Neuropathology		-0.25** (-0.44, -0.06)		0.11 (-0.05, 0.26)		-0.08 (-0.20, 0.03)
Observations	106	106	190	190	245	245
R^2	0.09	0.15	0.05	0.06	0.19	0.20
Adjusted R^2	0.06	0.10	0.03	0.04	0.18	0.18

Supplementary Table C. Continued

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Executive functions						
Constant	0.00 (-0.16, 0.16)	0.001 (-0.16, 0.16)	0.00 (-0.14, 0.14)	-0.0000 (-0.14, 0.14)	0.0002 (-0.13, 0.13)	0.0000 (-0.13, 0.13)
Age	0.04 (-0.17, 0.25)	0.04 (-0.17, 0.25)	-0.06 (-0.21, 0.10)	-0.06 (-0.21, 0.10)	0.07 (-0.07, 0.20)	0.07 (-0.07, 0.20)
Sex	-0.02 (-0.19, 0.14)	-0.02 (-0.19, 0.14)	0.20*** (0.06, 0.35)	0.20*** (0.06, 0.35)	0.01 (-0.12, 0.14)	0.01 (-0.12, 0.14)
Neuropathology	-0.17 (-0.38, 0.03)	-0.17 (-0.38, 0.03)	0.01 (-0.14, 0.16)	0.01 (-0.14, 0.16)	-0.05 (-0.19, 0.08)	-0.05 (-0.19, 0.08)
Education	0.53*** (0.37, 0.70)	0.53*** (0.37, 0.70)	0.17** (0.03, 0.31)	0.17** (0.03, 0.31)	0.07 (-0.06, 0.20)	0.07 (-0.06, 0.20)
Education* Neuropathology		-0.02 (-0.19, 0.16)		0.001 (-0.15, 0.15)		0.004 (-0.13, 0.14)
Observations	108	108	190	190	244	244
R^2	0.30	0.31	0.06	0.06	0.01	0.01
Adjusted R^2	0.28	0.27	0.04	0.03	-0.01	-0.01

Abbreviations: SCD = subjective cognitive decline; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease dementia. Values represent standardized coefficients (β) and corresponding 95% confidence interval (CI). *p<0.1; **p<.05; ***p<0.01.

Supplementary Table D. Sensitivity analysis without TMT ratio and delayed recall

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Episodic memory						
Constant	0.004 (-0.17, 0.18)	0.02 (-0.15, 0.19)	0.00 (-0.14, 0.14)	-0.003 (-0.14, 0.13)	0.00 (-0.13, 0.13)	0.004 (-0.12, 0.13)
Age	-0.09 (-0.31, 0.13)	-0.07 (-0.29, 0.14)	-0.17** (-0.32, -0.02)	-0.17** (-0.32, -0.02)	-0.04 (-0.17, 0.10)	-0.03 (-0.17, 0.10)
Sex	0.04 (-0.14, 0.23)	0.06 (-0.11, 0.24)	-0.08 (-0.22, 0.06)	-0.08 (-0.22, 0.06)	-0.04 (-0.17, 0.09)	-0.04 (-0.17, 0.09)
Neuropathology	-0.04 (-0.26, 0.18)	-0.05 (-0.26, 0.16)	0.15** (0.01, 0.30)	0.16** (0.01, 0.31)	-0.07 (-0.21, 0.06)	-0.08 (-0.21, 0.05)
Education	0.42*** (0.24, 0.60)	0.42*** (0.25, 0.60)	0.21*** (0.07, 0.35)	0.22*** (0.08, 0.35)	0.09 (-0.04, 0.21)	0.09 (-0.03, 0.22)
Education* Neuropathology		-0.25*** (-0.43, -0.07)		0.07 (-0.08, 0.22)		-0.08 (-0.21, 0.05)
Observations	108	108	190	190	244	244
R^2	0.40	0.40	0.17	0.17	0.14	0.14
Adjusted R^2	0.36	0.36	0.14	0.14	0.11	0.11
Executive functions						
Constant	0.00 (-0.14, 0.14)	0.01 (-0.14, 0.15)	0.00 (-0.13, 0.13)	-0.0000 (-0.13, 0.13)	0.001 (-0.12, 0.12)	0.002 (-0.12, 0.12)
Age	-0.06 (-0.24, 0.12)	-0.05 (-0.24, 0.13)	-0.21*** (-0.35, -0.07)	-0.21*** (-0.35, -0.07)	-0.11* (-0.24, 0.01)	-0.11* (-0.24, 0.01)
Sex	-0.08 (-0.22, 0.07)	-0.07 (-0.22, 0.08)	0.16** (0.02, 0.29)	0.16** (0.02, 0.29)	-0.03 (-0.15, 0.09)	-0.03 (-0.15, 0.09)
Neuropathology	-0.20** (-0.39, -0.02)	-0.21** (-0.39, -0.02)	-0.01 (-0.15, 0.14)	-0.01 (-0.15, 0.14)	-0.14** (-0.26, -0.01)	-0.14** (-0.26, -0.01)
Education	0.62*** (0.48, 0.77)	0.62*** (0.48, 0.77)	0.33*** (0.20, 0.47)	0.33*** (0.20, 0.47)	0.24*** (0.12, 0.37)	0.25*** (0.12, 0.37)
Education* Neuropathology		-0.09 (-0.24, 0.06)		-0.02 (-0.16, 0.13)		-0.01 (-0.14, 0.11)
Observations	108	108	190	190	244	244

Supplementary Table D. Continued

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
R^2	0.45	0.46	0.15	0.15	0.11	0.11
Adjusted R^2	0.43	0.43	0.14	0.13	0.09	0.09

Abbreviations: SCD = subjective cognitive decline; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease dementia. Values represent standardized coefficients (β) and corresponding 95% confidence interval (CI). *p<0.1; **p<.05; ***p<0.01.

Supplementary Table E. Sensitivity analysis with MTA in the interaction term

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Global cognition						
Constant	0.00 (-0.15, 0.15)	0.005 (-0.15, 0.16)	0.00 (-0.13, 0.13)	-0.01 (-0.14, 0.13)	0.00 (-0.12, 0.12)	0.001 (-0.12, 0.12)
Age	-0.06 (-0.26, 0.14)	-0.05 (-0.25, 0.15)	-0.24*** (-0.38, -0.09)	-0.24*** (-0.38, -0.09)	-0.06 (-0.19, 0.07)	-0.06 (-0.19, 0.07)
Sex	-0.05 (-0.21, 0.12)	-0.04 (-0.20, 0.12)	0.07 (-0.07, 0.20)	0.07 (-0.06, 0.21)	-0.06 (-0.19, 0.07)	-0.06 (-0.19, 0.07)
MTA	-0.09 (-0.27, 0.09)	-0.08 (-0.26, 0.10)	0.09 (-0.05, 0.24)	0.10 (-0.04, 0.24)	-0.04 (-0.16, 0.09)	-0.04 (-0.17, 0.09)
GA	-0.05 (-0.23, 0.13)	-0.07 (-0.25, 0.11)	0.08 (-0.07, 0.22)	0.08 (-0.06, 0.23)	-0.08 (-0.21, 0.06)	-0.08 (-0.21, 0.06)
WMH	-0.07 (-0.25, 0.12)	-0.05 (-0.24, 0.13)	-0.02 (-0.16, 0.13)	-0.02 (-0.16, 0.12)	-0.10 (-0.23, 0.03)	-0.10 (-0.23, 0.04)
Education	0.59*** (0.44, 0.75)	0.59*** (0.43, 0.74)	0.37*** (0.23, 0.50)	0.37*** (0.24, 0.51)	0.21*** (0.08, 0.33)	0.21*** (0.08, 0.34)
Education*MTA		-0.09 (-0.25, 0.07)		0.06 (-0.08, 0.20)		-0.02 (-0.14, 0.11)
Observations	108	108	190	190	245	245
R^2	0.38	0.39	0.19	0.19	0.09	0.09
Adjusted R^2	0.34	0.35	0.16	0.16	0.07	0.06
Episodic memory						
Constant	0.01 (-0.17, 0.18)	0.02 (-0.15, 0.19)	0.00 (-0.14, 0.14)	-0.01 (-0.15, 0.13)	-0.00 (-0.13, 0.13)	0.003 (-0.12, 0.13)
Age	-0.10 (-0.33, 0.13)	-0.08 (-0.30, 0.15)	-0.21*** (-0.36, -0.06)	-0.21*** (-0.36, -0.06)	-0.05 (-0.19, 0.08)	-0.05 (-0.19, 0.08)
Sex	-0.03 (-0.21, 0.16)	-0.02 (-0.20, 0.17)	-0.14** (-0.28, -0.002)	-0.13* (-0.27, 0.01)	-0.05 (-0.18, 0.08)	-0.05 (-0.18, 0.08)
MTA	0.08 (-0.13, 0.28)	0.09 (-0.10, 0.29)	0.07 (-0.08, 0.21)	0.08 (-0.07, 0.23)	-0.02 (-0.15, 0.12)	-0.02 (-0.15, 0.11)
GA	-0.10 (-0.31, 0.10)	-0.16 (-0.36, 0.05)	0.07 (-0.08, 0.22)	0.08 (-0.07, 0.23)	-0.07 (-0.21, 0.07)	-0.07 (-0.21, 0.07)
WMH	-0.08 (-0.29, 0.13)	-0.05 (-0.25, 0.16)	0.09 (-0.06, 0.24)	0.08 (-0.06, 0.23)	0.06 (-0.08, 0.20)	0.06 (-0.08, 0.20)
Education	0.37*** (0.19, 0.55)	0.36*** (0.18, 0.53)	0.17** (0.03, 0.31)	0.18** (0.04, 0.32)	0.06 (-0.07, 0.19)	0.07 (-0.06, 0.20)
Education*MTA		-0.26*** (-0.43, -0.08)		0.10 (-0.05, 0.24)		-0.04 (-0.17, 0.09)

Supplementary Table E. Continued

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Observations	106	106	190	190	245	245
R^2	0.17	0.24	0.10	0.11	0.02	0.02
Adjusted R^2	0.12	0.18	0.07	0.08	-0.01	-0.01
Executive functions						
Constant	0.00 (-0.15, 0.15)	-0.001 (-0.15, 0.15)	0.00 (-0.13, 0.13)	-0.01 (-0.14, 0.13)	0.002 (-0.12, 0.12)	0.004 (-0.12, 0.12)
Age	-0.05 (-0.25, 0.14)	-0.05 (-0.25, 0.14)	-0.18** (-0.32, -0.03)	-0.18** (-0.32, -0.03)	-0.11* (-0.24, 0.02)	-0.11* (-0.24, 0.02)
Sex	-0.01 (-0.17, 0.15)	-0.01 (-0.17, 0.15)	0.21*** (0.07, 0.34)	0.21*** (0.08, 0.35)	-0.01 (-0.13, 0.11)	-0.01 (-0.13, 0.11)
MTA	-0.10 (-0.28, 0.07)	-0.11 (-0.28, 0.07)	0.10 (-0.04, 0.24)	0.11 (-0.04, 0.25)	0.002 (-0.12, 0.13)	-0.001 (-0.13, 0.12)
GA	-0.01 (-0.18, 0.17)	-0.004 (-0.18, 0.18)	0.05 (-0.10, 0.19)	0.06 (-0.09, 0.20)	-0.03 (-0.16, 0.10)	-0.03 (-0.16, 0.10)
WMH	-0.07 (-0.25, 0.11)	-0.07 (-0.26, 0.11)	-0.11 (-0.25, 0.04)	-0.11 (-0.25, 0.03)	-0.10 (-0.23, 0.03)	-0.10 (-0.23, 0.03)
Education	0.62*** (0.46, 0.77)	0.62*** (0.46, 0.77)	0.31*** (0.18, 0.45)	0.32*** (0.18, 0.45)	0.31*** (0.18, 0.43)	0.31*** (0.18, 0.43)
Education*MTA		0.02 (-0.14, 0.17)		0.08 (-0.06, 0.22)		-0.02 (-0.14, 0.10)
Observations	108	108	190	190	244	244
R^2	0.40	0.40	0.17	0.17	0.14	0.14
Adjusted R^2	0.36	0.36	0.14	0.14	0.11	0.11

Abbreviations: SCD = subjective cognitive decline; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease dementia. Values represent standardized coefficients (β) and corresponding 95% confidence interval (CI). *p<0.1; **p<.05; ***p<0.01.

Supplementary Table F. Sensitivity analysis with GA in the interaction term

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Global cognition						
Constant	0.00 (-0.15, 0.15)	0.01 (-0.14, 0.16)	0.00 (-0.13, 0.13)	-0.001 (-0.13, 0.13)	0.00 (-0.12, 0.12)	0.0000 (-0.12, 0.12)
Age	-0.06 (-0.26, 0.14)	-0.06 (-0.26, 0.13)	-0.24*** (-0.38, -0.09)	-0.24*** (-0.38, -0.09)	-0.06 (-0.19, 0.07)	-0.06 (-0.19, 0.07)
Sex	-0.05 (-0.21, 0.12)	-0.04 (-0.20, 0.13)	0.07 (-0.07, 0.20)	0.07 (-0.07, 0.20)	-0.06 (-0.19, 0.07)	-0.06 (-0.19, 0.07)
MTA	-0.09 (-0.27, 0.09)	-0.11 (-0.29, 0.07)	0.09 (-0.05, 0.24)	0.10 (-0.05, 0.24)	-0.04 (-0.16, 0.09)	-0.04 (-0.16, 0.09)
GA	-0.05 (-0.23, 0.13)	-0.01 (-0.20, 0.18)	0.08 (-0.07, 0.22)	0.08 (-0.07, 0.22)	-0.08 (-0.21, 0.06)	-0.08 (-0.21, 0.06)
WMH	-0.07 (-0.25, 0.12)	-0.09 (-0.27, 0.10)	-0.02 (-0.16, 0.13)	-0.02 (-0.16, 0.13)	-0.10 (-0.23, 0.03)	-0.10 (-0.23, 0.04)
Education	0.59*** (0.44, 0.75)	0.60*** (0.44, 0.75)	0.37*** (0.23, 0.50)	0.37*** (0.23, 0.50)	0.21*** (0.08, 0.33)	0.21*** (0.08, 0.33)
Education*GA		-0.11 (-0.27, 0.04)		0.03 (-0.10, 0.16)		-0.002 (-0.13, 0.12)
Observations	108	108	190	190	245	245
R^2	0.38	0.39	0.19	0.19	0.09	0.09
Adjusted R^2	0.34	0.35	0.16	0.16	0.07	0.06
Episodic memory						
Constant	0.01 (-0.17, 0.18)	0.02 (-0.16, 0.20)	0.00 (-0.14, 0.14)	-0.003 (-0.14, 0.13)	-0.00 (-0.13, 0.13)	0.001 (-0.12, 0.13)
Age	-0.10 (-0.33, 0.13)	-0.10 (-0.34, 0.13)	-0.21*** (-0.36, -0.06)	-0.21*** (-0.36, -0.06)	-0.05 (-0.19, 0.08)	-0.04 (-0.18, 0.09)
Sex	-0.03 (-0.21, 0.16)	-0.01 (-0.20, 0.18)	-0.14** (-0.28, -0.002)	-0.14** (-0.28, -0.002)	-0.05 (-0.18, 0.08)	-0.06 (-0.19, 0.08)
MTA	0.08 (-0.13, 0.28)	0.05 (-0.16, 0.26)	0.07 (-0.08, 0.21)	0.08 (-0.07, 0.23)	-0.02 (-0.15, 0.12)	-0.02 (-0.15, 0.11)
GA	-0.10 (-0.31, 0.10)	-0.05 (-0.26, 0.17)	0.07 (-0.08, 0.22)	0.08 (-0.07, 0.23)	-0.07 (-0.21, 0.07)	-0.07 (-0.21, 0.07)
WMH	-0.08 (-0.29, 0.13)	-0.11 (-0.32, 0.11)	0.09 (-0.06, 0.24)	0.09 (-0.06, 0.24)	0.06 (-0.08, 0.20)	0.06 (-0.08, 0.20)
Education	0.37*** (0.19, 0.55)	0.38*** (0.19, 0.56)	0.17** (0.03, 0.31)	0.17** (0.03, 0.31)	0.06 (-0.07, 0.19)	0.07 (-0.06, 0.20)
Education*GA		-0.15 (-0.33, 0.03)		0.13* (-0.003, 0.27)		-0.08 (-0.21, 0.05)

Supplementary Table F. Continued

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Observations	106	106	190	190	245	245
R^2	0.17	0.19	0.10	0.12	0.02	0.02
Adjusted R^2	0.12	0.13	0.07	0.09	-0.01	-0.01
Executive functions						
Constant	0.00 (-0.15, 0.15)	0.01 (-0.15, 0.16)	0.00 (-0.13, 0.13)	-0.0002 (-0.13, 0.13)	0.002 (-0.12, 0.12)	0.001 (-0.12, 0.12)
Age	-0.05 (-0.25, 0.14)	-0.05 (-0.25, 0.14)	-0.18** (-0.32, -0.03)	-0.18** (-0.32, -0.03)	-0.11* (-0.24, 0.02)	-0.12* (-0.25, 0.01)
Sex	-0.01 (-0.17, 0.15)	-0.01 (-0.17, 0.15)	0.21*** (0.07, 0.34)	0.21*** (0.07, 0.34)	-0.01 (-0.13, 0.11)	-0.005 (-0.13, 0.12)
MTA	-0.10 (-0.28, 0.07)	-0.12 (-0.30, 0.06)	0.10 (-0.04, 0.24)	0.10 (-0.04, 0.25)	0.002 (-0.12, 0.13)	0.01 (-0.12, 0.13)
GA	-0.01 (-0.18, 0.17)	0.02 (-0.16, 0.20)	0.05 (-0.10, 0.19)	0.05 (-0.10, 0.19)	-0.03 (-0.16, 0.10)	-0.03 (-0.16, 0.10)
WMH	-0.07 (-0.25, 0.11)	-0.08 (-0.27, 0.10)	-0.11 (-0.25, 0.04)	-0.11 (-0.25, 0.04)	-0.10 (-0.23, 0.03)	-0.11 (-0.24, 0.02)
Education	0.62*** (0.46, 0.77)	0.62*** (0.46, 0.77)	0.31*** (0.18, 0.45)	0.31*** (0.18, 0.45)	0.31*** (0.18, 0.43)	0.30*** (0.18, 0.42)
Education*GA		-0.07 (-0.23, 0.08)		0.01 (-0.12, 0.14)		0.11* (-0.01, 0.24)
Observations	108	108	190	190	244	244
R^2	0.40	0.40	0.17	0.17	0.14	0.15
Adjusted R^2	0.36	0.36	0.14	0.13	0.11	0.12

Abbreviations: SCD = subjective cognitive decline; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease dementia. Values represent standardized coefficients (β) and corresponding 95% confidence interval (CI). *p<0.1; **p<.05; ***p<0.01.

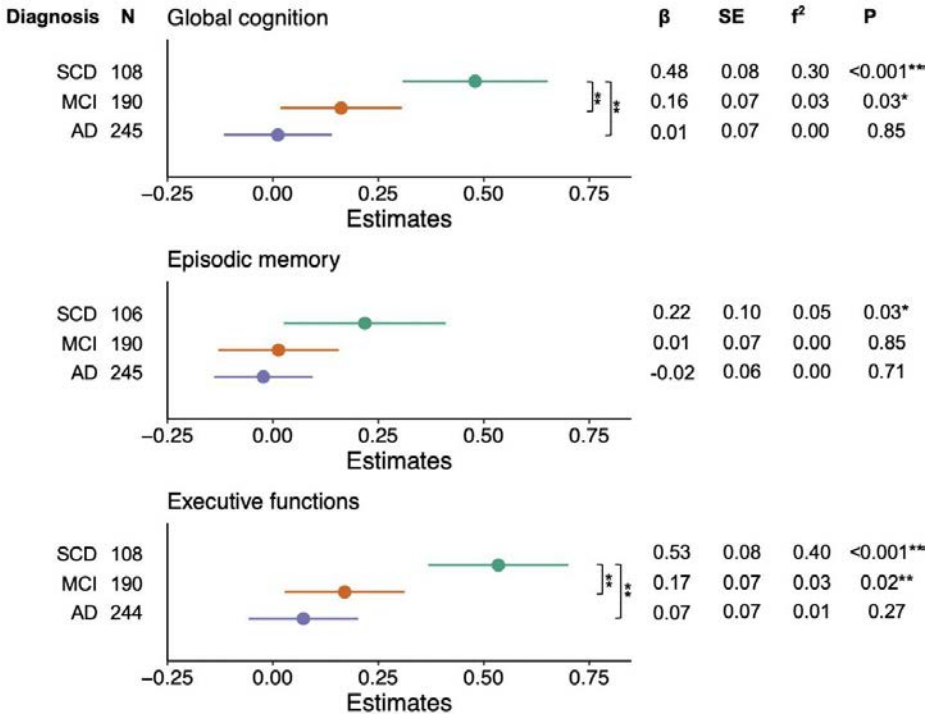
Supplementary Table G. Sensitivity analysis with WMH in the interaction term

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Global cognition						
Constant	0.00 (-0.15, 0.15)	-0.0001 (-0.15, 0.15)	0.00 (-0.13, 0.13)	-0.01 (-0.14, 0.13)	0.00 (-0.12, 0.12)	-0.002 (-0.12, 0.12)
Age	-0.06 (-0.26, 0.14)	-0.06 (-0.26, 0.14)	-0.24*** (-0.38, -0.09)	-0.24*** (-0.39, -0.10)	-0.06 (-0.19, 0.07)	-0.06 (-0.19, 0.07)
Sex	-0.05 (-0.21, 0.12)	-0.05 (-0.21, 0.12)	0.07 (-0.07, 0.20)	0.07 (-0.06, 0.20)	-0.06 (-0.19, 0.07)	-0.06 (-0.19, 0.06)
MTA	-0.09 (-0.27, 0.09)	-0.09 (-0.27, 0.09)	0.09 (-0.05, 0.24)	0.10 (-0.05, 0.24)	-0.04 (-0.16, 0.09)	-0.04 (-0.16, 0.09)
GA	-0.05 (-0.23, 0.13)	-0.05 (-0.23, 0.13)	0.08 (-0.07, 0.22)	0.08 (-0.07, 0.22)	-0.08 (-0.21, 0.06)	-0.08 (-0.21, 0.06)
WMH	-0.07 (-0.25, 0.12)	-0.07 (-0.25, 0.12)	-0.02 (-0.16, 0.13)	-0.02 (-0.16, 0.12)	-0.10 (-0.23, 0.03)	-0.10 (-0.23, 0.03)
Education	0.59*** (0.44, 0.75)	0.59*** (0.43, 0.75)	0.37*** (0.23, 0.50)	0.37*** (0.23, 0.50)	0.21*** (0.08, 0.33)	0.20*** (0.08, 0.33)
Education*WMH		0.004 (-0.15, 0.16)		-0.05 (-0.18, 0.09)		-0.04 (-0.17, 0.08)
Observations	108	108	190	190	245	245
R^2	0.38	0.38	0.19	0.19	0.09	0.09
Adjusted R^2	0.34	0.34	0.16	0.16	0.07	0.07
Episodic memory						
Constant	0.01 (-0.17, 0.18)	0.004 (-0.18, 0.18)	0.00 (-0.14, 0.14)	0.01 (-0.13, 0.14)	-0.00 (-0.13, 0.13)	-0.01 (-0.13, 0.12)
Age	-0.10 (-0.33, 0.13)	-0.11 (-0.34, 0.13)	-0.21*** (-0.36, -0.06)	-0.20** (-0.35, -0.05)	-0.05 (-0.19, 0.08)	-0.05 (-0.18, 0.09)
Sex	-0.03 (-0.21, 0.16)	-0.03 (-0.22, 0.16)	-0.14** (-0.28, -0.002)	-0.15** (-0.29, -0.005)	-0.05 (-0.18, 0.08)	-0.06 (-0.19, 0.07)
MTA	0.08 (-0.13, 0.28)	0.07 (-0.14, 0.28)	0.07 (-0.08, 0.21)	0.06 (-0.09, 0.21)	-0.02 (-0.15, 0.12)	-0.02 (-0.15, 0.12)
GA	-0.10 (-0.31, 0.10)	-0.09 (-0.30, 0.12)	0.07 (-0.08, 0.22)	0.07 (-0.08, 0.22)	-0.07 (-0.21, 0.07)	-0.06 (-0.20, 0.07)
WMH	-0.08 (-0.29, 0.13)	-0.08 (-0.29, 0.13)	0.09 (-0.06, 0.24)	0.09 (-0.06, 0.24)	0.06 (-0.08, 0.20)	0.06 (-0.08, 0.20)
Education	0.37*** (0.19, 0.55)	0.37*** (0.18, 0.55)	0.17** (0.03, 0.31)	0.17** (0.03, 0.31)	0.06 (-0.07, 0.19)	0.05 (-0.07, 0.18)

Supplementary Table G. Continued

	SCD		MCI		AD	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Education*WMH		0.06 (-0.12, 0.24)		0.05 (-0.09, 0.19)		-0.09 (-0.22, 0.04)
Observations	106	106	190	190	245	245
R^2	0.17	0.17	0.10	0.11	0.02	0.02
Adjusted R^2	0.12	0.11	0.07	0.07	-0.01	-0.005
Executive functions						
Constant	0.00 (-0.15, 0.15)	0.0004 (-0.15, 0.15)	0.00 (-0.13, 0.13)	-0.01 (-0.14, 0.13)	0.002 (-0.12, 0.12)	0.003 (-0.12, 0.12)
Age	-0.05 (-0.25, 0.14)	-0.05 (-0.25, 0.15)	-0.18** (-0.32, -0.03)	-0.18** (-0.33, -0.04)	-0.11* (-0.24, 0.02)	-0.11* (-0.24, 0.02)
Sex	-0.01 (-0.17, 0.15)	-0.01 (-0.17, 0.15)	0.21*** (0.07, 0.34)	0.21*** (0.07, 0.34)	-0.01 (-0.13, 0.11)	-0.01 (-0.13, 0.12)
MTA	-0.10 (-0.28, 0.07)	-0.10 (-0.28, 0.08)	0.10 (-0.04, 0.24)	0.10 (-0.04, 0.25)	0.002 (-0.12, 0.13)	0.001 (-0.12, 0.13)
GA	-0.01 (-0.18, 0.17)	-0.01 (-0.19, 0.17)	0.05 (-0.10, 0.19)	0.05 (-0.10, 0.19)	-0.03 (-0.16, 0.10)	-0.03 (-0.16, 0.10)
WMH	-0.07 (-0.25, 0.11)	-0.07 (-0.25, 0.11)	-0.11 (-0.25, 0.04)	-0.11 (-0.25, 0.03)	-0.10 (-0.23, 0.03)	-0.10 (-0.23, 0.03)
Education	0.62*** (0.46, 0.77)	0.62*** (0.46, 0.77)	0.31*** (0.18, 0.45)	0.31*** (0.18, 0.45)	0.31*** (0.18, 0.43)	0.31*** (0.18, 0.43)
Education*WMH		-0.02 (-0.17, 0.13)		-0.06 (-0.20, 0.07)		0.01 (-0.11, 0.13)
Observations	108	108	190	190	244	244
R^2	0.40	0.40	0.17	0.17	0.14	0.14
Adjusted R^2	0.36	0.36	0.14	0.14	0.11	0.11

Abbreviations: SCD = subjective cognitive decline; MCI = Mild Cognitive Impairment; AD = Alzheimer's disease dementia. Values represent standardized coefficients (β) and corresponding 95% confidence interval (CI). *p<0.1; **p<.05; ***p<0.01.



Supplementary Figure A. Effects of education on cognitive domains calculated with norm scores

Forest plots indicating the role of education in predicting cognitive performance across diagnosis groups, corrected for age, sex, and neuropathological burden. Effect sizes for the contribution of education were calculated with Cohen's f^2. P-values displayed are uncorrected. Differences in slopes (β) between diagnosis groups were compared using Welch's t-tests (SCD vs. MCI, SCD vs. AD, MCI vs. AD). Abbreviations: SCD = subjective cognitive decline; MCI = mild cognitive impairment; AD = Alzheimer's disease dementia. *Uncorrected $p < 0.05$; **FDR-corrected $p < 0.05$

Chapter 4

Association of cerebral small vessel disease burden with brain structure and cognitive and vascular risk trajectories in mid-to-late life

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Abstract

We characterize the associations of total cerebral small vessel disease (SVD) burden with brain structure, trajectories of vascular risk factors, and cognitive functions in mid-to-late life. Participants were 623 community-dwelling adults from the Whitehall II Imaging Sub-study with multi-modal MRI (mean age 69.96 SD = 5.18, 79% men). We used linear mixed-effects models to investigate associations of SVD burden with up to 25-year retrospective trajectories of vascular risk and cognitive performance. General linear modelling was used to investigate concurrent associations with grey matter (GM) density and white matter (WM) microstructure, and whether these associations were modified by cognitive status (Montreal Cognitive Assessment, MoCA). Severe SVD burden in older age was associated with higher mean arterial pressure throughout midlife (β = 3.36, 95% CI [0.42 - 6.30]), and faster 25- year cognitive decline in letter fluency (β = -0.07, 95% CI [-0.13 – -0.01]), and verbal reasoning (β = -0.05, 95% CI [-0.11 – -0.001]). Moreover, SVD burden was related to lower GM volumes in 9.7% of total GM, and widespread WM microstructural decline (FWE-corrected $p < 0.05$). The latter association was most pronounced in individuals with cognitive impairments on MoCA ($F_{3,608} = 2.14$, $p = 0.007$). These findings highlight the importance of managing midlife vascular health to preserve brain structure and cognitive function in old age.

Introduction

Cerebral small vessel disease (SVD) refers to a series of pathological processes, damaging the small perforating arterioles of the brain (Ter Telgte et al., 2018). Conventional MRI markers of SVD include, amongst others, white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), cerebral microbleeds (CMB), and lacunes (Ter Telgte et al., 2018; Wardlaw et al., 2013). The total SVD burden score combines the visual ratings of these markers, providing a more comprehensive measure of SVD than each individual component alone (Klarenbeek et al., 2013; Staals et al., 2014).

Accumulating evidence suggests that controlling vascular risk factors (e.g., blood pressure, obesity) earlier in the lifespan may preserve structural brain health in older ages and hence contribute to preventing dementia (Lane et al., 2019; Livingston et al., 2020; Muller et al., 2014; Suri et al., 2019; Zsoldos et al., 2020). However, previous research investigating longitudinal correlates of the SVD burden score have been limited to stroke patients or solely examined sociodemographic factors (e.g., intelligence at age 11) (Field et al., 2016; Lau et al., 2018). SVD burden varies considerably between healthy older adults (Field et al., 2016) and contributes to several other brain structural impairments (Ter Telgte et al., 2018). However, the relationship between total SVD scores and brain morphology is less clear (Blair et al., 2017). Studies investigating the longitudinal vascular and cognitive correlates of SVD, together with structural brain associations, may provide further insights into the stage in life when interventions designed to promote healthy aging could ideally be administered.

We investigated the associations of total SVD burden with up to (1) 25-year retrospective trajectories of vascular risk factors (mean arterial pressure [MAP]; body mass index [BMI]; Framingham Stroke Risk Score [FSRS]) and cognitive decline on several domains and (2) concurrent grey matter (GM) density and white matter (WM) microstructure in 623 elderly individuals from the Whitehall II Imaging cohort. We also examined whether the associations of SVD burden with brain structure were moderated by cognitive status in older age.

Methods

Study design and participants

Participants were selected from the Whitehall II Imaging cohort, a sub-study of the prospective Whitehall II cohort, established by University College London in 1985. Whitehall II participants have received detailed clinical follow-ups for up to 30 years in 1991-1994 (Wave 3), 1997-1999 (Wave 5), 2002-2004 (Wave 7), 2007-2009 (Wave 9), 2012-2013 (Wave 11), and 2015-2016 (Wave 12). For the Imaging Sub-study, 800 participants (60-85 years old) were randomly selected from the Whitehall II Wave 11 cohort and underwent a detailed neuropsychological assessment and multi-modal 3T brain MRI scans at the University of Oxford between 2012-2016 (MRI Wave) (Filippini et al., 2014). A total of 623 participants were included after removing participants with missing data for variables of interest in three or more waves (n = 36), the occurrence of gross MRI abnormalities (e.g., large strokes, cysts, tumours, hydrocephalus which failed the MRI pre-processing pipelines; n = 28), and missing or insufficient quality of MRI images for analysis (e.g., motion artefacts; n = 88). A detailed description and flowchart of participant inclusion is presented in Supplementary Methods and Figure S1. The Whitehall II cohort profile and the Imaging Sub-study protocol have been described previously (Filippini et al., 2014; Marmot & Brunner, 2005).

Standard protocol approvals, registrations, and patient consents

Participants gave informed written consent in a procedure approved by the University of Oxford Central University Research Ethics Committee (Application reference: MS IDREC-C1- 2011-71) for participating at the Whitehall II MRI Substudy and the University College London Medical School Committee on the Ethics of Human Research (reference: 85/0938) at each wave of the full Whitehall II cohort study, both in accordance with the Helsinki Declaration of 1975 (and as revised in 1983).

Demographics

Demographics included age, sex, Caucasian ethnicity, years of full-time education (self- reported at MRI Wave), and highest employment grade at Wave 3 in 1991-1994 to indicate socio-economic status (high = managers/ administrators, intermediate = professionals/ executives, low = clerical/ support staff).

Neuroimaging

MRI scans were acquired on a 3T Siemens Magnetom Verio scanner (Erlangen, Germany) between April 2012–December 2014 (*n* = 427). After a scanner upgrade, the remaining 196 scans were acquired on a 3T Siemens Magnetom Prisma scanner (Erlangen, Germany) between June 2015–April 2016. We examined the following sequences: high-resolution T1- weighted images; fluid-attenuated recovery imaging (FLAIR); T2*-weighted images; and diffusion weighted imaging. Sequences were closely matched between the two scanners and acquisition parameters are described in Table S1, and elsewhere (Filippini et al., 2014; Zsoldos et al., 2020).

Total SVD burden

Visual ratings were performed by experienced raters in accordance with the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria, and were blind to the clinical, cognitive, and other derived MRI variables (Wardlaw et al., 2013). Periventricular and deep WMH were rated on FLAIR images, lacunes on T1 and FLAIR images, EPVS on T1 images, and CMB on T2* images. Details on visual ratings and intra-rater reliability are provided in Supplementary Methods. These ratings were used to calculate total SVD scores to express SVD severity on an ordinal scale from 0-4; 1 point each was provided for a Fazekas score of deep WMH≥2 and/or periventricular WMH > 2, CMB count ≥ 1, lacunes ≥ 1, and EPVS ≥ 11 in the basal ganglia of one hemisphere (Klarenbeek et al., 2013; Staals et al., 2014). As only 2% of the sample (*n* = 13) had a SVD burden score of 4, we merged groups with scores of 3 and 4.

Vascular risk factors

Vascular risk factors were assessed six times at 5-year intervals from 1991-1994 (Wave 3) to 2015-2016 (Wave 12), using both questionnaires and clinical examinations (for details, see Supplementary Methods). Based on the literature linking vascular risk factors and cognitive decline (Lane et al., 2019; Livingston et al., 2020; Zsoldos et al., 2020), we selected three measures of vascular risk for the longitudinal trajectory analysis: MAP [(systolic BP + 2 x diastolic BP)/3], BMI (kg/m^2) and the FSRS. The FSRS predicts the likelihood of a stroke within 10 years, calculated with an algorithm which combines age, sex, systolic blood pressure, self- reported use of antihypertensives, diabetes, current smoking, current or previous atrial fibrillation, left ventricular hypertrophy, and cardiovascular disease (D'Agostino et al., 1994).

At the MRI Wave, weekly alcohol consumption was self-reported, and metabolic equivalents of task (METs) per week for moderate-to-vigorous activity was calculated using the self- administered Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire (Stewart et al., 2001).

Cognitive function

Cognitive function was evaluated five times at 5-year intervals from 1997-1999 (Wave 5) to 2015-2016 (Wave 12), covering letter fluency (number of 'S' words listed in one minute), semantic fluency (category 'animals'), short-term memory (recall of a list of 20 words in two minutes), and verbal and numerical reasoning as assessed with the Alice Heim 4-I test (Heim, 1970).

We also used a single measure of Montreal Cognitive Assessment (MoCA), evaluated only at the MRI Wave, to assess cognitive status outcome. We classified cognitive impairments as performance below the traditional established screening cut-offs (MoCA scores < 26) (Nasreddine et al., 2005). Detailed information on the above measures is provided in Supplementary Methods.

MRI Outcomes

MRI scans were analysed using FMRIB Software Library v6.0 (FSL; https://fsl.fmrib.ox.ac.uk/). Detailed information on pre-processing pipelines and harmonization of images acquired from the Verio and Prisma scanner have been described in previous work (Bordin et al., 2021; Filippini et al., 2014; Zsoldos et al., 2020), and in Supplementary Methods. Briefly, pre- processed T1 images were analysed using voxel-based morphometry (FSL-VBM) to produce GM density maps for each participant. Pre-processing of DTI images produced four maps for each participant: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD), which are widely used to estimate axonal and myelin integrity (Suri et al., 2014). We used Tract-Based Spatial Statistics (TBSS) to create a skeletonized (thinned) FA, MD, RD and AD maps. All maps were concatenated in 4D files for subsequent voxel-wise statistics. Measures of mean global FA, MD, RD and AD were extracted from the respective mean skeletonized maps. WMH were segmented on FLAIR images using the supervised FMRIB's Brain Intensity AbNormality Classification Algorithm (BIANCA) tool (Griffanti et al., 2016). Binarized WMH maps were generated by selecting voxels that exceeded a probability of 0.9 of being WMH on the BIANCA output, and used to quantify WMH volumes as % of total brain volume.

Statistical analysis

All statistical analyses were performed using R version 3.6.1. Effects were considered significant when $p < 0.05$ (two-tailed). We tested continuous variables for normality using the Shapiro-Wilks test. Participant characteristics and physiological measurements were compared between SVD groups (0-3) using one-way analysis of variance (ANOVA), Kruskall- Wallis test, and Chi-square test where appropriate. Effect sizes were calculated where possible and expressed with Cohen's f^2 ($f^2 = 0.02$ small; medium $f^2 = 0.15$; $f^2 = 0.35$ large).

Linear mixed effect models (LME) with random slopes and intercepts were used to investigate whether individuals in the four SVD burden groups differed in baseline measures and longitudinal trajectories of vascular risk factors (MAP, BMI, FSRS) and cognition (letter and categorical fluency, memory, verbal and numerical reasoning). A complete description of the LME models is provided in Supplementary Methods. We tested for non-normality of the residuals by using the Shapiro-Wilks test. FSRS was log-transformed due to the skewed distribution of the standardized residuals. A binary covariate was added to control for the effects of MRI scanner model. Further, we corrected for the effects of age, sex, and education, by scaling these variables and incorporating their main effects and interactions with the time terms. A linear model best described MAP and BMI trajectories; however, including an orthogonalized polynomial quadratic time term improved model fit for FSRS and cognitive trajectories (all $p<.05$) (Elbaz et al., 2014; Singh-Manoux et al., 2012). This quadratic time term expresses non-linear (exponential) changes in the LME model without inducing collinearity (Beck et al., 2021). We performed Bonferroni corrections for multiple comparisons across the 5 cognitive measures. Accordingly, results surpassing a strict significance threshold ($p<0.01$) are discussed in detail whereas those $0.01 < p < 0.05$ are interpreted with caution.

Voxel-wise associations of SVD burden with GM density and DTI-derived metrics (FA, MD, RD, AD) were investigated using general linear modelling (GLM) and permutation-based non- parametric testing (5000 permutations) using the FSL Randomize Tool. A separate voxel-wise GLM was performed for each DTI metric, and included the following covariates: age, sex, education, MRI scanner model, antihypertensive use, BMI, and MAP measured at the time of MRI. Analyses were corrected for multiple voxel-wise comparisons using family-wise error (FWE) corrections and reporting threshold-free cluster enhancement (TFCE) statistics. We applied a Bonferroni correction for multiple comparisons across the 4 DTI metrics, accepting a strict significance threshold

of $p<0.0125$. To examine whether the effects of SVD burden on DTI metrics were driven by the presence of WMH, we performed a sensitivity analysis which included the WMH spatial maps as voxel-wise confounds in the model.

We also examined whether the associations of SVD burden with global measures of GM and WM microstructure were moderated by cognitive status (MoCA<26 vs. MoCA≥26) at the time of MRI. Multivariate analysis of covariance (MANCOVA) was performed with cognitive status and SVD burden as independent variables, and global GM, mean global FA, MD, RD, and AD as dependent variables, and the same covariates as above.

Results

At the time of MRI, the mean age of the 623 participants was 69.96 years (SD = 5.18), 494 (79%) were men and 594 (95%) Caucasian, reflecting the demographics of the parent Whitehall II study. Sample demographics, physiological measurements, and the distribution of the total SVD score at the time of MRI (2012-2016) are presented in Table 1.

Individuals with higher SVD burden scores were older, more often female, demonstrated higher MAP, were more likely to be on antihypertensive treatment, and engaged in less physical activity. Participants' demographics and vascular risk factors at the five follow-up waves are shown in Table S2. The average follow-up time from Wave 3 to Wave 12 was 23.5 years (SD = 0.57, interquartile range [IQR] 23.17-23.91). The time from Wave 3 to the MRI was on average 22.15 years (SD = 1.40, IQR 21.02-23.39), and from Wave 5 to MRI was 16.38 years (SD = 1.30, IQR 15.27-17.56). The demographic characteristics of the 623 included participants did not differ from the starting sample of n = 775 with scans from the Whitehall II Imaging Sub-Study (Table S3). Thirty-four percent of the sample demonstrated total SVD scores of 0, followed by scores of 1 (33%), 2 (23%) and 3 (10%). Lacunes were the least frequently observed SVD feature (14%), whereas EPVS, WMH and CMB were all equally prevalent (32- 34%; see Figure S2 for a Venn-diagram).

Table 1. Participant characteristics and associations at the MRI wave (2012-2016)

		Total SVD score				P-value
	All	**0**	**1**	**2**	**3**	
N	**623**	**209**	**206**	**145**	**63**	
SVD markers						
Lacunes, N (%)	86 (14%)	0 (0%)	17 (8%)	32 (22%)	37 (59%)	
EPVS, N (%)	203 (33%)	0 (0%)	57 (28%)	90 (62%)	56 (89%)	
WMH, N (%)	209 (34%)	0 (0%)	53 (26%)	97 (67%)	59 (94%)	
CMB, N (%)	200 (32%)	0 (0%)	79 (38%)	71 (49%)	50 (79%)	
Participant characteristics						
Age, median (IQR)	69 (66.01-73.28)	67.39 (65.5-70.58)	68.12 (65.85-72.64)	71.2 (67.84-75.1)	72.18 (69-77.86)	< 0.001
Female, N (%)	129 (21%)	41 (20%)	31 (15%)	39 (27%)	18 (29%)	0.02
Caucasian ethnicity, N (%)	587 (94%)	198 (95%)	193 (94%)	134 (92%)	62 (98%)	0.38
Years of education, median (IQR)	13 (12-17)	14 (12-17	13.5 (12-17)	13 (12-17)	13 (11.25-16)	0.19
Highest employment grade, N (%)	319 (51%)	105 (50%)	103 (50%)	83 (58%)	28 (44%)	0.36
Intermediate employment grade, N (%)	264 (42%)	90 (43%)	91 (63%)	54 (37%)	29 (46%)	0.49
Lowest employment grade, N (%)	29 (4%)	9 (4%)	10 (5%)	6 (4%)	4 (6%)	0.89
MoCA, median (IQR)	28 (26-29)	28 (26-29)	27 (26-29)	28 (26-29)	28 (26.5-29)	0.41
BMI, median (IQR)	25.34 (23.34-28.07)	25.39 (23.13-28.29)	25.38 (23.19-27.9)	25.54 (23.46-28.22)	24.94 (23.46-27.87)	0.95
MAP, mean (sd)	98.84 (11.82)	97.67 (12.31)	99.38 (11.03)	98.09 (12.19)	102.39 (11.62)	0.02

Table 1. Continued

	Total SVD score					P-value
	All	**0**	**1**	**2**	**3**	
N	**623**	**209**	**206**	**145**	**63**	
Diabetes, N (%)	58 (9%)	16 (8%)	18 (9%)	20 (14%)	4 (6%)	0.18
Current smoking, N (%)	20 (3%)	7 (3%)	7 (3%)	5 (3%)	1 (2%)	0.90
Alcohol use, median (IQR)	11.22 (4.09-20.36)	10.5 (4.25-19)	12.02 (4.25-23.23)	9.5 (2.10-16.82)	12.60 (3.87-20.61)	0.09
Antihypertensive use, N (%)	192 (31%)	47 (22%)	62 (30%)	54 (37%)	29 (46%)	< 0.001
Physical activity, MET, median, (IQR)	1155 (495-2062.50)	1222.5 (525-2082.5)	1290 (592.5-2302.5)	982.5 (395.5-1792.5)	840 (300-1845)	0.02

Abbreviations: SVD = cerebral small vessel disease; EPVS = enlarged perivascular spaces; WMH = white matter hyperintensities; CMB = cerebral microbleeds; BMI = body mass index; BP = blood pressure, MET = metabolic equivalent task. Information on employment grade was missing in 2% ($n = 11$), alcohol use in 3% ($n = 21$), physical activity in 0.003% ($n = 2$).

Relative to the reference SVD burden group (SVD = 0), the highest SVD burden group had higher baseline MAP (measured approximately 22.15 years prior to the MRI Wave at mean age = 47.81; SD = 5.23; $p = 0.03$, Cohen's $f^2 = 0.01$) after correcting for age, sex, education, and MRI scanner model. However, the SVD groups did not differ in baseline BMI and FSRS, or rates of change of MAP, BMI and FSRS over the 30-year follow up period (Table 2; Figure 1).

After adjustments for age, sex, education and MRI scanner model, relative to the reference SVD group (SVD = 0), individuals with higher SVD burden had steeper linear declines in letter fluency ($p = 0.02$, Cohen's $f^2 = 0.002$) as well as linear ($p = 0.047$, Cohen's $f^2 = 0.002$) and exponential ($p = 0.04$, Cohen's $f^2 = 0.002$) declines in verbal reasoning. However, these associations did not survive Bonferroni corrections. The SVD burden groups did not differ on baseline cognitive performance or rate of cognitive decline for letter fluency, and verbal and numerical reasoning (summary statistics in Table 3; Figure 1).

Table 2. Longitudinal associations of vascular factors with SVD burden

	MAP		BMI		Log-FSRS	
	Beta	**95% CI**	**Beta**	**95% CI**	**Beta**	**95% CI**
Main effect of SVD burden group						
SVD 1 vs. 0	1.75	-0.18; 3.67	0.04	-0.63; 0.70	0.06	-0.002; 0.11
SVD 2 vs. 0	1.39	-0.79; 3.57	0.06	-0.70; 0.82	0.05	-0.02; 0.11
SVD 3 vs. 0	3.36	0.42; 6.30[a]	0.13	-0.89; 1.15	0.05	-0.03; 0.14
Interaction SVD group and time						
SVD 1 vs. 0	-0.02	-0.13; 0.08	0.01	-0.03; 0.01	0.001	-0.002; 0.005
SVD 2 vs. 0	-0.05	-0.17; 0.06	0.002	-0.02; 0.02	0.001	-0.002; 0.01
SVD 3 vs. 0	-0.06	-0.21; 0.10	-0.004	-0.03; 0.03	0.002	-0.003; 0.01
Interaction SVD group and time²						
SVD 1 vs. 0					-0.02	-0.04; 0.003
SVD 2 vs. 0					-0.01	-0.04; 0.01
SVD 3 vs. 0					0.001	-0.03; 0.04

Abbreviations: MAP = mean arterial pressure; BP = blood pressure; FSRS = Framingham Stroke Risk Score; CI = confidence interval; SVD = cerebral small vessel disease. Results of linear mixed effect models with random effects for the intercept and slope (time for MAP, BMI FSRS and time² for FSRS). Vascular risk factors were assessed between Wave 3 (1991-1994) and Wave 12 (2015-2016). All models were adjusted for age at baseline, sex, education, and scanner. [a] $p < 0.05$.

Table 3. Longitudinal associations of cognitive performance with SVD burden

	Letter fluency		Semantic fluency		Short-term Memory		Verbal reasoning		Numerical reasoning	
	Beta	**95% CI**	**Beta**	**95% CI**	**Beta**	**95% CI**	**Beta**	**95% CI**	**Beta**	**95% CI**
Main effect of SVD burden group										
SVD 1 vs. 0	0.62	-0.12; 1.35	0.17	-0.52; 0.87	-0.10	-0.50; 0.30	0.52	-0.24; 1.27	0.22	-0.68; 1.13
SVD 2 vs. 0	0.25	-0.58; 1.09	-0.28	-1.06; 0.50	-0.14	-0.60; 0.31	0.71	-0.14; 1.57	0.12	-0.90; 1.14
SVD 3 vs. 0	0.18	-0.95; 1.30	0.001	-1.06; 1.06	-0.09	-0.71; 0.53	1.12	-0.04; 0.28	0.24	-1.15; 1.63
Interaction SVD group and time										
SVD 1 vs. 0	-0.03	-0.07; 0.01	0.002	-0.03; 0.04	0.01	-0.02; 0.03	-0.02	-0.05; 0.02	0.01	-0.02; 0.05
SVD 2 vs. 0	-0.02	-0.07; 0.02	0.04	-0.003; 0.04	- 0.002	-0.03; 0.03	-0.02	-0.06; 0.02	0.02	-0.02; 0.06
SVD 3 vs. 0	-0.07	-0.13;- 0.01[a]	-0.01	-0.06; 0.05	0.01	-0.03; 0.05	-0.05	-0.11; -0.001[a]	-0.01	-0.06; 0.05
Interaction SVD group and time^2										
SVD 1 vs. 0	-0.05	-0.27; 0.18	-0.10	-0.30; 0.10	-0.07	-0.21; 0.08	-0.06	-0.25; 0.14	0.03	-0.17; 0.23
SVD 2 vs. 0	-0.07	-0.32; 0.19	-0.13	-0.36; 0.10	-0.21	-0.37; -0.04[a]	-0.16	-0.38; 0.06	0.15	-0.08; 0.38
SVD 3 vs. 0	-0.30	-0.64; 0.05	-0.09	-0.40; 0.22	0.08	-0.15;0.30	-0.31	-0.60; -0.01[a]	0.24	-0.07; 0.55

Abbreviations: CI = confidence interval; SVD = cerebral small vessel disease. Results of linear mixed effect models with random effects for the intercept and slope (time, time^2). Cognitive tests were assessed between Wave 5 (1997-1999) and approximately 16 ± SD years later at Wave 12 (2015-2016). All models were adjusted for age at baseline, sex, education, scanner model. [a]$p < 0.05$.

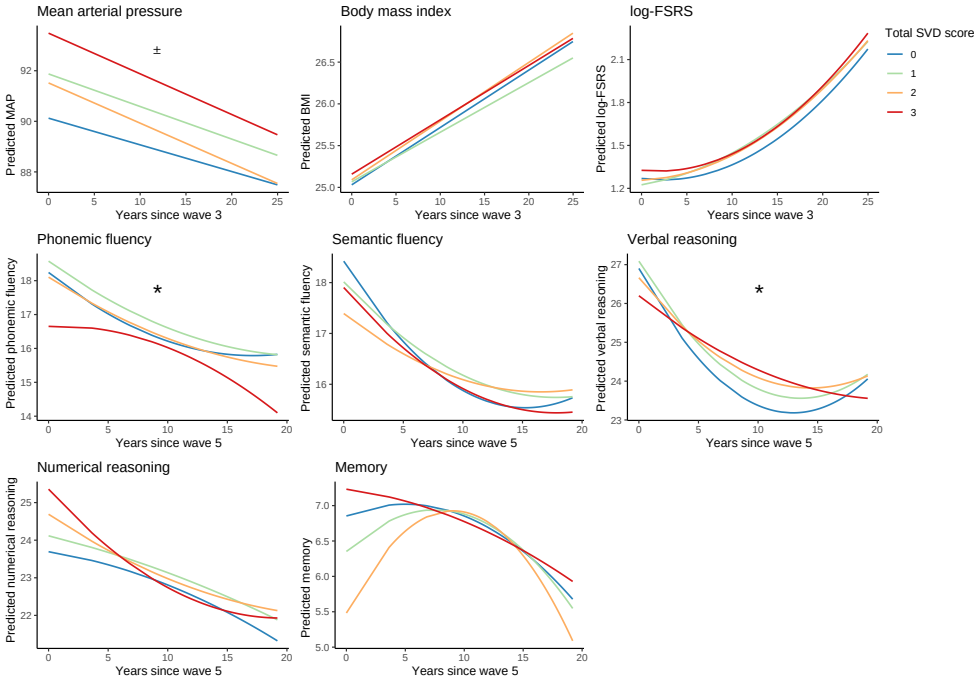

Figure 1. Predicted longitudinal trajectories for vascular risk and cognitive performance. Each figure depicts the predicted trajectories of the dependent variable of interest based on the linear mixed effect models. Measures for mean arterial pressure (MAP) and log-Framingham stroke risk score (log- FSRS) were obtained between 1995 and 2016. Measures on cognitive performance were obtained between 1997 and 2016. ± indicates significant main effects of SVD burden, where group 3 had higher baseline values compared to group 0 ($p < 0.05$). *Indicates significant interactions where SVD burden group 3 showed steeper rates of cognitive decline compared to group 0 ($p<0.05$). MAP: mean arterial pressure. BMI: body mass index; FSRS: Framingham Stroke Risk Score; SVD: cerebral small vessel disease.

VBM analysis revealed that higher SVD burden was associated with lower GM density in several areas, including the frontal pole, superior and inferior frontal gyrus, pre- and postcentral gyrus, precuneus, frontal orbital cortex, subcallosal cortex, left Heschl's gyrus, parahippocampal gyrus, and hippocampus (Figure 2, FWE-corrected $p < 0.05$). Together, these regions covered 9.7% of the total brain GM volume.

Voxel-wise TBSS analyses revealed that higher SVD MRI burden was associated with lower FA, and higher MD, RD, and AD (Bonferroni-corrected $p<0.0125$) throughout several projection and commissural WM tracts such as the corpus callosum, cingulum, corona radiata, and longitudinal fasciculus

(Figure 3). Associations were distributed across 17.0%, 16.7%, 15.4% and 23.8% of total WM tract skeletons for FA, MD, RD and AD, respectively. These results remained after a voxel-wise correction for WMH masks.

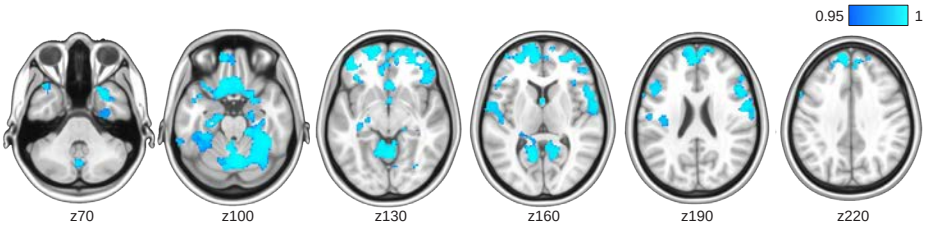

Figure 2. Voxel-wise associations between higher total cerebral small vessel disease (SVD) scores and lower grey matter density were primarily found cortical and hippocampal areas, shown in blue. TFCE- corrected statistical maps are overlaid on the MNI-152 template and thresholded at a 1-p value of 0.95, representing $p < 0.05$. Images are also FWE-corrected for multiple voxel-wise comparisons. Analysis was adjusted for age, sex, education, MRI scanner model, antihypertensive use, body mass index, and mean arterial pressure measured at the time of the MRI scan.

We observed an interaction between SVD burden and cognitive status ($F_{3,608} = 2.14$, $p = 0.007$, Cohen's $f^2 = 0.13$). Post-hoc univariate comparisons revealed that this interaction effect was driven by MD ($F_{3,608} = 3.27$, $p = 0.02$, Cohen's $f^2 = 0.13$), AD ($F_{3,608} = 3.72$, $p = 0.01$, Cohen's $f^2 = 0.14$), and RD ($F_{3,608} = 2.72$, $p = 0.04$, Cohen's $f^2 = 0.12$), but not FA ($F_{3,608} = 1.03$, $p = 0.38$) or GM ($F_{3,608} = 0.97$, $p = 0.41$). For each of these interactions, the association of SVD burden with poor WM microstructure was more pronounced in individuals with cognitive impairments (reflected by MoCA < 26, Figure 4).

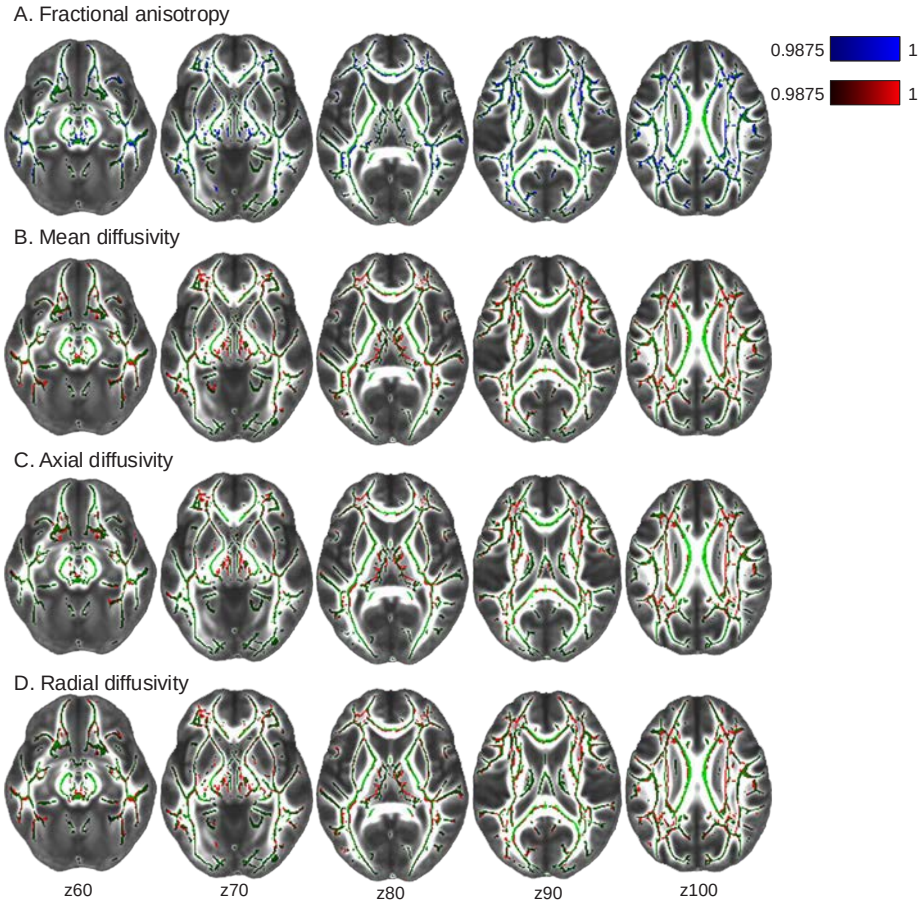

Figure 3. Voxel-wise associations between cerebral small vessel disease (SVD) burden and diffusion tensor imaging measures: fractional anisotropy (FA; A) mean diffusivity (MD; B); axial diffusivity (AD; C), and radial diffusivity (RD; D). Statistical maps were overlaid on the FMRIB58_FA standard image. Green tracts depict the standardized mean FA skeleton. Higher SVD burden is associated with lower FA (in blue), and higher MD, AD, RD (in red). All images are TFCE-corrected statistics thresholded at 1- p values of 0.9875, i.e. representing Bonferroni-corrected $p < 0.0125$ to adjust for multiple comparisons across 4 DTI metrics. Images are also FWE-corrected for multiple voxel-wise comparisons. Analyses were adjusted for age, sex, education, MRI scanner model, antihypertensive use, body mass index, and mean arterial pressure measured at the time of the MRI scan.

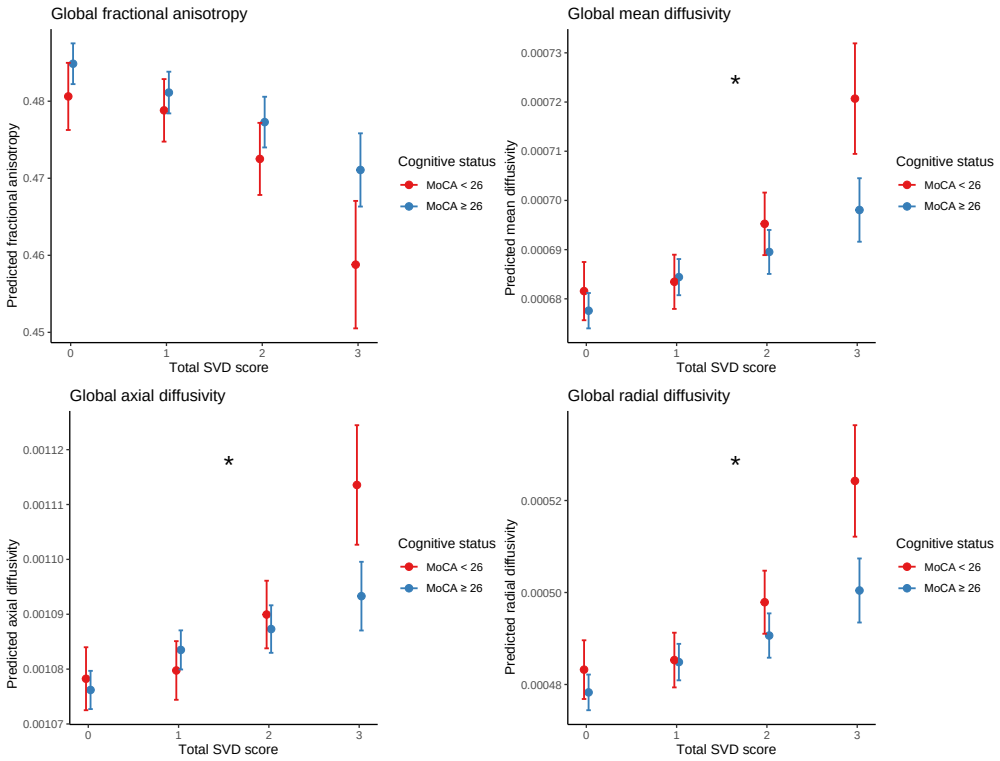

Figure 4. Interaction between cognitive status and cerebral small vessel disease burden on global diffusion metrics. Plots depict significant interactions between cognitive status (Montreal Cognitive Assessment [MoCA] < 26 vs. ≥ 26) and total SVD scores (0-3) on mean diffusivity, axial diffusivity, and radial diffusivity (all $p < 0.05$; depicted with *), but not for fractional anisotropy. The association between SVD burden and DTI parameters is more pronounced in individuals with cognitive impairments, reflected by MoCA < 26, and especially in the most severe SVD burden group. MoCA: Montreal Cognitive Assessment; SVD: cerebral small vessel disease.

Discussion

This study characterized late-life SVD burden across a large sample of community-dwelling older adults and has demonstrated several associations with 25-year retrospective trajectories of vascular risk factors, cognitive performance, and brain microstructure. We showed that individuals with severe SVD burden at the MRI Wave presented with elevated mean arterial pressure 25 years prior to their MRI (Wave 3). We also found that individuals with higher SVD had relatively faster rates of decline for letter fluency and verbal reasoning over this timespan. In addition, at the time of MRI, we revealed concurrent associations of SVD burden with widespread reductions

in GM density as well as hallmark indicators of WM structural integrity, reflected by reduced FA, and increased diffusivity. Importantly, the negative associations between SVD and diffusivity were stronger in individuals with cognitive impairments (MoCA<26). Overall, our findings could have important implications for optimizing strategies for maintaining brain and cognitive health during the lifespan.

While previous studies have revealed associations between higher midlife blood pressure and late-life SVD in normal aging, these have only examined either WMH, CMB, or brain infarcts individually (Lane et al., 2019; Muller et al., 2014). Here, we show that higher MAP in midlife (mean age 48, Wave 3) is associated with severe total SVD burden approximately 20 years later (mean age 70, MRI Wave), measured as a combination of four key MRI markers of SVD pathology (Klarenbeek et al., 2013). Our results thus indicate that elevated midlife MAP can have more diffuse effects on cerebrovascular health that go beyond the single associations with separate SVD features. Our findings are in line with previous studies showing that hypertension exacerbates SVD-related pathologies in aging individuals (Ter Telgte et al., 2018; Wardlaw et al., 2019). We found no evidence for the involvement of other midlife vascular risk factors (BMI or stroke risk scores) in late-life SVD burden, suggesting that midlife blood pressure may particularly aggravate SVD-related injuries and therefore may serve as the most important modifiable risk factor for SVD (Cannistraro et al., 2019). This study therefore adds to the accumulating evidence emphasizing the need for early prevention strategies with a focus on blood pressure management (Lane et al., 2019; Muller et al., 2014; Suri et al., 2019; Zsoldos et al., 2020). However, individuals with SVD are not always hypertensive, and given that our results are observational, we cannot determine causality, or rule out reverse causation (Østergaard et al., 2016). Therefore, our findings and potential clinical consequences warrant further investigation.

WMH, infarcts, CMBs have each individually been linked to cognitive decline and dementia, although the association with EPVS is less clear (Debette et al., 2019). Two previous studies demonstrated steeper rates of decline of global cognition and executive function, however these links were only established in hypertensive patients (Uiterwijk et al., 2016), and symptomatic SVD (Al Olama et al., 2020). Our findings add to this by showing for the first time that, among community-dwelling elderly without diagnosis of stroke or dementia, late-life SVD burden relates to cognitive decline on letter fluency and verbal reasoning measured over the previous 20-years. As SVD features are common in elderly

individuals and increase risk of all-cause dementia, including Alzheimer's and vascular dementia (Debette et al., 2019), these results highlight the importance of investigating how SVD links to preclinical cognition impairments. However, we made two key observations: first, that these associations were only present in participants with ≥3 SVD features, which occurred in 10% of the total sample. Similar to an earlier study (Xu et al., 2015), there appeared to be a threshold effect, where cognitive dysfunctions became noticeable only in those with moderate-to-severe SVD burden. Second, the effects of SVD on cognition were generally small, and did not survive strict corrections for multiple-comparison corrections. While it is possible that larger studies could confirm our observed associations at an uncorrected $p < 0.05$, accumulating evidence suggests that there is a large inter-individual variability in the effects of SVD burden on cognition, both with regards to the affected domains and severity (Dichgans & Leys, 2017; Wardlaw et al., 2019). Overall we observed that despite their high SVD burden, individuals displayed relatively modest increases in earlier rates of cognitive decline. This could partially be explained by the concept of reserve, which refers to the ability to alleviate the effects of neuropathology through variations in brain structure (i.e., brain reserve) or adaptability of functional processes (i.e. cognitive reserve) (Stern et al., 2018). Brain reserve is generally considered to be a less dynamic construct, whereas cognitive reserve is thought to be more adjustable through life experiences (e.g., by increasing cognitive engagement, physical activity, leisure activities; Stern et al., 2018) and therefore may serve as viable target to improve clinical management of the consequences of SVD (Livingston et al., 2020; Wardlaw et al., 2019).

Additionally, we found specific GM and WM correlates of current SVD-related burden. More specifically, we identified GM density reductions predominantly in the medial-frontal, orbito- frontal, and medial-temporal regions. This pattern of cortical atrophy has been recognized in earlier studies examining WMH or lacunes alone (Lambert et al., 2016; Lambert et al., 2015). These associations were most pronounced in the medial temporal and hippocampal regions, which are traditionally linked to AD pathology (Jack et al., 2018). This is especially important given the growing recognition of the prevalence of SVD and cerebrovascular dysfunction in AD (Sweeney et al., 2019).

Grey matter atrophy may result from secondary neurodegenerative processes elicited by SVD- related damage to the WM tracts that disrupt the connections between remote brain regions (Ter Telgte et al., 2018; Wardlaw et al., 2019). Indeed, in this study we also noted widespread alterations of WM tracts in

relation to SVD burden, reflected by decreased FA, and increased MD, AD, and RD, all of which are established markers of WM microstructural damage in ageing and dementia (Suri et al., 2014). It is noteworthy that these associations remained after adding WMH masks as voxel-wise confounds, indicating that WMH alone did not explain these associations, but that SVD severity beyond WMH instead concurs with white matter microstructural abnormalities (Croall et al., 2017). These findings thus underscore that total SVD burden scores more comprehensively characterize the consequences of SVD than the sole consideration of single MRI features (Klarenbeek et al., 2013; Staals et al., 2014). We also revealed that, relative to cognitively healthy adults, those with cognitive impairments (MoCA < 26) had more pronounced negative associations between SVD and WM diffusivity, highlighting the central role of WM microstructure in the emergence of cognitive impairments (Croall et al., 2017; Dichgans & Leys, 2017). Altogether, we demonstrate that the accumulation of SVD-related damage may manifest clinically through diffuse effects on WM tracts throughout the brain, and relate to gross changes in brain regions distant from the initial lesion site (Ter Telgte et al., 2018; Wardlaw et al., 2019).

The importance of managing midlife vascular health to maintain cognition in late life has been demonstrated previously in the Whitehall II and other observational cohorts (Lane et al., 2019; Muller et al., 2014; Suri et al., 2020; Suri et al., 2019; Zsoldos et al., 2020). Our findings suggest that SVD may also play an important part in this relationship. However, the mechanisms linking SVD-associated injuries with our observed changes in mid-life blood pressure, diffuse brain microstructural alterations, and subsequent cognitive dysfunction remain to be elucidated (Østergaard et al., 2016). One potential mediator in this pathway which could provide a direct link between peripheral and central vascular damage may be large artery stiffening, which has been associated with SVD burden (Song et al., 2016), midlife hypertension, damage to the blood-brain barrier, subsequent brain atrophy, and cognitive impairment (Pase et al., 2016; Suri et al., 2020). Future longitudinal studies which include multiple assessments of SVD features would help unravel these complex mechanisms and temporal dynamics in further detail.

Strengths of the current study include the detailed examination of participants over a 25-year period, including repeated assessments of vascular risk and cognitive functions and the acquisition of advanced and multi-modal MRI scans in old age, allowing for a comprehensive characterization of total SVD burden. However, several limitations should be noted. First, the generalizability of our

findings is limited as participants of the Whitehall II study are predominantly Caucasian, generally more highly educated and healthier as compared to nationally representative samples, and only 20.7% individuals were female in this study (Akasaki et al., 2020; Anatürk et al., 2021). Second, in contrast to most of the previous work that investigated global SVD burden among patient groups (e.g., stroke or hypertensive populations; Al Olama et al., 2020; Lau et al., 2018; Staals et al., 2014; Uiterwijk et al., 2016) our sample was relatively healthy, partially due to our selection criteria (e.g., MRI compatibility; no gross brain abnormalities). Third, T2-weighted images were not acquired in this cohort, so instead we incorporated both T1-weighted and FLAIR images to rate EPVS and lacunes. This approach is in accordance with the STRIVE criteria and has been adopted by previous studies (Gutierrez et al., 2013; Wiegertjes et al., 2019). However, as T2-weighted images allow for an easier detection of cavitation relatively to FLAIR images, we note that the possibility that approach may have led to misclassification errors (Potter et al., 2015; Ramirez et al., 2016; Wardlaw et al., 2013). Fourth, the prevalence of CMB was relatively high in this study (32%) as compared to participants of similar age ranges in other healthy cohort studies (10-30%; Graff-Radford et al., 2020; McGrory et al., 2019; Poels et al., 2010). Prevalence of microbleeds increases considerably with magnetic field strength (Puy et al., 2021). The fact that most of the previous studies were performed on 1.5T scanners (McGrory et al., 2019; Poels et al., 2010) and our study used a 3T scanner may partially explain this discrepancy. Nonetheless, although we incorporated previously established criteria as well as a consensus strategy to rate CMBs and to recognize potential mimics (Kuijf et al., 2013; Linn, 2015), we cannot exclude the possibility of having included some false positives. Lastly, as in other studies (Field et al., 2016; Klarenbeek et al., 2013; Lau et al., 2018; Staals et al., 2014), the distribution of SVD burden in this sample was skewed, with low frequency of severe SVD. Together, this may have resulted in an underestimation of the strength of our observed associations and may in part explain why our observed effects were only small-to-medium. We therefore emphasize the need to replicate our findings in diverse cohort studies.

We demonstrated longitudinal associations of late-life SVD burden with vascular and cognitive functioning. Importantly, we observed that midlife blood pressure (mean age of 48) may contribute to SVD burden 20 years later (mean age 70). Furthermore, SVD burden related to slightly faster rates of cognitive decline, together with more pronounced and widespread differences in GM and WM microstructure. Together, our findings further emphasize the importance of midlife vascular health to maintain brain structure and function.

Acknowledgments

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Data availability statement

The study follows Medical Research Council data sharing policies (https://mrc.ukri.org/research/policies-and-guidance-for-researchers/data-sharing/), and data from the Whitehall II Study and Whitehall II Imaging Sub-study are accessible via application to the Dementias Platform UK (https://portal.dementiasplatform.uk/).

Supplements

Supplementary methods

Description of cohort profile

The Whitehall II study targeted all civil servants that worked in the London offices of 20 Whitehall departments between 1985–1988, established by University College London. The initial Wave included 10 308 British Civil servants (6895 men), aged 35–55 years. Whitehall II Study participants have received detailed clinical follow-ups for up to 30 years at 5-year intervals (1991-1994, Wave 3; 1997- 1999, Wave 5; 2002-2004, Wave 7; 2007-2009, Wave 9; 2012-2013, Wave 11); 2015-2016, Wave 12).

Since the inception of the Whitehall II study, the retention rate for this cohort has been relatively high; about 87% of Wave 9 participants returned for the follow-up at Wave 11. The Whitehall II Imaging-Sub study randomly selected 774 participants aged 60-85 years from the Whitehall II Wave 11 cohort for multi-modal brain MRI work-up and cognitive tests at the University of Oxford. For the Imaging Sub- study, participants were included with contraindications to MRI scanning (e.g., particular metallic implants) or who were unable to travel to Oxford without assistance.[1, 2]

Description of SVD ratings on MRI

Periventricular and deep white matter hyperintensities (WMH) were rated by trained raters (C.L.A., A.G.T., V.V.; see acknowledgments) on FLAIR images using the Fazekas scale, providing a score between 0-3 depending on the severity of WMH in the corresponding brain areas.[3] Enlarged perivascular spaces (EPVS) and lacunes were rated by an experienced rater (M.G.J.) following extensive training, and in consensus with other experienced raters (S.S., L.M.). Lacunes were rated using both T1-weighted and FLAIR images, following established criteria to distinguish lacunes from EPVS.[4, 5] The intra-rater reliability for lacune ratings indicated high similarity, as reflected by an intraclass correlation (ICC) of 0.91, based on a random sample of 25 participants. EPVS were assessed in the basal ganglia on T1-weighted images using the validated qualitative EPVS rating scale, as T2-weighted images were not acquired in this cohort.[6] The ICC for EPVS was 0.85, based on a random sample of 30 participants, indicating good intra-rater reliability. We used a semi-automatic detection method to identify possible cerebral microbleeds (CMBs), based on the radial symmetry transform.[7] Subsequently, one experienced rater (S.S.) evaluated all possible CMBs using previously established criteria[7, 8], and in consensus with a clinical psychiatrist (K.P.E.). The intra-rater reliability yielded excellent results (ICC = 0.92, based on a random sample of 100 participants).

MRI pre-processing steps

MRI scans were analysed using FMRIB Software Library v6.0 (FSL; https://fsl.fmrib.ox.ac.uk/).[9]

T1 images were bias corrected, brain extracted using FSL-ANAT and segmented using FSL-FAST to provide estimates of grey matter (GM, white matter (WM) and total brain volume (TBV).[10] All segmentations were visually inspected to ensure quality.

Diffusion-weighted images were pre-processed using FMRIB's diffusion toolbox.[11] Briefly, after applying motion and eddy current corrections with FSL-TOPUP, diffusivity maps for each metric was extracted using DTIFit and aligned into standard space using FMRIB's Nonlinear Registration Tool (FNIRT).

FLAIR scans were used to extract WMH using the Brain Intensity AbNormality Classification Algorithm (BIANCA).[12] This algorithm uses both intensity features (provided from FLAIR, T1 images, and fractional anisotropy) and spatial features to classify all voxels. BIANCA was initially trained on manually segmented WMH masks of participants who were scanned on the Prisma scanner (n = 24), Verio scanner (n = 24), and an independent sample from the UK Biobank Study (n = 12) to avoid scanner- dependent bias effects. This approach was specifically designed to improve the consistency of BIANCA output, and has been shown to result in better intra- and inter-rater reliability relatively to manual segmentations.[12-14]

Additional information on pre-processing was mentioned previously.[1, 15] With regards to **harmonization between scanners**, several of the aforementioned pre-processing steps were specifically incorporated to minimize scanner effects (i.e. bias correction on T1 images, and training BIANCA on the Prisma, Verio, and an independent sample of the UK Biobank). In addition, we have compared volumetric measures between the Prisma and Verio scanner in previous work, where measures of GM and CSF were relatively increased at the Prisma scanner, and measures of WM were relatively increased at the Verio scanner.[16] To ensure that our results were not affected by scanner effects, we also included scanner as confounding variable in all of our analyses.

Study variables

The **FSRS** was based on age, sex, systolic blood pressure, use of antihypertensive medications, diabetes mellitus, current smoking, current or history of atrial fibrillation, left ventricular hypertrophy, and current or history of cardiovascular disease.[17] These measurements were obtained using both questionnaires and clinical assessments, using standard operating protocols, as described previously.[18, 19] **Blood pressure** measurements were obtained in sitting position after five minutes rest; the average of two measurements

was used for further analysis. The use of **antihypertensive medication** was self- reported (e.g., diuretics, beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers). **Diabetes** was defined by having a fasting glucose level of ≥ 7.0 mml/L or a 2hr post-load glucose level of ≥ 11.1 mml/L, based on glucose measurements obtained from venous blood; self- reported diabetes diagnosed by a doctor or use of diabetes medication.[20] **Smoking behaviour** was self- reported (current, past/no smoking). A standard electrocardiogram analysis combined with manual review and Minnesota code classification system for electrocardiographic findings was used to identify **atrial fibrillation** and **left ventricular hypertrophy**.[21] **Cardiovascular disease** was evaluated using corroborated records from the general practitioner, hospital, and electrocardiogram and angiogram examinations at Wave 1, 3 and 5. Subsequently, the FSRS was computed using the beta coefficients of the Cox proportional hazards regression model in the Framingham Study, to indicate an individual's 10-year risk of stroke.[22]

The longitudinal test battery of the Whitehall II cohort includes several cognitive tests, proven to be sensitive to detect changes in cognitive functions in this study population.[23] The complete test battery took 30 minutes to complete. To measure **letter fluency**, participants were instructed to recall as many words beginning with an "S" within one minute. For **semantic fluency**, participants were given similar instructions, but instead needed to recall as many animal names. **Short-term memory** was evaluated by initially presenting a list of 20 one or two syllable words at two seconds intervals. Subsequently, participants were asked to recall as many of the word list, within two minutes. The Alice Heim 4-I test composes 65 verbal and mathematical reasoning items with increasing difficulty (e.g., where participants had to identify certain patterns or rules), covering **verbal and numerical reasoning**.[24] Participants were given 10 minutes to complete the test. Besides this, the test battery also included the Mill Hill vocabulary test[25] and the Mini Mental State Examination[26], however these tests were not included in the present study due to the observed ceiling effects.

Additional information on the vascular and cognitive study variables was mentioned previously.[16, 23, 27, 28]

Description of linear mixed effect models

To investigate the association between the cerebral small vessel disease (SVD) MRI score and trajectories of vascular risk and cognitive performance over 25 years, we employed the following equation for each dependent variable of interest (V):

$$V_{ij} = \beta_0 + \beta_1 time_{ij} + \beta_2 time^2 + \beta_3 SVD_{ij} + \beta_4 SVD_{ij} time_{ij} + \beta_5 SVD_{ij}\, time^2 + \beta_6 X_{1i} + \beta 7 X_{2i} + \beta_8 X_{2i} time_{ij} + \beta_9 X_{1i} time^2 + U_{0i} + U_{1i}\, time_{ij} + e_{ij}$$

V_{ij} is the dependent variable of interest of the i^{th} participant at the j^{th} occasion, $time_{ij}$ is years since the baseline measurement between 1995-1999 for the i^{th} participant at the j^{th} occasion, $time^2$ is the orthogonalized polynomial quadratic time term for the i^{th} participant at the j^{th} occasion, SVD_i is the total SVD score obtained during the Whitehall Imaging Sub-study of the i^{th} participant, X_{1i} is the covariate for scanner model (Prisma vs. Verio) for the i^{th} participant, X_{2i} is a vector of covariates (age at baseline, sex, education) for the i^{th} participant, U_{0i} is the random intercept, U_{1i} is the random slope, and e_{ij} is the residual.
The dependent variables of interest focused on vascular risk and cognitive performance.

Vascular risk was defined using the Framingham Stroke Risk Score (FSRS) and mean arterial pressure (MAP). Due to the skewed distribution of the residuals, FSRS was log-transformed.

Cognitive performance was covered for the following domains: letter fluency, semantic fluency, verbal reasoning, numerical reasoning, and global cognition.

Vascular risk factors were measured at six waves (j= 1, 2, 3, 4, 5, 6), whereas measures for cognitive performance were included from five waves (j = 1, 2, 3, 4, 5).

Parameter estimates were obtained with the Maximum Likelihood method from the *nlme* in R version 3.6.1.

Main effects of SVD burden are indicative of whether SVD burden scores (1-3) differed from the reference score (no burden; 0) on the variable of interest at baseline. The interaction of SVD burden with time indicates whether a higher SVD burden (1-3) is associated with different longitudinal trajectories (i.e., slopes) of the respective variable of interest as compared to the reference score. To allow for individual rates of change of the dependent variables over time for each participant, we fitted the intercept and slope as random effects. We implemented a continuous autoregressive moving-average correlation structure to consider repeated measures for each individual.

Supplementary Table 1. MRI acquisition parameters

	TR (ms)	TE (ms)	TI (ms)	Flip angle (°)	Field of view (mm)	Matrix (voxels)
T1-weighted						
Verio	2530	1.79/3.65/ 5.51/7.37	1380	7	256	1.0x1.0x1.0
Prisma	1900	3.97	904	8	192	1.0x1.0x1.0
FLAIR						
Verio	9000	73	2500	150	220	0.9x0.9x3.0
Prisma	9000	73	2500	150	220	0.4x0.4x3.0
T2*-weighted						
Verio	36	30	-	15	220	0.7x0.7x1.5
Prisma	1230	13.4	-	25	206	0.8x0.8x5.0
DWI						
Verio	8900	91.2	-	-	192	2.0x2.0x2.0
Prisma	8900	91	-	-	192	2.0x2.0x2.0
B0						
Verio	8900	91.2	-	-	192	2.0x2.0x2.0
Prisma	8900	91	-	-	192	2.0x2.0x2.0

Abbreviations: FLAIR = fluid-attenuated inversion recovery; DWI = diffusion-weighted imaging; TR = repetition time; TE = echo time; TI = inversion time

Supplementary Table 2. Sample characteristics for the 623 participants of the Whitehall II study

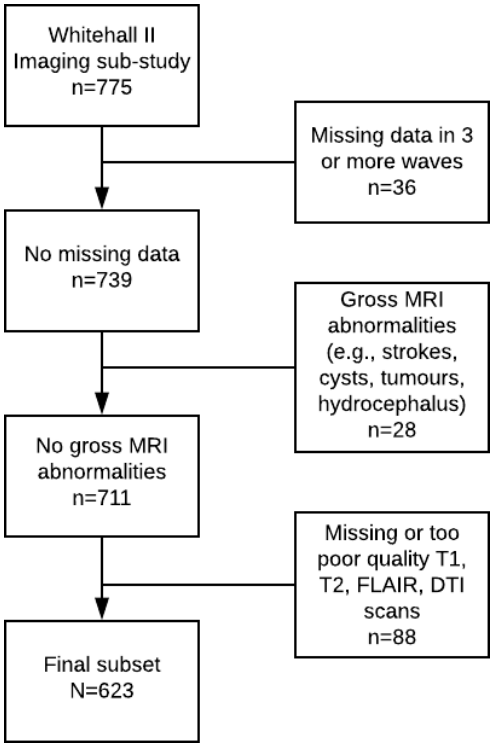
	Wave 3 (1991-1994)		Wave 5 (1997-1999)		Wave 7 (2002-2004)		Wave 9 (2007-2009)		Wave 11 (2012-2013)		Wave 12 (2015-2016)	
General characteristics	**N**	**Mean (SD) or median (IQR)**	**N**	**Mean (SD) or median (IQR)**	**N**	**Mean (SD) or median (IQR)**	**N**	**Mean (SD) or median (IQR)**	**N**	**Mean (SD) or median (IQR)**	**N**	**Mean (SD) or median (IQR)**
Age	623	47.81 (5.23)	608	53.58 (5.22)	609	59.07 (5.20)	620	64.01 (5.21)	623	68.10 (5.22)	610	71.30 (5.23)
Vascular risk factors												
MAP	608	91.63 (9.71)	585	90.64 (11.24)	603	90.08 (10.90)	619	87.94 (10.66)	623	88.64 (10.46)	606	89.19 (10.78)
BMI	607	24.80 (3.32)	517	25.26 (3.70)	603	26.21 (3.91)	620	26.29 (4.10)	623	26.28 (4.11)	606	26.39 (4.09)
FSRS	588	3 (3-4)	869	3 (3-4)	594	4 (3-6)	603	5 (4-7)	602	6 (5-10)	578	7 (5-11)
Cognitive performance												
Letter fluency	290	17.84 (4.17)	560	17.72 (4.19)	593	16.87 (3.81)	615	16.13 (3.64)	622	16.09 (4.01)	602	15.58 (4.28)
Semantic fluency	290	16.69 (3.44)	559	17.21 (4.00)	596	16.56 (3.59)	617	15.93 (3.58)	622	15.77 (3.59)	602	15.80 (3.54)
Verbal reasoning	289	25.17 (4.49)	561	25.30 (4.23)	596	24.10 (4.35)	618	23.79 (4.58)	622	23.72 (4.59)	603	23.98 (4.77)
Numerical reasoning	289	24.44 (5.28)	561	24.39 (5.16)	596	23.31 (5.11)	618	22.89 (5.42)	622	22.75 (5.53)	603	21.84 (5.64)
Memory	288	6.15 (2.15)	558	7.31 (2.30)	595	7.35 (2.17)	618	6.59 (2.19)	622	6.58 (2.24)	599	5.68 (2.20)

Abbreviations: SD = standard deviation; IQR = interquartile range; MAP = mean arterial pressure; FSRS: = Framingham Stroke Risk Score.

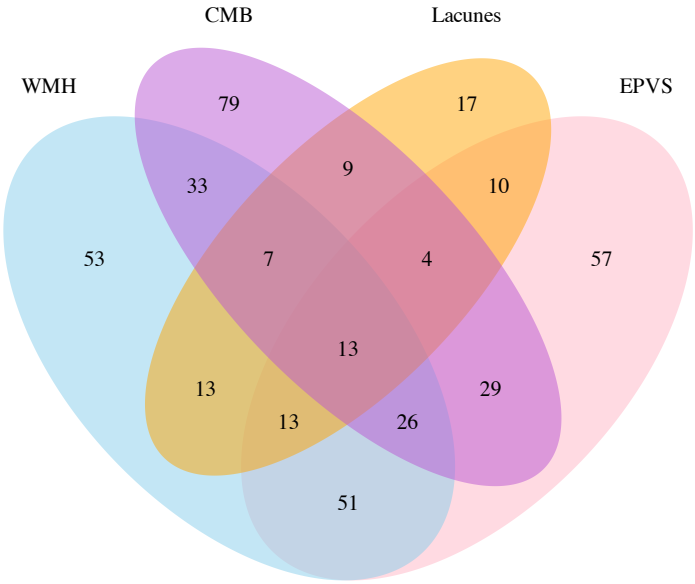
Supplementary Table 3. Included vs. complete sample of Whitehall II Imaging Sub-study at MRI wave

	Included sample	Complete sample	P-value
Number of participants	623	775	
Age, mean (SD)	69.96 (5.18)	69.81 (5.19)	0.59
Female, N (%)	129 (21%)	150 (19%)	0.58
Education, mean (SD)	14.11 (3.05)	14.06 (3.06)	0.74
MoCA, median (IQR)	28 (26-29)	28 (26-29)	0.74
MAP, mean (SD)	98.84 (11.82)	98.79 (11.70)	0.95
BMI, mean (SD)	25.96 (4.14)	26.15 (4.17)	0.38

Abbreviations: MoCA = Montreal cognitive assessment; MAP = mean arterial pressure; BMI = body mass index. Differences in characteristics were compared using independent *t*-test, Chi-square test or Mann-Whitney U test where appropriate. Data on MAP was missing in 4 (0.05%) from the complete sample.



Supplementary Figure 1. Flowchart of subject inclusion



Supplementary Figure 2. Venn diagram of cerebral small vessel disease MRI score

Abbreviations: WMH = white matter hyperintensities; CMB = cerebral microbleeds; EPVS = enlarged perivascular spaces. Numbers depict how many participants were within a certain category. Only 13 participants demonstrated all four features of cerebral small vessel disease on MRI.

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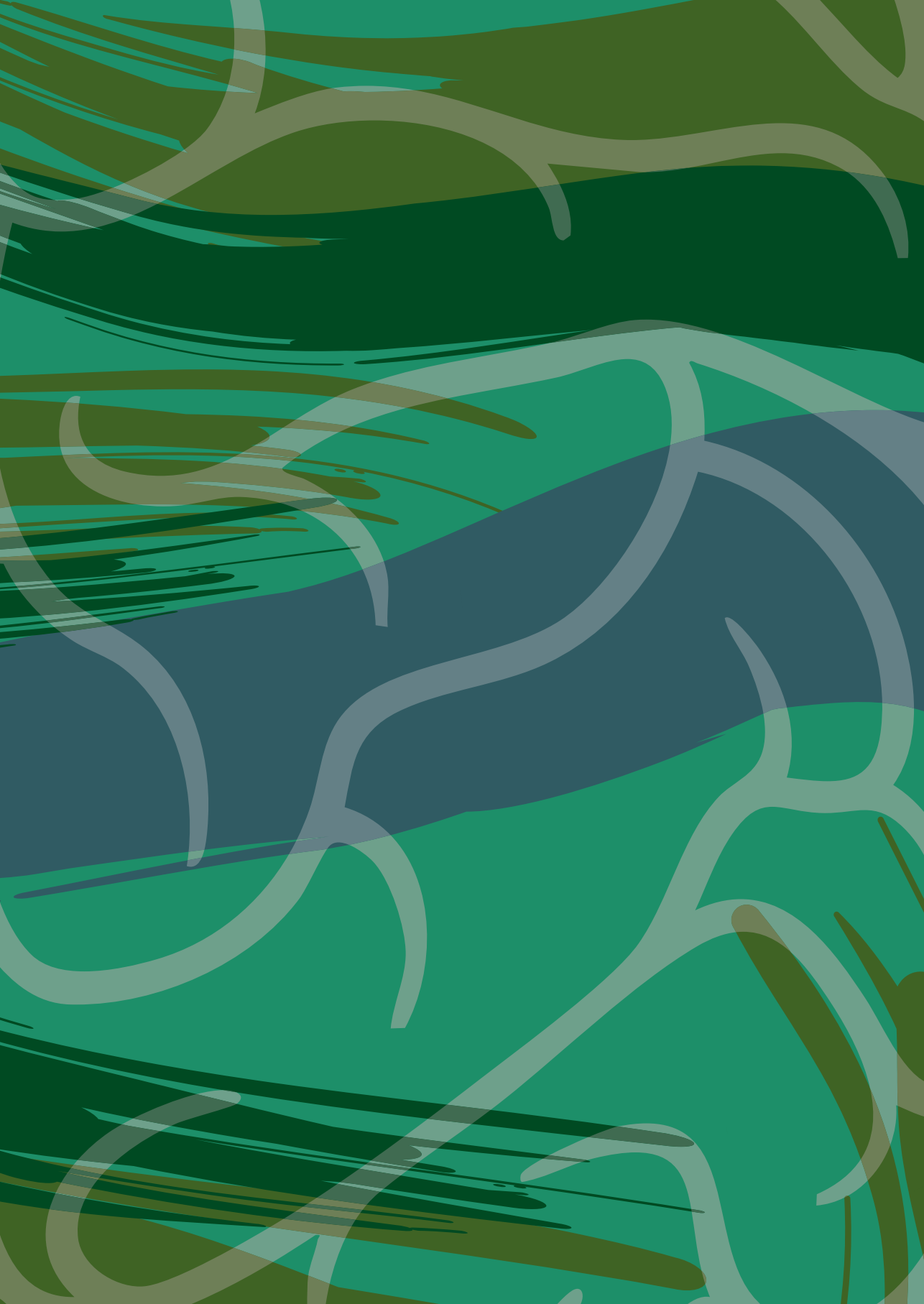

Part II.

Advancing research on cognitive ageing

Chapter 5

The Advanced BRain Imaging on ageing and Memory (ABRIM) data collection: Study design, data processing, and rationale

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Abstract

To understand the neurocognitive mechanisms that underlie heterogeneity in cognitive ageing, recent scientific efforts have led to a growing public availability of imaging cohort data. The Advanced BRain Imaging on ageing and Memory (ABRIM) project aims to add to these existing datasets by taking an adult lifespan approach to provide a cross-sectional, normative database with a particular focus on connectivity, myelinization and iron content of the brain in concurrence with cognitive functioning, mechanisms of reserve, and sleep-wake rhythms. ABRIM freely shares MRI and behavioural data from 295 participants between 18-80 years, stratified by age decade and sex (median age 52, IQR 36-66, 53.20% females). The ABRIM MRI collection consists of both the raw and pre-processed structural and functional MRI data to facilitate data usage among both expert and non-expert users. The ABRIM behavioural collection includes measures of cognitive functioning (i.e., global cognition, processing speed, executive functions, and memory), proxy measures of cognitive reserve (e.g., educational attainment, verbal intelligence, and occupational complexity), and various self-reported questionnaires (e.g., on depressive symptoms, pain, and the use of memory strategies in daily life and during a memory task). In a sub-sample (n = 120), we recorded sleep-wake rhythms using an actigraphy device (Actiwatch 2, Philips Respironics) for a period of 7 consecutive days. Here, we provide an in-depth description of our study protocol, pre-processing pipelines, and data availability. ABRIM provides a cross-sectional database on healthy participants throughout the adult lifespan, including numerous parameters relevant to improve our understanding of cognitive ageing. Therefore, ABRIM enables researchers to model the advanced imaging parameters and cognitive topologies as a function of age, identify the normal range of values of such parameters, and to further investigate the diverse mechanisms of reserve and resilience.

Introduction

Due to the worldwide ageing of the population, the proportion of adults who are suffering from or are at risk of cognitive impairment increases. This emphasizes the need to understand the building blocks of healthy cognitive ageing to reduce or even mitigate the decline in cognition that is associated with ageing (Beard et al., 2016; Livingston et al., 2020). Normal ageing is accompanied by heterogeneous trajectories of cognitive decline within and across individuals, and predominantly affects processing speed, episodic memory, and reasoning (Salthouse, 2016; Salthouse, 2019). Where some individuals maintain a high level of cognitive functioning even throughout advanced age, others experience cognitive deficits that profoundly impact their daily lives (Cabeza et al., 2018; Stern et al., 2020).

A growing body of research therefore seeks to explain individual variability in cognitive ageing by focusing on the underlying neural mechanisms (Cabeza et al., 2018; Cabeza et al., 2016). Brain ageing features that have been associated with lower cognitive functioning include a loss of brain volume and cortical thinning (Fjell & Walhovd, 2010; Fjell et al., 2014), alterations in microstructural integrity, white matter organization, and cortical myelination (Bennett & Madden, 2014; Buyanova & Arsalidou, 2021; Grydeland et al., 2013), accumulation of iron content (Howard et al., 2022), and alterations in resting-state functional connectivity (Ferreira & Busatto, 2013; Geerligs et al., 2015). However, patterns of brain ageing are highly variable across individuals, and marked differences exist in the extent of age-related brain changes as well as in the regional specificity of such alterations (Nyberg & Pudas, 2019; Patel et al., 2022; Poulakis et al., 2021). The concurrent investigation of brain ageing metrics therefore could provide complementary information on brain-cognition dynamics in ageing (Biondo et al., 2022; Patel et al., 2022).

Another approach to study heterogeneity in cognitive ageing involves identifying the factors that contribute to risk or resilience (Baumgart et al., 2015; Cabeza et al., 2018; Livingston et al., 2020; Nyberg & Pudas, 2019). Factors such as hypertension, diabetes, obesity, physical inactivity, sleep disturbances, and depressive symptoms contribute to an increased risk of cognitive decline (Baumgart et al., 2015; Livingston et al., 2020). In contrast, protective factors include, for example, educational attainment, occupational complexity, engagement in mentally stimulating activities, and social engagement (Baumgart et al., 2015; Livingston et al., 2020; Nyberg & Pudas,

2019). It is assumed that risk factors of cognitive decline impact cognitive abilities through their associations with decreased brain health (Gardener et al., 2015; Han et al., 2021). However, it remains to be elucidated whether protective factors promote cognition through neuroprotective effects (i.e., brain maintenance), stable neural advantages (i.e., brain reserve), and/or moderate the effects of neurodegeneration on cognition (i.e., cognitive reserve, CR) (Barulli & Stern, 2013; Cabeza et al., 2018; Nyberg & Pudas, 2019; Pettigrew & Soldan, 2019). As brain health measures only partially explain heterogeneity in cognitive functioning, further insights on the precise working mechanisms of these protective factors are especially important (P. A. Boyle et al., 2021).

Taken together, an extensive characterization of brain health parameters together with other factors of risk and resilience in cognitive ageing is warranted to increase our understanding of differing trajectories in ageing. Consequently, increasing efforts are made to facilitate the public availability of large neuroimaging datasets, directly via online repositories (Babayan et al., 2019; Bookheimer et al., 2019; Nugent et al., 2022; Spreng et al., 2022), or upon request and/or application (Filippini et al., 2014; Miller et al., 2016; Taylor et al., 2018; Taylor et al., 2017; Wardlaw et al., 2011).

The Advanced BRain Imaging on ageing and Memory (ABRIM) project aims to add to these existing datasets in several ways. First, only a few databases cover the adult lifespan (Nugent et al., 2022; Taylor et al., 2017), whereas it is critical to map cognitive performance and brain health across all age groups. We therefore collected a cross-sectional, normative database of adults between 18-80 years old, stratified by age decade and sex. Second, quantitative imaging techniques are scarcely available in large population studies (Babayan et al., 2019; Miller et al., 2016; Nugent et al., 2022). Quantitative imaging is particularly useful to investigate myelination and iron depositions in the brain (Khattar et al., 2021; Marques & Gruetter, 2013; Shams et al., 2019), and has been associated with cognitive performance in normal aging (Ghadery et al., 2015; Howard et al., 2022). Our neuroimaging protocol therefore not only matches the sequences of the aforementioned datasets (i.e., conventional structural T1- and T2-weighted imaging, multi-shell diffusion weighted imaging, and resting-state functional MRI), but also facilitates quantitative imaging with Magnetization Prepared 2 RApid Gradient Echoes (MP2RAGE) and Multi Echo Gradient Echo Imaging (MEGRE) sequences. Where MP2RAGE allows to compute longitudinal relaxation rates (R1 = 1/T1), MEGRE allows to derive

apparent transverse relaxation rates (R2*) and quantitative susceptibility maps (QSM) (Langkammer et al., 2010; Marques et al., 2010). Lastly, in addition to cognitive test performance, we measured several variables associated with risk or resilience in cognitive ageing with self-reported questionnaires (e.g., on depressive symptoms and memory strategy use), a semi-structured interview (e.g., on educational attainment, occupational complexity, and leisure activities), and actigraphy (for sleep and physical activity estimates). This allows us to map the interactions of these variables with brain health across the lifespan more comprehensively. A complete overview of the variables that are included in ABRIM, in addition to the aforementioned neuroimaging datasets, is provided in Supplementary Table A.

Below, we outline the study protocol of ABRIM, participant inclusion and exclusion procedures, behavioural and cognitive assessment, MRI sequences, and pre-processing pipelines. Furthermore, we describe our data sharing and management policies, as guided by the FAIR (Findable, Accessible, Interoperable, and Reusable) principles (Wilkinson et al., 2016).

ABRIM makes it possible to model imaging parameters and cognitive topologies throughout the adult lifespan, identify the normal range of values of such parameters, and further investigate the mechanisms that contribute to cognitive performance across the adult lifespan.

Materials and methods

Participants

The study was performed at the Donders Institute for Brain, Cognition, and Behaviour, Radboud University Nijmegen the Netherlands. Recruitment of participants occurred between February 2017 and May 2022. The present study focused on a healthy, adult lifespan sample (18–80 years old).

We aimed to include approximately 25 male and 25 female participants per approximate age decade of adult life (18–30, 31–40, 41–50, 51–60, 61–70, 71–80). We recruited 301 participants from the general population, predominantly from the Nijmegen area. Several methods were employed to facilitate recruitment, including online and offline advertisements (e.g., on social media or in local supermarkets) and word of mouth. Participants were provided with a reimbursement of 10 euros per hour per bank transfer.

Potential participants were screened for inclusion via telephone or e-mail with a standardized questionnaire. Exclusion criteria consisted of the presence of any conditions with a profound impact on the brain and cognitive health, beyond normal aging, including current psychiatric disorders (e.g., major depressive disorder, bipolar disorder, schizophrenia), neurological conditions (e.g., dementia, history of stroke, epilepsy), substance use disorders (e.g., addiction to hard drugs), and history of other major health conditions that could impact cognition (e.g., history of brain tumour). Participants were additionally excluded if any MRI contraindications were present (e.g., ferromagnetic metal implants, claustrophobia, pregnancy).

It should be noted that an additional $n = 108$ participants were recruited prior to the start of the MRI acquisition, which was delayed due to a scanner upgrade. However, once the MRI acquisition was started (approximately 4-6 months after initial inclusion), these participants did not undergo the MRI protocol due to various reasons (e.g., no answer, lack of interest, unavailability, or MRI contraindications that were not previously mentioned). To ensure that our final MRI study sample included approximately 300 participants, we extended our recruitment.

Ethical approval

The entire study was conducted in compliance with the Helsinki declaration. The study fell under the blanket ethics approval "Image Human Cognition" (Commissie Mensgebonden Onderzoek Arnhem-Nijmegen, 2014/288), and was additionally approved by the Social Sciences Ethical Committee of the Radboud University (ECSW 2017-3001-46) and was conducted in compliance with all local procedures and applicable national legislation. All participants provided written informed consent prior to participation.

Data management

We follow the requirements of the European General Data Protection Regulation (GDPR; https://gdpr.eu/) and the Dutch Act on Implementation of the General Data Protection Regulation.

To ensure anonymity of participants, privacy sensitive participant information (i.e., personal data) was separately stored in a password-protected database and only accessible to the main investigators. Participant data (i.e., scientific data) was anonymized and stored using study-specific numerical identification codes. A separate password-protected key file, that serves just to link participant identification codes to participant's names, was kept by one

researcher in strict confidence. We destroyed all privacy sensitive information and the key file one year after study completion, unless permission was granted by participants to be contacted in the future to be asked to participate in other studies. Signed informed consents and screening forms were locally archived in a closed locker at the Donders Institute, Nijmegen, the Netherlands, for at least 15 years after study completion. The original documents from the behavioural and cognitive examination (e.g., paper-and-pencil tests, self-reported questionnaires) were archived in a similar manner.

During data acquisition and analysis, raw actigraphy data was stored on a network directory from the Radboud University, Nijmegen, the Netherlands. With regards to MRI data, data were stored in a similarly secured way on network directory at the Donders Institute. Data storage is provided for by the main investigators of the study (MGJ, JMO, DGN) and is accessible only for researchers involved in the processing of ABRIM.

With regards to data management of demographic variables and outcome measures of neuropsychological tests, self-reported questionnaires, and actigraphy, we used Castor (https://www.castoredc.com/). Castor provides a secured, cloud-based platform that supports researchers with adhering to Good Clinical Practice (GCP) guidelines (e.g., by saving all entered data and any changes that are being made). The study data is archived in Castor for 15 years for traceability purposes in accordance with GCP. All data stored in Castor is available for researchers involved in processing of the study after access has been granted by the main investigators.

For archiving purposes, raw DICOM MRI images, raw actigraphy data, and the Castor export were transferred to the Radboud Data Repository (https://data.ru.nl/). All research data is archived for at least 10 years after study completion.

Notably, the Radboud Data Repository consists of non-shared data collections for archiving purposes (i.e., data acquisition collection, DAC), as well as shared data collections of pre-processed or anonymized data (i.e., data sharing collection, DSC).

ABRIM data sharing is facilitated through the Radboud Data Repository, with one DSC for the neuroimaging data (ABRIM MRI collection) and a second DSC for the cognitive and behavioural data (ABRIM behavioural collection). A complete description of the included measures in both data sharing collections

are provided below. To facilitate data sharing and ensure pseudonymization, data were stored using non-identifiable codes, data were minimized as much as possible (e.g., no birth data, only age), and all anatomical scans were defaced prior to further processing (see "Methods" for details).

All data sharing procedures are in accordance with the agreements specified in the participants' signed informed consent, and in consultation with the local privacy officer to ensure compliance to the relevant regulations, sharing as openly as possible but as restricted as needed due to privacy legislation.

Cognitive and behavioural data

Cognitive and behavioural examination

The cognitive and behavioural examinations were performed by trained researchers and consisted of a neuropsychological assessment, several self-report questionnaires, and a semi-structured interview to evaluate cognitive reserve.

The complete assessment took up to 2 hours and was performed in a quiet office-like environment without any distractions. Due to participant availability and logistics, not all assessments were performed on the same day as the MRI protocol (median days between assessments = 0, IQR 0-33.75). The order of the protocol was fixed to ensure that during the delay intervals for each memory test no new verbal stimuli to memorize were introduced. Below, we provide a detailed description of the different procedures and measures that were obtained. Notably, ongoing efforts to improve the cognitive and behavioural assessment introduced several novel components to the protocol throughout the course of the study, as indicated below.

Demographics, general health, and lifestyle variables

Standardized, self-report questionnaires were used to obtain information on demographics (age, sex, highest level of completed education), relevant medical conditions (e.g., hypertension, rheumatism), use of medication, and lifestyle habits (e.g., smoking behaviour, use of alcoholic beverages).

We used the International Standard Classification of Education (ISCED-11), to classify educational attainment into three levels: low education (early childhood, primary, and lower secondary education; ISCED 0-2), medium education (upper secondary and post-secondary non-tertiary education;

ISCED 3-4), high education (short cycle tertiary education, bachelor, master, and doctoral or equivalent education, ISCED 5-8; UNESCO, 2011).

With regards to relevant medical conditions, participants were asked to report any current or previous psychiatric or neurological conditions, substance abuse, cerebrovascular accidents, cardiovascular disease, rheumatism, hypertension, hypercholesteremia, diabetes, sleep disorders, and chronic pain conditions. We evaluated the presence of these conditions not only to ensure compliance with the inclusion criteria, but also to inform on several, frequently occurring age-related conditions that did not warrant exclusion for the present study (e.g., rheumatism, hypertension, hypercholesteremia, diabetes, sleep disorders, chronic pain). In addition, participants were asked to rate their current and monthly pain using a numerical rating scale ranging between 0 (no pain) and 10 (worst pain imaginable).

Furthermore, participants were asked to provide a list of their current medication use. Subsequently, we classified them into the following categories: 1) psychoactive medication (e.g., antidepressants or antipsychotics); 2) tranquilizers or sleep medication (e.g., benzodiazepines); 3) anticoagulants (e.g., heparin); 4) antiplatelets (e.g., acetylsalicylic acid); 5) blood pressure medication (e.g., diuretics); 6) cholesterol medication (e.g., statins); and 7) diabetes medication (e.g., insulin).

We incorporated a customized, self-report questionnaire to the study after data were collected for ±100 participants to obtain information on smoking behaviour (current, ever smoking, or no smoking) and use of alcoholic beverages, in terms of average drinking frequency (never, monthly or less, 2-4 times a month, 2-3 times per week, 4 or more times per week), average number of alcoholic beverages when drinking (none, 1-2, 3-4, 5-6, 7-9, 10 or more beverages), and how often more than 6 alcoholic beverages are consumed (never, monthly or less, monthly, weekly, daily or almost daily).

Neuropsychological assessment

The neuropsychological examination consisted of a variety of tests measuring global cognitive functioning, verbal intelligence, memory functions, executive functions, and processing speed.

The Montreal Cognitive Assessment (MoCA) was used as a measure of global cognitive functioning (Nasreddine et al., 2005). The MoCA consists of 11 items,

tapping into several distinct cognitive domains. Visuospatial functions are measured using a cube- and clock- drawing task (4 points). Short-term memory involves learning 5 nouns and delayed recall after an interval of 5 minutes (5 points). Executive functions are measured using an alternation task (1 point), a phonemic fluency task (1 point), and a verbal abstraction task (2 points); attention, concentration and working memory by using a forward and backward digit-span task (2 points), a sustained attention task (1 point), and a serial subtraction task (3 points). Language was assessed using a three-item naming task with animals (3 points), the repetition of two sentences (2 points), and the beforementioned phonemic fluency task. Lastly, orientation to place and time is evaluated using different questions (e.g., "Tell me today's date"; 6 points). As such, a total of 30 points can be obtained.

We used the Dutch Version of the National Adult Reading Test (DART) to obtain a measure of verbal IQ (Schmand et al., 1991). This test consists of a list of 50 written words that need to be read aloud by the participant that are scored by the experimenter based on pronunciation. To obtain a measure of verbal IQ, the raw scores are corrected for effects of age and sex, and subsequently transformed to indicate verbal IQ, based on Dutch norms. This test is often used as a proxy measure of CR and may be a more sensitive measure of CR than education level (R. Boyle et al., 2021; Opdebeeck et al., 2016).

We evaluated memory functions using three different tests: The Story Recall subtest from the Rivermead Behavioural Memory Test – Third Edition (RBMT-3) (Wilson, 2008), the Doors Test (Baddeley et al., 1994), and the Verbal Paired Associates (VPA) subtest of the Wechsler Memory Scale – Fourth Edition (WMS-IV-NL) (Hendriks et al., 2014). Notably, the VPA was introduced after data was collected for ±100 participants already.

The RBMT-3 evaluates everyday memory functioning by using stimuli that correspond more to everyday life contexts compared to more traditional, laboratory tests of memory. During the Story Recall Subtest, the experimenter reads a 21-element story to the participant with the instructions to repeat as many items as possible afterwards (immediate recall). After an interval of about 15 minutes, the participant is again asked to recall as many elements as possible from this story (delayed recall). Completely correct elements are awarded one point, whereas partially correct elements are awarded half a point.

The Doors Test (part A and B) evaluates visual recognition memory (Baddeley et al., 1994). For each part, participants are presented with 12 different target doors, each presented for 3 seconds. Immediately afterwards, the participant is asked to identify the target door on an array of 2 x 2 doors that includes 3 distractor doors. In part A, the distractors consist of different door types (e.g., a front door vs. a stable door, garage door, and café door). In contrast, distractors of visually similar door types are shown in part B (e.g., all front doors). Each correct response is rewarded with one point, and a total score of 24 can be obtained.

The VPA is a measure of associative memory (Hendriks et al., 2014). The test consists of two parts. First, a list of 14 word-pairs is read to the participant that contains both semantically related (e.g., door-open) and semantically unrelated word pairs (plant-happy). Subsequently, the experimenter provides the participant with the first word of a particular pair and asks the participant to recall the associated word. This procedure is then repeated three times, where the experimenter provides feedback on the participant's responses (immediate recall). Second, after an interval of 20-30 minutes, the participant is asked to recall the paired words, again by providing the participant with the first word of a particular pair, but now without feedback from the experimenter (delayed recall). Subsequently, the delayed recall is followed by a yes/no recognition test of word pairs, and a free-recall test of words from the word pairs. During the free-recall test, the words can be recalled as single items as they do not necessarily have to be recalled within a particular pair. For each part of the VPA, we recorded the participant's responses and the number of correct responses.

We used three different tests to obtain measures for executive functions and processing speed: the Stroop Colour Word Test (SCWT) (Houx et al., 1993), the Trail Making Test (TMT) (Reitan, 1958), and the digit span test (DST) of the Wechsler Memory Scale - Revised (WMS- R) (Wechsler, 1987).

The SCWT evaluates processing speed and inhibition (Houx et al., 1993). Here, participants are asked to perform three tasks as fast as possible: 1) to read names of colours (Word Naming; W); 2) to name different colours (Colour Naming; C); 3) and to name the colour of the ink instead of reading the word itself while the colour-words are displayed in an incongruent colour (Colour-Word Naming; CW). For each task, we recorded the completion time and the number of errors made.

The TMT consists of part A and part B, and allows to measure attention and processing speed (Reitan, 1955; Reitan, 1958). In part A, participants connect a set of 25 consecutive numbers. In part B, a set of 25 circles is connected by alternating between numbers and letters. During both parts, participants are instructed to work as fast and accurately as possible. For each part, the time to complete the task and the number of errors is recorded.

We used the DST to measure working memory (Wechsler, 1987). The experimenter reads a list of numbers and asks the participant to recall this list immediately afterwards in forward order. Subsequently, a second list is presented, where the participant is asked to recall the numbers in backward order. For both lists, the total number of digits increases after each sequence of two trials, until the participant fails a complete sequence or reaches the end of the test list that each consists of 6 sequences. The total number of correct reproductions on the forward and the backward versions are recorded.

Cognitive reserve index questionnaire

We used the Cognitive Reserve Index questionnaire (CRIq) to obtain an indication of CR. The CRIq is a semi-structured interview focusing on several proxy measures of CR, namely: education, working activity, and leisure activities. These domains have been suggested to predominantly contribute to the lifetime experiences that contribute to CR (Nucci et al., 2012; Stern et al., 2020). The CRIq hence does not capture CR directly, but instead provides an overall indication of CR that has been accumulated throughout the lifespan as well as sub-scores for each separate domain (Nucci et al., 2012). Previous literature demonstrated that CRIq scores indeed could explain the discrepancy between cognitive performance and brain pathology in various study populations (i.e., from healthy to pathological ageing), indicating that this is a valid indicator of CR (Kartschmit et al., 2019; Stern et al., 2020).

Self-report questionnaires

Self-report questionnaires included the Beck Depression Inventory, Brief Pain Inventory, Self- Report Psychopathy-short form, and the Metamemory in Adulthood Questionnaire-short form (Beck & Steer, 1987; Cleeland & Ryan, 1994; Dixon et al., 1988; Paulhus et al., 2009; Ponds & Jolles, 1996; Tan et al., 2004). Notably, as mentioned earlier, ongoing efforts to improve the cognitive and behavioural assessment introduced several novel components to the protocol throughout the course of the study. After the inclusion of ±100 participants, the Everyday Memory Questionnaire (revised), Cognitive

Failure Questionnaire, and a customized strategy use questionnaire were added to our protocol (Broadbent et al., 1982; Ponds et al., 2006; Royle & Lincoln, 2008).

The Beck Depression Inventory (BDI) was implemented to identify potentially high levels of depressive symptoms and evaluates depressive symptoms on a 4-point scale across 21 items, where higher scores indicate increased presence of depressive symptomatology (Beck & Steer, 1987). A score between 0-9 indicates that an individual is experiencing no or minimal depression, 10-18 indicates mild depression, 19-29 indicates moderate depression, and 30-63 indicates severe depression.

The Brief Pain Inventory (BPI-SF) measures presence and location of pain, pain severity, pain interference on daily functions, pain treatment and (the percentage of) pain relief following treatment. Pain severity (4 items) and pain interference (7 items) are rated on an 11-point rating scale ranging from 0 to 10 (Cleeland & Ryan, 1994; Tan et al., 2004).

The Self-Report Psychopathy – Short Form (SRP-SF) evaluates psychopathy-related traits (Paulhus et al., 2009). This questionnaire consists of 28 items, rated on a 5-point scale, and comprises four subscales: Interpersonal Manipulation, Callous Affect, Erratic Lifestyle, and Criminal Tendencies.

The Metamemory in Adulthood questionnaire – Short Form (MIA-SF) evaluates subjective memory functions and knowledge of memory processes (Dixon et al., 1988). In the present study, we use the abridged Dutch version of this questionnaire (Ponds & Jolles, 1996). The questionnaire consists of 74 items, rated on a 5-point scale, and allows to calculate separate scores for the following domains: Task, Capacity, Change, Anxiety, Achievement, Locus and Strategy. The Strategy domain contains 16 items and is additionally divided into External Strategies (e.g., memory aids, 8 items) and Internal Strategies (e.g., mental imagery, 8 items).

The Everyday Memory Questionnaire – Revised (EMQ) measures subjective memory failure in everyday life (Royle & Lincoln, 2008). This questionnaire consists of 13 items, rated on a 5-point scale. Each item focuses on the frequency of memory failures in daily life, such as forgetting when a certain event happened (e.g., whether this occurred yesterday or last week), or forgetting to tell someone something important (e.g., passing a message from someone else).

The Cognitive Failure Questionnaire (CFQ) evaluates subjective cognitive functioning and consists of 25 items, rated on a 5-point scale (Broadbent et al., 1982; Ponds et al., 2006). Each item focuses on the frequency of daily cognitive mistakes, such as missing appointments or experiencing difficulties in making decisions. Four additional questions inform on potential increases in the occurrence of these mistakes and the extent to which an individual finds these experiences troublesome, annoying, or worrisome; however, these items are not used in scoring this questionnaire.

We incorporated a separate, custom-made questionnaire to obtain information on strategy use during the VPA. Here, after completing the VPA, participants are asked to describe whether they used strategies to recall the word pairs, and the type of strategies they used (e.g., concentrating, repetition, visualization, association; see Supplementary Methods for an English translation of this questionnaire).

Actigraphy

We used the Actiwatch 2 (Philips Respironics, Eindhoven, the Netherlands), a wristband-type actigraphy device with an internal accelerometer and light sensor to infer sleep-wake rhythms. As we did not have enough devices, we were unable to acquire actigraphy data among all participants. The decision to give a participant an actiwatch was based on the availability of the devices, while also aiming to achieve an equal age distribution of this sub-sample. Actigraphy was acquired for 7 consecutive days. Participants were asked to report any sleep disorders, as these could affect the data collection (e.g., insomnia, sleep apnea, restless leg syndrome). Epoch length was set at 15 seconds. All data was processed with Actiware software (v6.0.9).

All actograms were visually checked to ensure quality of the data. Data were excluded when the algorithm failed to register any sleep/wake rhythms or was unable to delineate these (e.g., because the device was not worn at all or too irregularly). A minimum of 5 days of usable data was required for inclusion of the data in our database.

With regards to sleep, we recorded the following outcomes measures: total sleep time (summation of sleep epochs within the sleep phases), wake after sleep onset (WASO; summation of wake epochs between begin and end of a sleep phase), sleep latency, sleep efficiency, and number of awakenings. Although this device has been predominantly shown to measure sleep in an

objective and reliable manner (Shin et al., 2015), recent studies demonstrated that valid measures of physical activity can also be calculated, for example, by using the activity counts per minute or cycle recorded by the device (Neil-Sztramko et al., 2017).

MRI

Data acquisition

All scans were acquired on a 3T Siemens Magnetom Prisma System (Siemens, Erlangen, Germany) using the standard 32-channel receive coil. We used an auto-align localizer sequence to automatically align all imaging sequences, additionally each alignment was visually checked and manually adjusted when necessary. The duration of the complete scanning session was approximately 55 minutes. Participants were held with head cushions and were additionally fixed using a small piece of tape to reduce head movement (Krause et al., 2019).

The following MRI scans were acquired: 1) T1-weighted 3D Magnetization Prepared - RApid Gradient Echo (MPRAGE; TR = 2200 ms, TE = 2.64 ms, voxel size 0.8 mm isotropic); 2) T1- weighted MP2RAGE (TR = 6000 ms, TE = 2.34 ms, voxel size 1.0 mm isotropic); 3) Fast turboFLASH B1 mapping (TR = 10000 ms, TE = 2.23 ms, voxel size 3.3x3.3x2.5 mm); 4) T2- weighted turbo spin echo (TSE) sequence (TR = 3200 ms, TE = 569 ms, voxel size = 0.8 mm isotropic); 5) multi-shell High Angular Resolution Diffusion Imaging (HARDI; TR = 2940 ms, TE = 74.80 ms, voxel size 1.8 mm isotropic, 11 x b = 0, 86 x b = 1250, 85 x b = 2500 s/mm2); 6) Multi-echo gradient echo (MEGRE; TR = 44 ms, TE_1 / ΔTE / TE_9 = 6.14 / 4 / 38.14 ms); and 7) 10 minutes resting-state BOLD fMRI (GE-EPI; TR = 1000 ms, TE = 34 ms, voxel size = 2.0 mm isotropic). A complete overview of the sequence parameters can be found in Table 1.

Furthermore, among n = 76 participants, task-based fMRI was collected during a prospective memory paradigm, together with the prospective and retrospective memory questionnaire (Altgassen et al., 2021; Altgassen et al., 2017; Smith et al., 2000). However, as the prolonged duration of the total MRI scanning protocol (±2.5 hours) led to significant recruitment difficulties, the acquisition of the task was discontinued to preserve the feasibility of the study.

Table 1. Overview of neuroimaging sequences and parameters

Scan type	Sequence	TR (ms)	TE (ms)	Flip angle (°)	Voxel size (mm)	FOV (RL/AP/ FH)	Other
T1-weighted	MPRAGE	2200	2.64	11	0.8x0.8x0.8	180x320x256	GRAPPA: 3; TI = 1100
	MP2RAGE	6000	2.34	6/6	1.0x1.0x1.0	263x350x350	GRAPPA: 3; TI_1/TI_2 = 700/2400
B1 map	turboFLASH	10000	2.23	8	3.3x3.3x2.5	350x263x350	
T2-weighted	TSE	3200	569	n/a	0.8x0.8x0.8	180x320x256	GRAPPA: 3; variable flip angle
Diffusion- weighted	PGSE-EPI	2940	74.80	90	1.8x1.8x1.8	216x216x146	GRAPPA: 2; SMS factor = 3 (interleaved); 11 b=0 s/mm^2 volumes; 86 b=1250 s/mm^2; 85 b=2500 s/mm^2
MEGRE	Bipolar multi-echo GRE	44	$TE_1/\Delta TE/TE_9$ = 6.14/4/38.14	20	0.8x0.8x0.8	186x230x141	GRAPPA: 3
Resting- state fMRI	Multi-band GRE-EPI	1000	34	60	2.0x2.0x2.0	210x210x132	Acquisition time: 10 minutes.
	Inverted Distortion GRE-EPI	1000	34	60	2.0x2.0x2.0	210x210x132	

Abbreviations: TR = repetition time; TE = echo time; TI = inversion time; FOV = field of view; MPRAGE = Magnetization Prepared Rapid Acquisition Gradient Echo; GRAPPA = GeneRalized Autocalibrating Partial Parallel Acquisition; MP2RAGE = Magnetization Prepared 2 Rapid Acquisition Gradient Echoes. TSE = Turbo Spin Echo; PGSE = Pulsed-gradient spin-echo; EPI = echo planar imaging; SMS = simultaneous multi-slice; GRE = Gradient Echo Imaging.

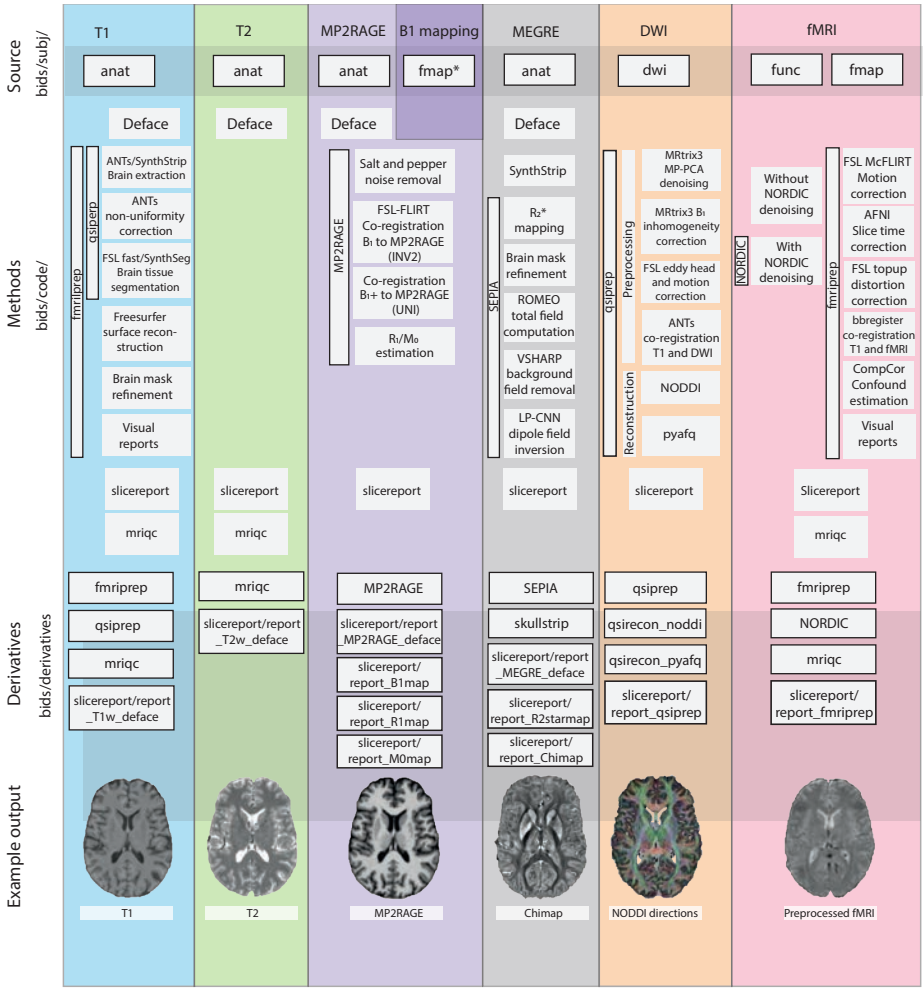


Figure 1. Schematic illustration of the methodological steps that were applied for each imaging modality, and its corresponding Brain Imaging Data Structure (BIDS) folders of the ABRIM MRI collection. Each column in the figure represents a different imaging modality, and is distinguished by a unique colour (e.g., T1 images in blue). Each row represents a specific methodological step (e.g., fMRIprep; Esteban et al., 2019) with its corresponding sub-steps (e.g., brain extraction). BIDS folders are denoted with black frames. The process starts with the source data (e.g., bids/subj/anat/ folder) and progresses to the derivatives (e.g., bids/derivatives/fmriprep/ folder). For each imaging modality, an example output image is displayed at the bottom. All code utilized can be found in the bids/code folder. Note that a certain imaging modality may be processed by multiple methods (e.g., T1 images with both fMRIprep and QSIprep; Cieslak et al., 2021; Esteban et al., 2019). *fmap is available under bids/subj/derivatives/SIEMENS/

Several efforts were made to facilitate the shareability, reproducibility, and reusability of ABRIM MRI data (Niso et al., 2022). First, we adhere to the guidelines outlined in the Brain Imaging Data Structure (BIDS) (Gorgolewski et al., 2016), and COBIDAS MRI reporting framework (Nichols et al., 2017). Second, we used standard containerized neuroimaging pipelines specifically developed for BIDS data (i.e., BIDS apps) (Gorgolewski et al., 2016), to process the raw MRI images and to provide visual quality control (QC) reports. Below, we explain our MRI sequences and (pre-)processing pipelines in more detail. A schematic illustration of the various methodological steps that were applied to each imaging modality, and corresponding BIDS folders, is displayed in Figure 1.

BIDS conversion

To transform raw DICOM files to BIDS, we used version 3.7.4 of the open-source BIDScoin application (https://github.com/Donders-Institute/bidscoin) (Zwiers et al., 2021). The resulting data complied to version 1.8 of the BIDS standard, which was verified by application of the bids-validator version 1.11 (https://github.com/bids-standard/bids-validator) After BIDS conversion was completed for all participants, we proceeded with de-identification of all anatomical MRI data by applying the deface BIDS app of BIDScoin. The deface app is a wrapper of *pydeface* (https://github.com/poldracklab/pydeface) and ensures that the output corresponds to the BIDS standard. All output was visually inspected by one author (MGJ) to ensure successful de-identification, while a second author was consulted (MPZ) in case of any uncertainties. Manual masks were created in case of any remaining unique personal features that could led to potential identification (e.g., nasal features), and masked out from the anatomical images using *fslmaths* from FMRIB Software Library (FSL; https://fsl.fmrib.ox.ac.uk/).

T1- and T2-weighted imaging derivatives

We incorporated the T1-weighted MPRAGE and T2-weighted TSE sequences to allow for the characterization of conventional markers of brain ageing, such as the volume and thickness of various brain regions (Bethlehem et al., 2022; Rutherford et al., 2022). Furthermore, these sequences can be combined to obtain more detailed measurements of brain morphology and maps of the structural organization of the cerebral cortex (e.g., relative myelin content) (Glasser et al., 2016). As explained below, the T1-weighted images are minimally processed together with the resting-state fMRI and diffusion-weighted sequences. For both T1- and T2- weighted images, we provide visual QC reports.

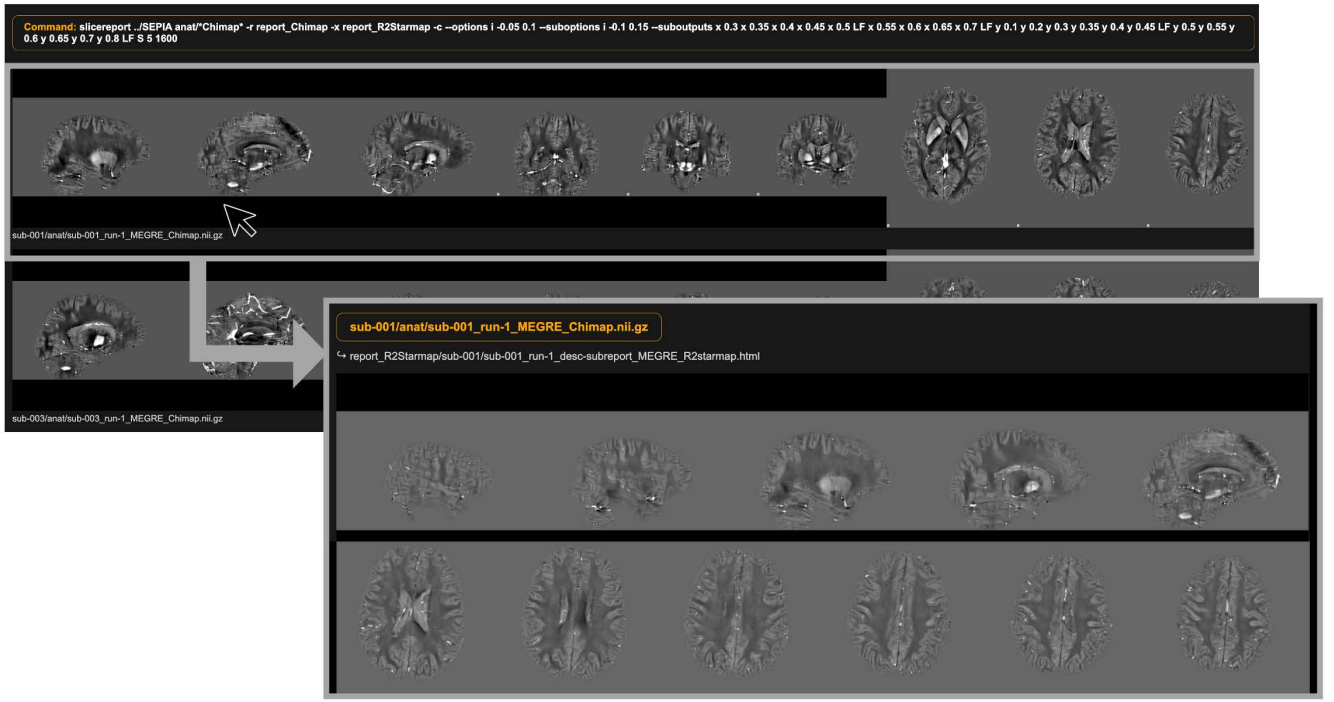


Figure 2. An example of the slicereport-tool to create visual quality control reports for Quantitative Susceptibility Mapping (QSM) output in ABRIM. The top left image displays the generated web-page, featuring rows of image slices per subject. In this case, the researchers opted for several sagittal, coronal, and axial slices to enable visual inspection of physiological noise (e.g., motion, ringing) and streaking artifacts. Upon clicking on the image slices of a specific subject, it leads to a sub-page (right bottom image). In this case, the sub-page displays a more detailed representation of the various slice orientations to further facilitate visual inspection. To facilitate the delineation of motion artifact, the sub-page additionally contains a weblink that enables the user to view the corresponding R2* maps ("report_R2Starmap/sub-001/sub-001_run-1_desc-subreport_MEGRE_R2starmap.html").

We used the general purpose slicereport-tool of BIDScoin to generate visual QC reports unless otherwise specified. Slicereport facilitates the generation of a web page, displaying rows of image slices for each subject, and optionally provides individual sub-pages with more detailed information. In addition, it provides the flexibility to customize the displayed information. Therefore, slicereport enables efficient and thorough visual inspections of MRI data. For an example of its application in ABRIM, see Figure 2.

Asides from this, we applied the MRI Quality Control tool (MRIQC) to provide additional QC reports and image quality metrics for the T1, T2, and fMRI images (Esteban et al., 2017).

MP2RAGE and Fast turboFLASH B1 mapping

The MP2RAGE sequence was developed to obtain T1-weighted images that are less dependent of transmit and receive field inhomogeneities (B1+ and B1-) and improve the contrast between white matter and grey matter tissue (Marques et al., 2010) by removing residual dependency on water density and transverse relaxation (M0 and T2*). We acquired MP2RAGE from which quantitative longitudinal relaxation rate (R1) and proton density maps were derived (Marques & Gruetter, 2013). The turbo flash B1 maps were utilized to correct transmit field inhomogeneities. Previous studies revealed that R1 maps are useful to delineate cortical myelination in group studies (Shams et al., 2019), and to study white matter tissue maturation over the lifespan (Yeatman et al., 2014). Proton density maps can be used to compute the surrogate Macromolecular Tissue Volume fraction (Mezer et al., 2013).

To process the MP2RAGE images, we used BIDS compatible Matlab scripts that are hosted on Github (https://github.com/Donders-Institute/MP2RAGE-related-scripts). For the purpose of anatomical referencing, the typical salt and pepper noise of the MP2RAGE was reduced using the regularization method as described in (O'Brien et al., 2014). Quantitative R1 maps were obtained using bids_T1B1correct.m from the above repository: (i) The magnitude image from the turbo flash B1 map was registered to the MP2RAGE image with proton density contrast (INV2) using SPM12 (Greve & Fischl, 2009); (ii) The resulting transform matrix was then used to co-register a spatially smoothed version of the B1+ map to the MP2RAGE image; (iii) To correct for B1 transmit inhomogeneities in R1 estimations (and derive M0 maps over a large range of R1 values), instead of the traditional MP2RAGE lookup table, a fingerprinting-like approach was used to estimate R1 (Ma et al., 2013). Here, the maximum of the inner product of the

signal at the two inversion times is used by a dictionary to determine the voxel R1 and M0. MP2RAGE signal dictionaries were computed at steps 0.005 nominal B1 field. Finally, visual QC reports were generated for the R1 and M0 maps.

Gradient echo imaging

We used MEGRE for apparent transverse relaxation rate (R_2*) mapping and quantitative susceptibility mapping (QSM) to obtain quantitative measurements that relate to local concentrations of iron and myelin in the brain. Both techniques are sensitive to the change of tissue magnetic susceptibility *(χ)*. Conventionally, the magnitude of the MEGRE data is used to derive R2* maps and the phase of the MEGRE data is used for QSM. Previous studies demonstrated that increases of iron and myelin concentration enhance the R2* values (Langkammer et al., 2010; Langkammer et al., 2012; Lee et al., 2012). In QSM, however, these two constituents produce opposite image contrasts since iron is paramagnetic (+χ) and myelin is diamagnetic (-χ) with respect to water (Langkammer et al., 2010; Lee et al., 2012; Liu et al., 2015). As ageing is characterized by changes in both myelination and iron depositions throughout the brain (Betts et al., 2016; Khattar et al., 2021), processing both the QSM and R2* maps provides a more complete picture of these alterations at no extra cost as both maps can be derived from the same data.

We used custom BIDS wrapper code around the SEPIA toolbox (v1.2.2.3) for generation of the R2* and QSM maps (Chan & Marques, 2021). Prior to applying the SEPIA toolbox, we acquired brain masks using SynthStrip, a novel learning-based brain extraction tool with highly accurate performance across different imaging modalities and populations (Hoopes et al., 2022). More specifically, we implemented SynthStrip using the skullstrip BIDS app from BIDScoin.

R2* maps were derived by extracting the magnitude of the MEGRE data based on a closed- form solution (Chan & Marques, 2021; Gil et al., 2016). Additionally, we generated the corresponding visual QC reports.

We acquired QSM maps through multiple steps in SEPIA (Chan & Marques, 2021). First, the MEGRE brain masks were initially refined by masking out high R2* voxels on the mask edge associated with non-tissue of interest (e.g., air and vein) that can create strong susceptibility artefacts. Subsequently, total field computation was performed with ROMEO (Dymerska et al., 2021), background field removal with VSHARP (Li et al., 2011), and dipole field inversion using LP-CNN (Lai et al., 2020). As QSM only provides relative values, we used the mean

susceptibility of the whole brain as a reference to facilitate data comparison between subjects. Visual QC reports were generated for the QSM maps.

In addition to the QC reports, we provide subjective quality assessment ratings for physiological noise (e.g., motion, ringing) and streaking artifacts in QSM. Both aspects can have a profound impact on the contrast of the resulting images and validity of results (Marques et al., 2021). The presence of both quality aspects was visually rated on a scale from 0 (optimal quality) to 5 (multiple / gross artefacts). Subsequently, these scores are summed to indicate the total quality. The quality assessment file also includes a dichotomous rating to indicate if any parts of the cerebellum or cerebrum were missing (0 = complete; 1 = missing).

Diffusion-weighted imaging

Diffusion-weighted imaging allows to investigate the microstructural properties of the brain in a non-invasive manner. We used multi-shell HARDI with 182 diffusion directions (HARDI, 11 x b = 0, 86 x b = 1250, 85 x b = 2500 s/mm^2) to derive different microstructural properties, such as fractional anisotropy (FA) and mean diffusivity (MD) from diffusion tensor imaging (DTI) (Beaulieu, 2002), or neurite density index (NDI) and orientation dispersion index (OD) from neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012). HARDI also allows for fibre tractography, where diffusion-derived measures are modelled along the trajectories of white matter pathways (Berman et al., 2013). Age-related differences and neurodegenerative diseases have been frequently related to these metrics, where loss of white matter integrity is typically characterized by decreased FA and increase MD values (Goveas et al., 2015; Suri et al., 2014).

It is well-known that diffusion imaging data are sensitive to corruption from various sources of physiological and scanner noise, and that the images are typically geometrically distorted due to local (susceptibility-induced) and global (eddy-current-induced) magnetic field distortions (Tax et al., 2022). We used the state-of-the-art BIDS compatible QSIPrep pre- processing pipeline (v0.18.0) to correct for artifacts and to offer high-quality data (Cieslak et al., 2021).

In short, QSIprep processes both structural MRI and diffusion MRI, and automatically incorporates pre-configured workflows based on the data provided to estimate various popular HARDI models, QC metrics, and visual QC reports (Cieslak et al., 2021). For ABRIM structural MRI, QSIprep uses Advanced Normalization Tools (ANTs, https://www.nitrc.org/projects/ants) to

correct for intensity non-uniformity (Tustison et al., 2010) and for non-linear registration of T1 images to the MNI152 template (Avants et al., 2008). Brain extraction is performed using SynthStrip (Hoopes et al., 2022), and tissue segmentation using SynthSeg (Billot et al., 2023). For ABRIM diffusion data, QSIprep applies MP-PCA denoising as implemented in MRtrix3's dwidenoise (https://www.mrtrix.org/) (Tournier et al., 2019; Veraart et al., 2016), B1 field inhomogeneity correction using dwibiascorrect from MRtrix3 with the N4 algorithm (Tustison et al., 2010), head motion and eddy current correction using FSL's eddy (Andersson & Sotiropoulos, 2016), and rigid co- registration to the T1-weighted image using antsRegistration (ANTs) (Avants et al., 2008). The complete QSIprep pre-processing configuration is described within the ABRIM MRI collection (*/bids/derivatives/qsiprep/logs*).

We subsequently used QSIprep to apply two preconfigured reconstruction workflows. The first workflow (*mrtrix_multishell_msmt_pyafq_tractometry*) distinguishes major white matter pathways and estimates its corresponding tissue properties. More specifically, besides providing FA and MD estimates, this workflow applies automatic fiber-tract quantification (AFQ) (Yeatman et al., 2012; Kruper et al., 2021) and uses IFOD2 from MRtrix3 to generate many more microstructural measures and tractography data (Tournier et al., 2010). The second workflow (*amico_noddi*) was utilized to estimate the NODDI model (Zhang et al., 2012) with the AMICO implementation (Daducci et al., 2015). The resulting outputs include the intra- cellular volume fraction (ICVF), isotropic volume fraction (ISOVF), and orientation dispersion (OD).

Resting-state fMRI

Resting-state fMRI was incorporated because of its relation to task-activation, brain network organization and cognition (Smith et al., 2009; Smith et al., 2015). With advancing age, brain networks are characterized by less distinct functional networks and decreased local efficiency, predominantly among the brain networks responsible for higher order cognitive processes (Geerligs et al., 2015).

We applied the BIDS compatible fMRIprep pre-processing pipeline (v23.1.2), which facilitates the pre-processing of structural and fMRI data by combining different software packages (Esteban et al., 2019). Briefly, T1 images are corrected for intensity non-uniformity and brain extracted using ANTs (Tustison et al., 2010). Brain surfaces are reconstructed using Freesurfer (v7.3.2. https://surfer.nmr.mgh.harvard.edu/) and used to refine the initially estimated brain mask. Non-linear registration of T1 images to the ICBM152 template is

performed with ANTs (Avants et al., 2008), and brain tissue segmentation with FSL FAST (Zhang et al., 2001). With regards to fMRI, susceptibility-induced distortion corrections are performed using FSL topup (Andersson et al., 2003), slice time corrections with Analysis of Functional NeuroImages (AFNI, https://afni.nimh.nih.gov/), and motion corrections with FSL McFLIRT (Jenkinson et al., 2002). Co-registration between the T1 images and fMRI data is facilitated using bbregister from Freesurfer (Greve & Fischl, 2009). Confounds are estimated for nuisance regression using CompCor (Behzadi et al., 2007). In addition, visual QC reports are saved that allow for a complete evaluation of the fMRIprep procedures. The complete fMRIprep pre-processing configuration is described within the ABRIM MRI collection (*bids/derivatives/fmriprep/logs*).

In addition, we applied Noise Reduction with Distribution Corrected (NORDIC) denoising on the fMRI data, using both the magnitude and phase time series (https://github.com/SteenMoeller/NORDIC_Raw), before running the fMRIprep pre- processing pipeline on the denoised data. Briefly, NORDIC allows to further improve the spatial temporal resolution of fMRI data by reducing thermal noise (i.e., white noise due to thermal fluctuations of the subject and/or receive coil). In contrast to more traditional denoising algorithms (e.g., ICA-AROMA) (Pruim et al., 2015), NORDIC does not affect structured, non-white noise (e.g., due to respiration or the cardiac cycle), and therefore complements other algorithms (Moeller et al., 2021; Vizioli et al., 2021).

Results

Sample characteristics

Among the 301 participants tested, 6 participants were excluded from the dataset, either due to incidental MRI findings (*n = 5)* or because of the presence of a condition with a profound impact on the brain and cognitive health (*n = 1)*, resulting in 295 participants in the final study sample (53.20% females, median age 52 years, interquartile range [IQR] 36-66). An overview of the demographics of the ABRIM study per age decade is displayed in Figure 3. A more extensive description is provided in Supplementary Table B.

Study characteristics of the sub-sample of 108 participants who solely took part in the behavioural and cognitive assessment are provided in Supplementary Table C.

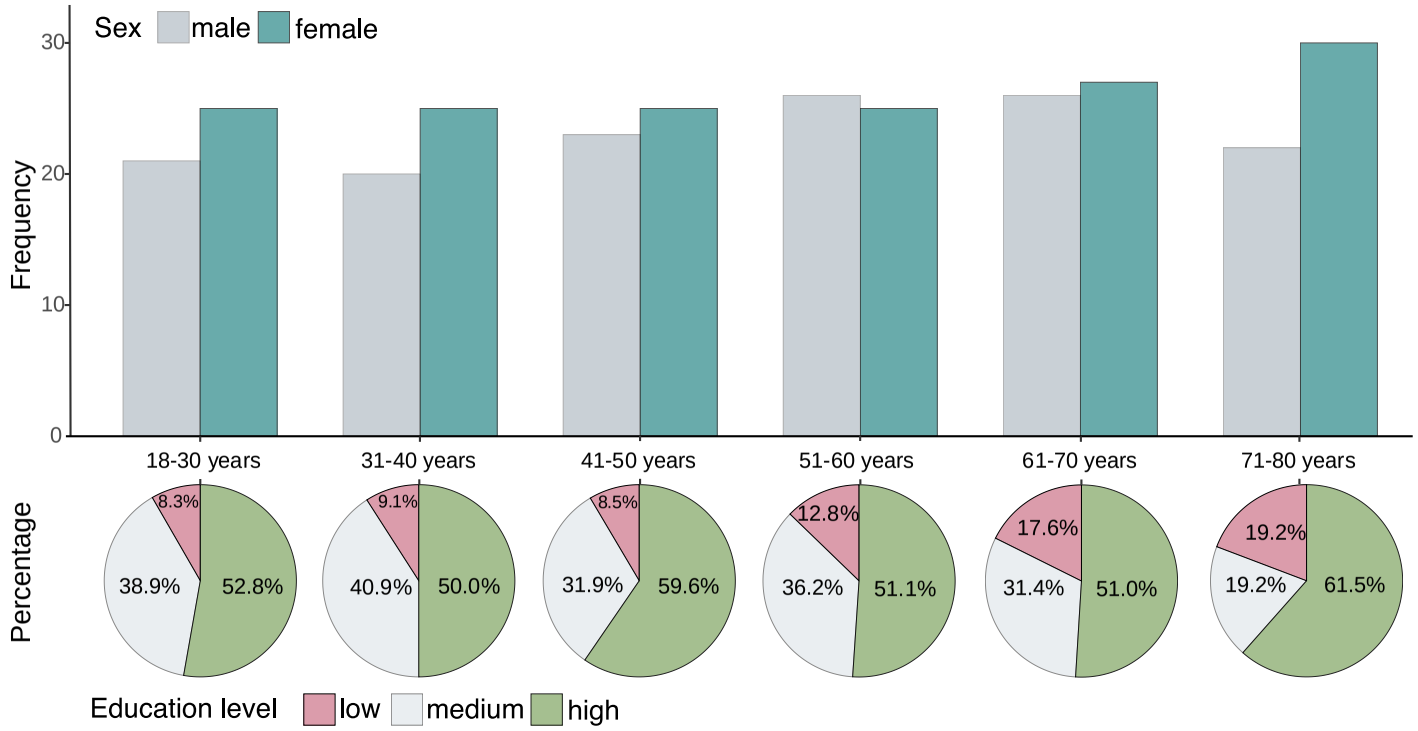


Figure 3. Demographics of the ABRIM study by age decade. The upper section displays the distribution of male and female participants for each age decade. The lower section consists of several pie charts, displaying the relative distribution of participants with low, medium, and high educational attainment within each age decade. Levels of education were classified using the International Classification of Education (ISCED-11): low education (ISCED 0-2), medium education (ISCED 3-4), and high education (ISCED 5-8). Data on educational attainment were not available for *n* = 18 participants.

Actigraphy data was acquired in a sub-sample of 134 participants. After visually inspecting the data, this resulted in the exclusion of 14 participants (*n = 6* failed to register any activity, *n* = 3 unable to properly distinguish sleep/wake rhythm, *n* = 5 with less than 5 days of usable data). Therefore, a total of 120 participants were included in our database. Demographics of this sub-sample are displayed in Supplementary Table D. Amongst the sub-sample of participants who only participated in the cognitive and behavioural measurements, actigraphy was acquired among 11 participants (*n* = 1 failed to register any activity and was excluded, resulting in *n* = 10 participants).

ABRIM MRI collection

The ABRIM MRI collection consists of the raw and pre-processed MRI data of 295 participants, together with several automated and/or manual quality control indices in BIDS format. Furthermore, various demographic details are included (age, sex, height, and weight). This collection has been made available on the Radboud Data Repository in December 2023 (https://doi.org/10.34973/7q0a-vj19). Access to the data is available for registered users under the data user agreement for identifiable human data – scientific use (RU-HD-SU-1.0). Detailed instructions are provided on the Radboud Data Repository (https://data.ru.nl/).

A complete overview of the ABRIM BIDS folder structure is provided in Figure 4. Briefly, raw MR images are stored in the subject-specific folders within the bids root directory. These folders additionally contain metadata files that provide a more detailed account of the MRI acquisition parameters. Pre-processed MR images are available in the *bids/derivatives* folder, while the scripts to generate these derivatives are in the *bids/code* folder. Furthermore, within the *bids/derivatives* folder, we included visual QC reports generated with the slicereport-tool. Examples of the acquired MRI images and derivatives for the ABRIM MRI collection for a single subject are provided online in an interactive format, covering the sagittal, coronal, and axial orientations (https://doi.org/10.1371/journal.pone.0306006.s008).

In addition, we processed the T1-weighted MPRAGE, T2-weighted TSE and resting-state fMRI scans with MRIqc to provide additional QC metrics and group reports. An illustration of the QC group report from MRIqc, derived from the T1-weighted MPRAGE scans, is provided in Figure 5. The QC group reports for the T2-weighted scans and resting-state fMRI images are available in Supplementary Figure A and B.

For the QSM output, additional subjective quality assessment ratings for physiological noise (e.g., motion, ringing) and streaking artifacts are available in *bids/derivatives/slicereport/report_Chimap/qcscores.tsv.*

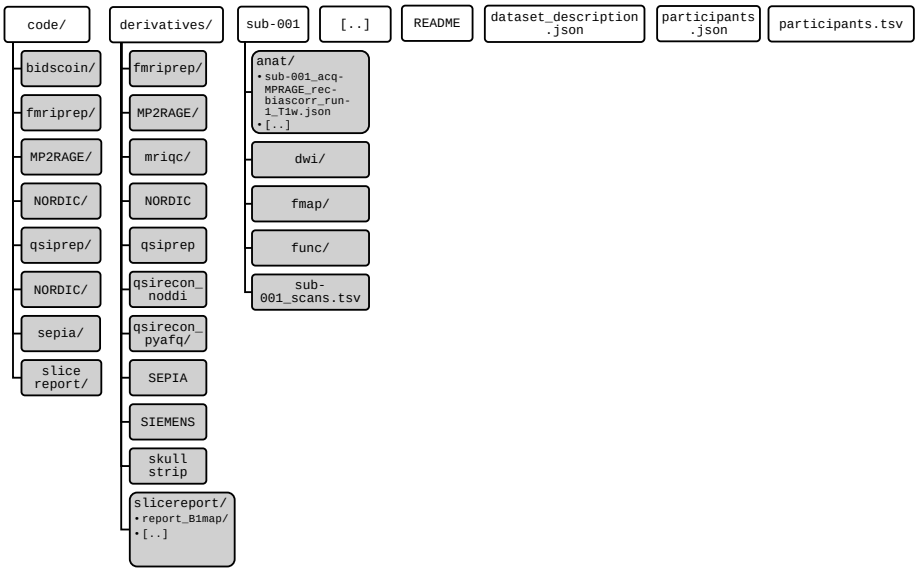


Figure 4. Hierarchical overview of ABRIM MRI data collection folder structure following the Brain Imaging Data Structure (BIDS) standard. The "code" folder contains all scripts that have been applied for data processing. The "derivatives" folder contains all processed and derived data that has been generated from the raw MRI data (e.g., "NORDIC", "SEPIA", etc.). Individual subject-specific folders (e.g., "sub-001", "sub-002", etc.) contain modality-specific sub-folders with different types of MRI data (e.g., "anat" contains structural MRI data, whereas "dwi" contains diffusion-weighted imaging data).

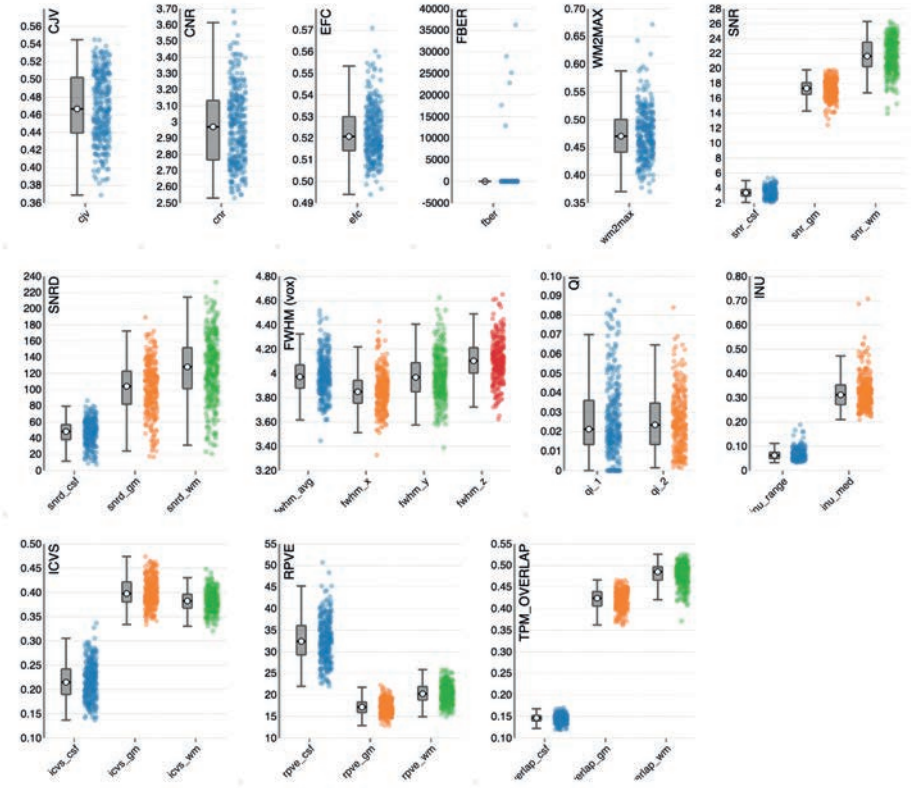


Figure 5. Group anatomical report of T1 scans in ABRIM as generated by the MRI Quality control tool (MRIQC). Contains separate strip-plots for different image quality metrics (IQMs). Abbreviations: CJV = coefficient of joint variation; CNR = contrast-to-noise-ratio; EFC = entropy focus criterion; FBER = foreground-to-background energy ratio; WM2MAX = white-matter to maximum intensity ratio; SNR = signal-to-noise-ratio; SNRD = Dietrich's signal-to-noise-ratio; FWHM (vox) = full width half maximum in units of voxels; QI = quality index; INU = intensity non-uniformity; ICVS = intracranial volume fraction; RPVE = residual partial volume effect; TPM_OVERLAP = overlap of issue probability maps of the images and maps from the ICBM nonlinear-asymmetric 2009a template.

ABRIM behavioural collection

This data collection will include the measures obtained from the neuropsychological examination, self-reported questionnaires, and actigraphy. Participants who solely participated in the cognitive and behavioural part prior to the start of the MRI phase are also included, resulting in a total of *n* = 404 participants. Cognitive and behavioural data will be released in November 2028 (ABRIM behavioural collection, https://doi.org/10.34973/7eq5-8y44).

Discussion

To increase our understanding of why we all age differently, an extensive characterization of brain health in concurrence with other factors of risk and resilience in cognitive ageing is warranted (Baumgart et al., 2015; Cabeza et al., 2018; Livingston et al., 2020; Nyberg & Pudas, 2019). Conversely, this has led to the growing availability of large datasets to study the dynamics of cognitive ageing (Babayan et al., 2019; Bookheimer et al., 2019; Filippini et al., 2014; Miller et al., 2016; Nugent et al., 2022; Spreng et al., 2022; Taylor et al., 2018; Taylor et al., 2017; Wardlaw et al., 2011).

With ABRIM, we aimed to add to existing study cohorts by 1) collecting a cross-sectional, normative database of adults between 18-80 years old, stratified by age and sex; 2) incorporating both conventional imaging sequences as well as quantitative imaging methods; 3) concurrently measuring cognitive functions with mechanisms of reserve (e.g., cognitive reserve), and actigraphy (e.g., to establish sleep-wake rhythms). The present study provides a publicly shared cross-sectional data repository on healthy adults throughout the lifespan, including numerous parameters relevant to improve our understanding of cognitive ageing.

The ABRIM MRI collection includes BIDS-compliant raw and pre-processed MRI measures and derivatives of T1- and T2-weighted imaging, quantitative imaging (MP2RAGE and gradient echo imaging), multi-shell diffusion-weighted imaging, and resting-state fMRI. The pipelines that we used were specifically developed for BIDS data, facilitating the reproducibility of these analyses (Gorgolewski et al., 2016). Together with the wide range of MRI measures that are readily available, we hope that this enables both expert and non-expert users to utilize our dataset. To allow users to evaluate the quality of both the raw MR images and pre-processed MR images, we generated several visual QC reports as well as several automated and/or manual quality indices. Importantly, while we emphasize that QC is essential for neuroimaging studies, we refrained from making any decisions about including or excluding specific images modalities or subjects. This decision was made based on the current absence of a "gold- standard" to ensure sufficient quality of MRI data, and because such evaluations may depend on specific research objectives (Hendriks et al., 2024). The ABRIM behavioural data collection complements the MRI measures with the outcomes of a neuropsychological examination (e.g., on executive functioning, processing speed, memory, and global

cognition), self-reported questionnaires (e.g., on lifestyle factors, depression, pain, psychopathy, memory strategy use), and actigraphy measures (e.g., sleep-wake parameters).

Nevertheless, there are several limitations that need to be addressed. First, the generalizability of our sample is limited as participants are relatively healthier and more highly educated as compared to the general population. Furthermore, we only covered the adult lifespan between 18-80 years old to minimize potential confounding factors associated with extreme age ranges and for feasibility purposes. Consequently, our sample is not fully reflective of the ageing population. In addition, as ABRIM is a cross-sectional database, this merely allows us to examine cognitive performance within a specific age range at a single point in time, while mapping of individual trajectories of cognitive decline is impossible. Lastly, our sample size remains relatively small as compared to other publicly available datasets. Therefore, we emphasize the importance of replicating findings across multiple cohort studies to increase our understanding of the generalizability and robustness of such data. For instance, comparing MRI measures from ABRIM with those of other currently available datasets itself could provide valuable insights into the consistency of such findings across diverse populations and contexts. We hope that the ABRIM dataset thus will also contribute to open and reproducible research in the field of cognitive ageing and embrace the ongoing growth in availability of such datasets (Niso et al., 2022).

Conclusion

Altogether, ABRIM enables researchers to model the advanced imaging parameters and cognitive topologies as a function of age, identify the normal range of values of such parameters, and to further investigate the diverse mechanisms of reserve and resilience.

Acknowledgments

We express our gratitude to all ABRIM participants for their valuable contributions and dedication of their time.

Data availability statement

Data required to replicate the results presented in this study are available via: https://doi.org/10.34973/jyeh-kp46.

Supplements

Supplementary Table A. Overview variables in ABRIM relative to other databases

Dataset name	Age range	N	Cognitive assessment	Actigraphy	T1-weighted	T2-weighted	MP2RAGE	DWI	T2* or GRE	Resting-state fMRI
Cambridge Centre for Ageing and Neuroscience (Cam-CAN)	18-87	~650	X		X	X		X		X
MPI-Leipzig Mind-Brain- Body	20-35; 59-77	227; 74	X			X	X	X	X	X
Neurocognitive aging data release	18-34; 60-89	181; 120	X		X					X
The Lifespan Human Connectome Project in Aging	36-100+	725	X		X	X		X		X
The National Institute of Health (NIMH) Intramural Healthy Volunteer Dataset	18-72	155	X		X	X		X	X	X
UK Biobank	40-70	~50,000	X	X	X			X	X	X
Whitehall II Imaging Sub- study	60-85	775	X		X	X		X		X
Lothian Birth Cohort 1936	±70	866	X		X	X	X	X	X	
The Advanced BRain Imaging on ageing and Memory	18-80	295	X	X	X	X	X	X	X	X

Supplementary Table B. Sample characteristics of full sample, per age decade and sex

		Full sample	18-30 years	31-40 years	41-50 years	51-60 years	61-70 years	71-80 years
Full sample	N	295	46	45	48	51	53	52
	Age, median (IQR)	52 (36-66)	25 (22-28)	35 (33-38)	47 (44-49)	55 (53-57)	65 (62.50-68)	73 (72-76)
	Low education, N (%)	36 (13%)	3 (8.3%)	4 (9.1%)	4 (8.5%)	6 (12.8%)	9 (17.6%)	10 (19.2%)
	Medium education, N (%)	90 (32.6%)	14 (38.9%)	18 (40.9%)	15 (31.9%)	17 (36.2%)	16 (31.4%)	10 (19.2%)
	High education, N (%)	151 (54.7%)	19 (52.8%)	22 (50%)	28 (59.6%)	24 (51.1%)	26 (51%)	32 (61.5%)
Females	N	157	25	25	25	25	27	30
	Age, median (IQR)	52 (36.5-66.5)	23 (23-26)	36 (33-38)	47 (44-49)	55 (53-58)	65 (62-68)	73 (72-76)
	Low education, N (%)	22 (15.1%)	1 (5.3%)	3 (12.5%)	2 (8.3%)	3 (13%)	7 (26.9%)	6 (20%)
	Medium education, N (%)	49 (33.6%)	8 (42.1%)	10 (41.7%)	7 (29.2%)	10 (43.5%)	7 (26.9)	7 (23.3%)
	High education, N (%)	75 (51.4%)	10 (52.6%)	11 (45.8%)	15 (62.5%)	10 (43.5%)	12 (46.2%)	17 (56.7%)
Males	N	138	21	20	23	26	26	22
	Age, median (IQR)	52 (35.75-66)	27 (24-29)	33 (32-37.75)	46 (43-48)	55 (52.75-57)	66 (63.50-68)	73.50 (72-76)
	Low education, N (%)	14 (10.7%)	2 (11.8%)	1 (5%)	2 (8.7%)	3 (12.5%)	2 (8%)	4 (18.2%)
	Medium education, N (%)	41 (31.3%)	6 (35.3%)	8 (40%)	8 (34.8)	7 (29.2%)	9 (36%)	3 (13.6%)
	High education, N (%)	76 (58%)	9 (52.9%)	11 (55%)	13 (56.5%)	14 (58.3%)	14 (56%)	15 (68.2%)

Data on educational attainment were not available for $n = 18$ participants (6.4% of the total sample). For females and males, the respective numbers were $n = 11$ (7% of all females) and $n = 7$ (5.1% of all males).

Supplementary Table C. Characteristics of actigraphy sample

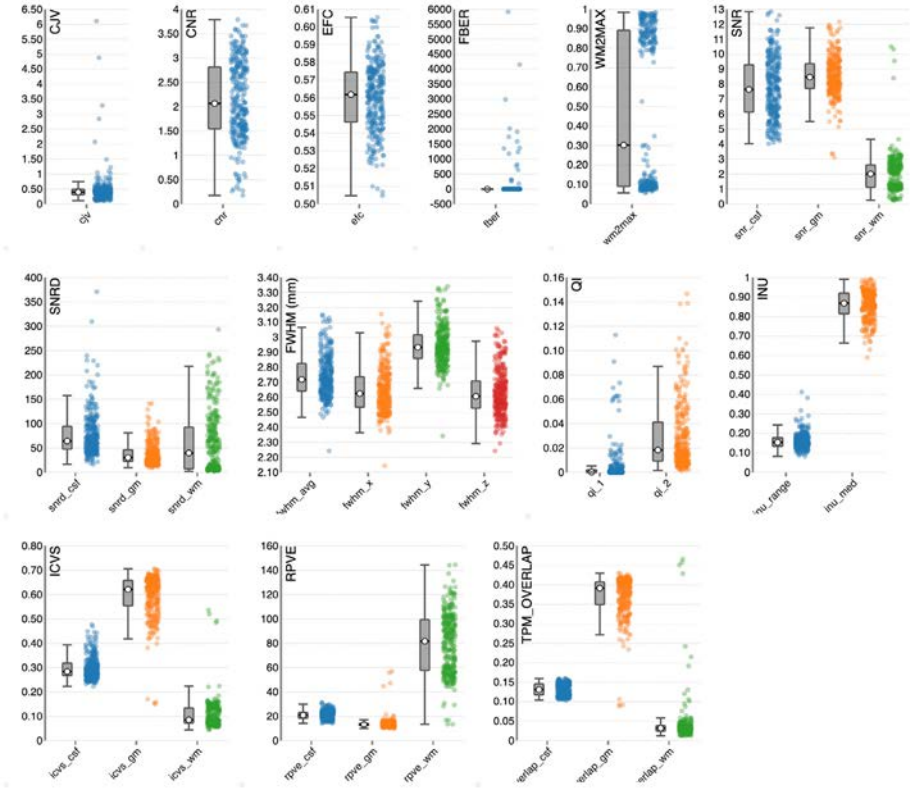
	Full sample	18-30 years	31-40 years	41-50 years	51-60 years	61-70 years	71-80 years
N	120	13	11	16	26	28	26
Age, median (IQR)	57 (44.3-69)	26 (24-30)	33 (31-37)	45.50 (44-48.75)	54.50 (52-57)	65 (62-68)	73 (72-76)
Females, N (%)	68 (56.6%)	10 (76.9%)	7 (63.6%)	8 (50%)	12 (46.2%)	17 (60.7%)	14 (53.8%)
Low education, N (%)	14 (12.2%)	0 (0%)	1 (9.1%)	1 (6.3%)	1 (4.2%)	5 (19.2%)	6 (23.1%)
Medium education, N (%)	30 (26.1%)	6 (50%)	3 (27.3%)	4 (25%)	9 (37.5%)	4 (15.4%)	4 (15.4%)
High education, N (%)	71 (61.7%)	6 (50%)	7 (63.6%)	11 (68.8%)	14 (58.3%)	17 (65.4%)	16 (61.5%)

Data on educational attainment was not available for *n* = 5 participants (4.2%).

Supplementary Table D. Sample characteristics of behavioural and cognitive assessment only participants

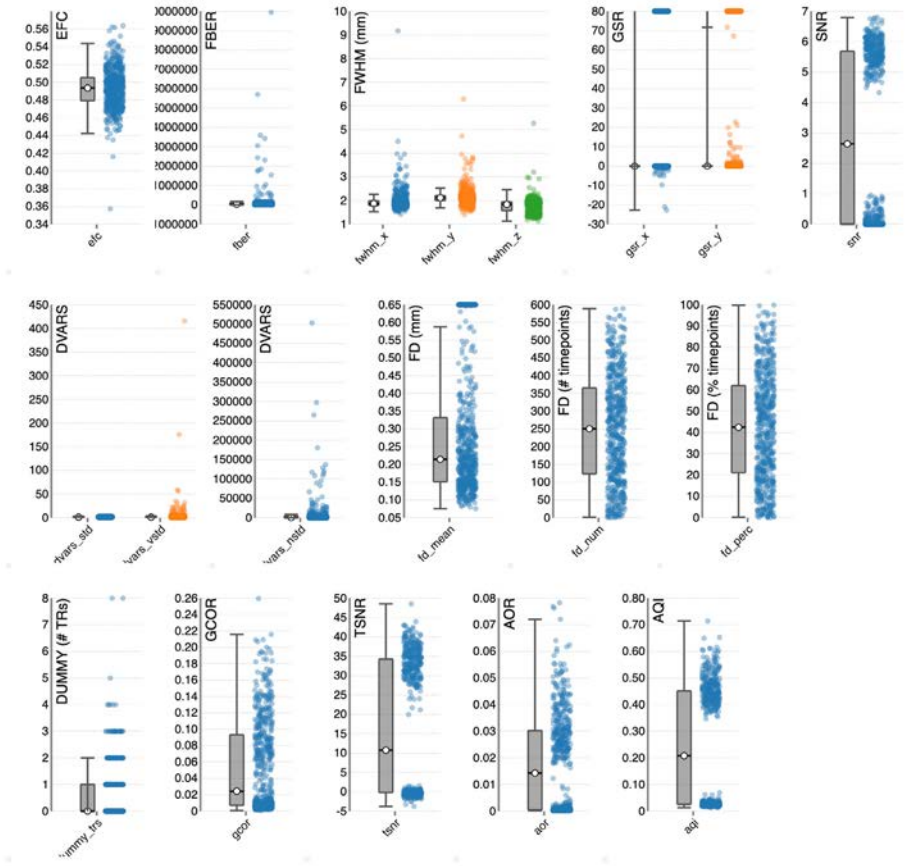
	Full sample	18-30 years	31-40 years	41-50 years	51-60 years	61-70 years	71-80 years
N	108	37	7	14	22	20	8
Age, median (IQR)	48 (24-61)	22 (21-24.5)	32 (32-35)	47 (43-48)	55 (52-57.25)	64.5 (62-67)	72 (71.25-74.75)
Females, N (%)	64 (59.3%)	24 (64.9%)	5 (71.4%)	9 (64.3%)	9 (40.9%)	11 (55%)	6 (75%)
Low education, N (%)	5 (4.7%)	0 (0%)	1 (14.3%)	0 (0%)	0 (0%)	2 (10%)	2 (25%)
Medium education, N (%)	32 (31.1%)	16 (45.7%)	4 (57.1%)	5 (38.5%)	5 (22.7%)	2 (10%)	0 (0%)
High education, N (%)	68 (64.2%)	19 (54.3%)	2 (28.6%)	8 (61.5%)	17 (77.3%)	16 (80%)	6 (75%)

Data on educational attainment was not available for *n* = 3 participants (2.8%).



Supplementary Figure A. Group report of T2 images from the MRI Quality Control tool

Group anatomical report of T2 scans in ABRIM as generated by the MRI Quality control tool (MRIQC). Contains separate strip-plots for different image quality metrics (IQMs). CJV = coefficient of joint variation; CNR, contrast-to-noise-ratio; EFC = entropy focus criterion; FBER = foreground-to- background energy ratio; WM2MAX = white-matter to maximum intenstiy ratio; SNR = signal-to- noise-ratio; SNRD = Dietrich's signal-to-noise-ratio; FWHM (vox) = full width half maximum in units of voxels; QI = quality index; INU = intensity non-uniformity; ICVS = intracranial volume fraction; RPVE = residual partial volume effect; TPM_OVERLAP = overlap of issue probability maps of the images and maps from the ICBM nonlinear-asymmetric 2009a template.



Supplementary Figure B. Group report of fMRI images from the MRI Quality Control tool

Group anatomical report of T2 scans in ABRIM as generated by the MRI Quality control tool (MRIQC). Contains separate strip-plots for different image quality metrics (IQMs). EFC = entropy focus criterion; FBER = foreground-to-background energy ratio; FWHM = full width half maximum in units of millimetres; GSR = ghost-to-signal ratio; SNR = signal-to-noise ratio; DVARS = index of rate of change of BOLD signal across the entire brain; FD = framewise displacement (number of timepoints and percentage of timepoints above threshold); DUMMY = number of dummy scans; GCOR = global time-series correlation; TSNR = temporal signal-to-noise ratio; AOR = AFNI's outlier ratio; AQI = AFNI's quality index.

Supplementary methods

English translation of memory strategy descriptions

Many people use techniques or strategies to improve their recall of word combinations. Have you utilized any techniques or strategies to memorize the word pairs you heard? Could you provide a description of these strategies with as much detail as possible below?

_____
_____
_____
_____
_____
_____
_____

[next page]

The following list consists of strategies or techniques that people can use to remember word combinations. Read the list of strategies and tick the applicable boxes to indicate which strategies you have employed to enhance your recall of the word pairs. Indicate all strategies that you have used, even if you already described them on the previous page.

Concentrate ☐
Repeat in your head ☐
Visualize (create imagesin your head) ☐
Making associations between the words of a pair ☐
Making a story containing words of a pair ☐
Making a sentence containing both words of a pair ☐
Visualize with yourself in a mental image ☐
Remember specific letters or syllables ☐
Memorize sounds of word combinations ☐
Something different, namely..... ☐

5

Chapter 6

Multiple neural pathways to successful visual short-term memory across the adult lifespan

Submitted as
Jansen, M.G., Salami, A., Martínez, F.R., Mitchell, D.J., Oosterman, J.M., Cam-CAN, Geerligs, L. Multiple neural pathways to successful visual short-term memory across the lifespan.

Abstract

Cognitive task performance can be supported through multiple neural pathways, a concept referred to as brain degeneracy. We used a novel approach to consider brain degeneracy during a visual short-term memory task (VSTM) across the adult lifespan in the Cam-CAN study (n = 113, 23-87 years old). Our main goal was to identify subgroups of participants whose VSTM performance was characterized by distinct brain activation patterns. First, we identified seven brain modules that responded similarly to the VSTM task and resembled previously identified functional networks (adjusted mutual information [aMI] = 0.45). Subsequently, latent profile analysis revealed four distinct subgroups of participants. Each subgroup was characterized by different recruitment patterns of these brain modules, predominantly in the frontal control module (FCM), visual module (VM), and default mode module (DMM). Subgroups did not differ in demographics or task performance. However, associations between brain activity and performance varied across subgroups, particularly in the FCM, suggesting that individuals may use different cognitive operations to perform the VSTM task. Further analyses revealed group differences in white matter integrity, mostly in the uncinate fasciculus, suggested that individual differences in structural brain properties may shape the different brain activation patterns. Altogether, our study contributes to our understanding of how multiple neural pathways could underlie cognitive performance.

Introduction

Over the past decades, research sought to elucidate how the brain's functional and structural architecture gives rise to cognitive functioning (Finn et al., 2023; Genon et al., 2022; Park & Friston, 2013; Poldrack, 2006). Nevertheless, this relationship is far from straightforward. Not only do brain measures typically account for only a small portion of the variance in cognitive functioning (Hedden et al., 2016), but there are also several contradictory findings in terms of which neural mechanisms are adaptive or maladaptive for cognitive performance. For example, age-related increases in prefrontal activation have been linked to both superior and inferior performance in older adults (Grady, 2012; Nyberg et al., 2020). The complex nature of brain-cognition associations is further emphasized by previous studies showing that the extent to which brain structure or function relates to cognitive performance varies substantially across individuals (Lindenberger, 2014; Lövdén et al., 2018; Patel et al., 2022; Salami et al., 2018).

To gain a better understanding of how cognitive functions are supported throughout the lifespan, we may need to revisit the common assumption that most individuals exhibit similar patterns of neural activity to perform a certain cognitive task (one-to-one mapping) (Seghier & Price, 2018; Westlin et al., 2023). Conversely, brain degeneracy suggests that a specific task could be executed through multiple neural pathways (many-to-one mapping) (Edelman & Gally, 2001; Noppeney et al., 2004; Price & Friston, 2002). Degeneracy is evident in many neural systems, including those supporting cognitive functions (Kelso, 2012; Noppeney et al., 2004). In line with this, previous studies have identified subgroups of individuals showing unique neural activity patterns while performing the same task (Cerliani et al., 2017; Kherif et al., 2009; Seghier et al., 2008). Interestingly, this neural variability was associated with the use of different strategies to complete the task (Kherif et al., 2009; Noppeney et al., 2006), despite similar levels of task performance (Fischer-Baum et al., 2018; Noppeney et al., 2006). This illustrates how multiple neural routes can lead to successful cognitive performance. However, if we focus on similarities across individuals these possibilities are overlooked, emphasizing the need to understand brain degeneracy and what it might mean for how we study the associations between brain and cognition.

Building on the concept of many-to-one mapping, it has been suggested that secondary activation repertoires may be prompted when the primary circuit is

unable to sustain successful task completion (Mason et al., 2015; Noppeney et al., 2004; Price & Friston, 2002). For instance, studies using transcranial magnetic stimulation showed that younger adults adapt to temporary functional lesions by recruiting alternative neural circuits (Lee et al., 2003; Pascual-Leone et al., 2005). Furthermore, differential recruitment of brain regions during task performance has been related to functional recovery after acquired brain injury (Nudo, 2013). In the context of normal ageing, alterations in brain activity have been linked to the degradation of major white matter tracts (Burzynska et al., 2013; Lucas et al., 2018), and localized grey matter loss (Kalpouzos et al., 2012; Salami et al., 2012; Salami et al., 2014).

Although this involves functional deterioration, older adults are able to compensate for impaired brain function by recruiting additional brain regions, particularly in the frontal lobes (Cabeza et al., 2002; Grady, 2012; Park & Reuter-Lorenz, 2009). In contrast, structural preservation in older individuals (i.e., brain maintenance; Nyberg et al., 2012) has been related to neural activation patterns more closely resembling those typically observed in younger adults (Cabeza et al., 2018; Nyberg et al., 2012). Together, these findings stress that it is important to consider interindividual variability in brain structure to understand why different neural systems may be recruited during task performance.

In the present study, we aimed to investigate brain degeneracy across the adult lifespan in the context of visual short-term memory (VSTM), using data from the Cam-CAN project (n = 122, 23-87 years old). VSTM is particularly interesting in the context of degeneracy, given that high performance can be achieved via different strategies (Ritakallio et al., 2024). VSTM refers to our ability to maintain visual information and is crucial for many other cognitive functions (Luck & Vogel, 2013; Pearson & Keogh, 2019). However, the precise neural mechanisms underlying successful VSTM performance are not fully understood, partially due to inconclusive findings in prior research that did not consider the possibility of different brain activation patterns (Pearson and Keogh, 2019). Our primary aim was therefore to identify subgroups of participants whose VSTM performance was characterized by distinct brain activation patterns. We first identified modules of brain regions that showed similar responses across participants during the VSTM task. Next, we applied latent profile analysis to identify sub-groups of participants that demonstrated differential recruitment patterns of the previously identified brain modules. To better understand the variability in brain activity during the VSTM task, we characterized the most significant differences in brain activity across subgroups.

Furthermore, we sought to elucidate factors contributing to the observed subgroup differences in brain activity patterns. Specifically, we investigated the extent to which these subgroups differed in demographic variables (i.e., age, sex, educational attainment) and task performance. We were particularly interested in the role of age, as this factor was previously related to both performance and neural correlates of the VSTM task (Lugtmeijer et al., 2023; Mitchell & Cusack, 2018; Morcom & Henson, 2018; Sander et al., 2012). For example, if age-related differences in brain function were the largest source of inter-individual variability in brain activation patterns during the VSTM task, we expected to identify subgroups that differed in their age and task performance. Conversely, if age-invariant inter-individual differences were most prominent, we expected to see participant subgroups that were roughly age-matched. Additionally, we investigated whether structural brain characteristics, such as grey matter volumes and white matter integrity, would explain variations in brain activity among the subgroups, as reflected by subgroup differences in these measures.

Lastly, we assessed associations between brain activation profiles and task performance within each subgroup. For example, increased activity in brain module X might have been beneficial for performance for subgroup Y but hindered this for subgroup Z. Such unique associations would not only provide further evidence for the presence of different neural routes to facilitate successful VSTM performance, but also potentially suggest cognitive strategies that were used to succeed.

Materials and methods

Participants

This study included data from 122 participants (59 female, 48.4%) who were aged 23–87 (mean age 53.9, SD = 18.1) from the healthy, population-derived cohort tested in Stage III of the Cam-CAN project (Shafto et al., 2014; Taylor et al., 2017).

A complete overview of the study procedures and inclusion criteria have been described previously (Shafto et al., 2014; Taylor et al., 2017). Briefly, in Stage I, participants engaged in home-based interviews where demographic information, cognitive measures, and other measures of health (e.g., mental and physical health) were collected. In Stage II, participants engaged in three testing sessions, including cognitive and behavioural assessments, structural MRI (e.g., T1-weighted imaging and diffusion-weighted imaging), functional

MRI (e.g., resting-state), and MEG recordings. During Stage III, among other things, structural MRI (e.g., T1-weighted images) and task-related functional MRI (fMRI) data during a VSTM task were acquired. In this manuscript, we use the demographic information from Stage I, the diffusion-weighted images from Stage II, and the T1-weighted images and VSTM fMRI paradigm from Stage III. Participants were native English-speakers with normal or corrected-to-normal vision and hearing and had no neurological disorders. Additional exclusion criteria were history of drug or alcohol abuse, and poor hearing or vision.

The study was conducted in accordance with ethical approval obtained from the Cambridgeshire 2 (now East of England - Cambridge Central) Research Ethics Committee. All participants gave written informed consent prior to participation.

We excluded a total of 9 participants from our analyses due to poor VSTM task performance (n = 8) or data quality issues (n = 1), leaving a final sample of 113 participants (see below for more details).

Demographics

Demographic information, including age, sex, and educational attainment, was acquired during home-based interviews during Stage I of the Cam-CAN project. Educational attainment in this study was based on the highest level of completed education (i.e., categorized in 1 = no education above the age of 16 years old; 2 = GCSEs or equivalent; 3 = A levels or equivalent; 4 = university levels or equivalent).

MRI acquisition

MRI data was acquired on a 3T Siemens TIM Trio System scanner at the MRC Cognition Brain and Sciences Unit, Cambridge, UK. During each of three VSTM task runs, functional data were acquired using a multi-echo, T2*-weighted EPI sequence (TR = 2000 milliseconds, TE = 12 milliseconds, 25 milliseconds, 38 milliseconds, flip angle = 78 degrees, 32 axial slices of thickness of 3.7 mm with an interslice gap of 20%, FOV = 294mm × 294 mm, voxel-size = 3 mm × 3 mm × 3.48 mm). Each volume had 34 axial slices (acquired in descending order), slice thickness of 2.9 mm, with an interslice gap of 20%. The multiple echoes were combined by computing their average weighted by their estimated T2* contrast. The number of scans acquired varied per run, depending on reaction time, between 294 and 349.

A high-resolution 3D T1-weighted structural image was acquired using a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence, with the following parameters: TR = 2250 ms; TE = 2.99 ms; TI = 900 ms; flip angle = 9 degrees; FOV = 256 × 240 × 192 mm; voxel size = 1 mm isotropic; GRAPPA acceleration factor = 2. This T1 image was missing for two of the participants in this sample, however for these participants T1 images were acquired during the scanning session that took place during Stage II of Cam-CAN, approximately 1-3 years earlier.

Diffusion-weighted images (DWIs) were acquired with a twice-refocused spin-echo sequence during Stage II of Cam-CAN. Thirty diffusion gradient directions were obtained for each of two b-values: 1000 and 2000 s/mm2, plus three images acquired with a b-value of 0. These parameters were optimized for estimation of the diffusion kurtosis tensor and associated scalar metrics (Shafto et al., 2014). Other DWI parameters were TR = 9100, TE = 104 ms, FOV = 192 mm × 192 mm, voxel size 2 mm isotropic, 66 axial slices, with acquisition time 10 minutes and 2 seconds.

Visual short term memory task (VSTM)

During fMRI scanning, participants performed a VSTM paradigm (see Figure 1), based on Emrich et al. (2013). A detailed description of the task is provided in Lugtmeijer et al. (2023).

Briefly, three displays containing different coloured moving dots (red, yellow and blue) were presented sequentially on each trial. Each trial began with a grey fixation dot for 5 seconds. Subsequently, the fixation dot brightened for 2 seconds and was followed by the coloured dot displays. Each coloured dot display was shown for 500ms, with a 250ms black screen in between. As a manipulation of the number of items in memory, trials could contain one, two or three arrays of dots moving in a single direction (load 1, 2, and 3, respectively).

Participants were instructed to remember the direction of motion for dot displays in which all dots moved in a single direction, and to ignore any dot displays that rotated around the fixation location (the encoding phase). As three displays were shown in each trail, the memory load was manipulated by varying the number of rotating dots in relation to the number of moving dot displays. After the third coloured dot display, there was a blank display of 8 seconds (the maintenance phase), followed by a probe display. The probe display consisted of a coloured circle that indicated which of the three dot

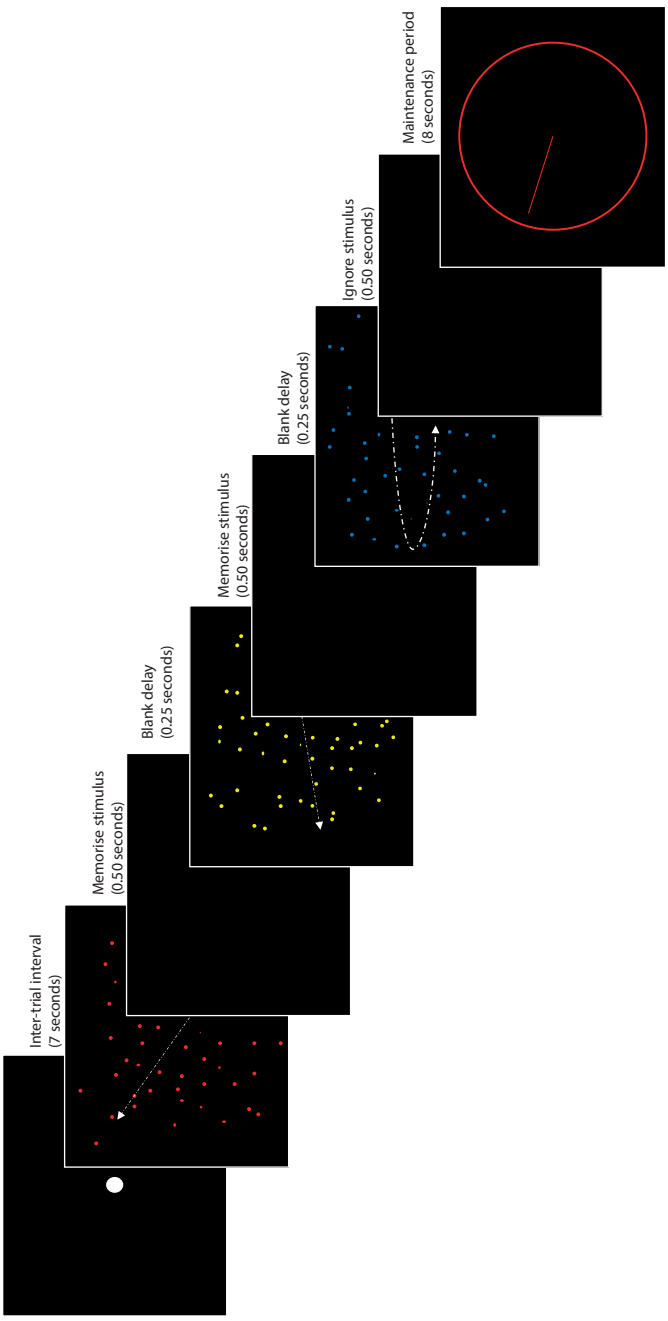


Figure 1. Adapted from Morcom and Henson (2018). An example of the VSTM task. Trials began with a fixation dot for 7 seconds. On each trial, three moving dot displays were then presented in red, yellow, and blue for 500 ms each (250 ms in between). After the last display, the screen was blank for an 8 second maintenance period and then a probe display was presented. A coloured circle indicated which dot display participants should recall (red, yellow, or blue). Participants had up to 5 seconds to adjust a pointer until its angle matched the motion direction of the probed display.

displays (red, yellow, or blue) the participant should recall. Participants had up to 5 seconds to adjust a pointer on the circle until it matched the direction of motion of the probed dot display (the response phase).

VSTM performance

Several factors can limit VSTM performance. For example, memory imprecision (e.g., uncertainty between 80 or 85 degrees), random guessing (e.g., when forgetting an item entirely), and reporting an incorrect item (mis-binding, e.g., reporting the angle of the red dots instead of the blue dots). To distinguish these different sources of error, we applied a three- component mixture model (Bays et al., 2009). A complete description of the application of the mixture model to the VSTM task is provided in previous work (Mitchell et al., 2018; Lugtmeijer et al., 2023).

For our subsequent analyses, we used the estimates of a memory item's precision (the inverse of the standard deviation in degrees) and the number of items (directions) that were stored in memory (K). Eight participants in our sample showed very poor performance for memory of a single item (>30 degrees deviation on average). This suggests that they may not have understood the task instructions and were therefore excluded from further analyses. Since there was a ceiling effect for the number of items in memory at load 1 (mean = 0.96, SD = 0.06) and to some extent at load 2 (mean = 1.76, SD = 0.24), we decided to focus on performance at load 3 (mean = 2.40, SD = 0.46). The distribution of scores for the number of items in memory at each load is shown in Supplementary Figure A.

MRI pre-processing and first level analyses

All MRI data were pre-processed using SPM 12 (http://www.fil.ion.ucl.ac.uk/spm) and "automatic analysis" software (Cusack et al., 2015). The T1 and T2 weighted structural images were rigid body registered with a MNI template, bias corrected and segmented into six tissue classes using the newer segment protocol in SPM 12 (Ashburner & Friston, 2005). Non-linear transformation using DARTEL normalization was performed to match a grey matter template created from the Cam-CAN stage III sample. The functional images were spatially realigned and interpolated to correct for differences in acquisition times, and co-registered to the structural image using rigid body transformations. Both grey matter volume images and functional images were transformed to MNI space using the warps and affine transformation estimated from the structural images. For grey matter volume images, this was done while preserving the total amount of signal

from each region in the images. The functional images were resliced to 3x3x3 mm voxels, while grey matter volume images were resliced to 1.5x1.5x1.5 mm voxels and both were smoothed with an 8 mm full-width half-maximum (FWHM) Gaussian kernel. For the two participants with missing T1-weighted scans, normalization and co-registration were performed based on the T1 images collected during stage II of the Cam-CAN project. One participant was excluded from further analyses due to data quality issues.

For each participant and voxel, we fit a general linear model (GLM) with three phases of each trial per run: encoding, maintenance, and response. The encoding phase was modelled as an epoch of 2 seconds starting from the beginning of the first dot display movement. The maintenance phase was modelled as an epoch of 8 seconds (i.e., the duration of the blank display that was shown after all probes were displayed). The response phase was modelled as an epoch of the time between the probe onset and response. These three components were each split into three regressors: one for each load. Six additional regressors were added per run, representing the motion parameters estimated in the realignment stage. The means of each run were also modelled separately. The main contrast of interest in this study was the difference between the highest and the lowest memory load during the maintenance period (load 3 vs. load 1). This contrast allows us to equate the amount of visual information that was presented just before the maintenance period as well as the motor response that was required just after, while maximizing the difference in memory load.

Identifying modules with similar inter-individual variability

To make the analyses more computationally efficient in later stages, we reduced the dimensionality of the data by grouping voxels into a set of small regions of interest (ROI). Specifically, we used the 748 (out of 840) regions from the Craddock atlas (2012) that had sufficient coverage in our recent paper (Geerligs et al., 2015), allowing us to use the network labels defined in our previous study. To select ROIs that might be involved in task-performance in a subset of participants, we first extracted the average t-values for the contrast of interest (i.e., load 3 vs. load 1 during the maintenance period) across all voxels in each ROI for each participant. To further reduce the dimensionality of the data, we only included ROIs that showed increased or reduced activation in load 3 versus load 1 in at least 10% of the participants at a liberal significance threshold ($T > 1.96$, $p < 0.05$). This resulted in the final inclusion of 418 ROIs.

For each included ROI, we extracted the average beta-values. Subsequently, we calculated the correlation values between ROIs for load 3 vs. load 1 across participants (i.e., ROI-by-ROI correlation matrix). A high correlation coefficient between two ROIs suggests that these regions show similar inter-individual variability in load-dependent modulation of the BOLD response, and therefore may contribute to the same brain module.

In the next step, we used the Brain Connectivity Toolbox to identify groups of ROIs, or brain modules, that showed similar brain activity patterns across participants (Rubinov & Sporns, 2010). Specifically, we applied consensus partitioning based on the Louvain modularity algorithm (Bassett et al., 2013; Lancichinetti & Fortunato, 2012). The ROI-by-ROI correlation matrix was used to create an initial partition of the ROIs into distinct modules with the Louvain modularization algorithm (Blondel et al., 2008), and was further refined using an optimization procedure (Sun et al., 2009). This partitioning procedure was repeated 500 times, and all the repetitions were assembled into an ROI-by-ROI agreement matrix, where each number indicates the proportion of repetitions in which a pair of ROIs were assigned to the same module. The ROI-by-ROI agreement matrix was then used as an input for consensus partitioning, where a permuted version of the agreement matrix was used for thresholding. This was repeated until the algorithm converged into a matrix of ones and zeros, indicating that a single partition was reached.

The complete partitioning procedure was performed for multiple values of the resolution parameter γ, ranging from 1 to 1.5 with steps of 0.05. The γ parameter is a penalty term that biases the size of the communities to be found. Smaller values of γ will result in larger modules, while higher values will result in smaller modules. As an γ value of 1.5 already resulted in 49 modules, we did not explore a wider range of this parameter space.

Next, we selected the partition with the highest resemblance to a previously defined set of age-representative networks (Geerligs et al., 2015b), as measured with the adjusted mutual information (aMI), as our final set of brain modules. The optimum we identified was at $\gamma = 1.25$, resulting in 13 distinct modules (aMI = 0.45). However, as many modules consisted of only one ROI or a few ROIs, we only included modules with at least 15 ROIs in our analyses. This resulted in the exclusion of 6 brain modules, comprising of 28 ROIs in total. The final set of 7 brain modules was used for further analyses (see "Results").

Within each brain module and for each participant, we computed the average brain activity for load 3 vs. load 1. However, we observed strong correlations between the average brain activity values across all brain modules (ranging from r=0.39 to 0.77). This is consistent with prior research which demonstrated that overall network responsivity, rather than module-specific activation patterns, were related to age and task performance (Samu et al., 2017). To be able to look beyond this general factor in our subsequent analyses, we computed the residual activity within each brain module after regressing out the mean activity across the 418 ROIs. To be able to retain information about the engagement of each network during the task, the mean activity across all subjects was added back after computing the residuals. The extent to which the mean activity across these ROIs explained the variance within each brain module varied between 0.61-0.75, as indicated by the adjusted R^2 values.

Brain activity profiles

To identify latent subgroups of participants characterized by different patterns of brain activity, we applied latent profile analysis (LPA) using the *Mclust* package in R (Scrucca et al., 2016). Briefly, LPA is a data-driven Gaussian mixture modelling method to identify hidden subgroups in a population (Vermunt & Magidson, 2002). A Gaussian mixture model assumes a multivariate Gaussian distribution for each subgroup. Therefore, every observation (here, participant) will have a specific probability of belonging to a specific subgroup, as specified by a probability density function determined by the average, the variance, and the covariance of each of the subgroup distributions.

We applied LPA using both the residual activity in each brain module and the overall responsivity across all networks, specifying between 1 and 5 subgroups. This allowed us to look at module-specific variations in responsivity in addition to the overall responsivity across brain modules. We restricted the model space to models that do not allow for covariance between modules within subgroups of participants (i.e., models with a spherical or diagonal distribution of the within-group covariance matrix). This way, our model assumes that any correlations between modules must be caused by participants with different brain activity profiles (similar to Lövdén et al., 2018). The Bayesian Information Criterion (BIC), Integrated Completed Likelihood (ICL) and bootstrapped Likelihood Ratio Test were used to select the most optimal model and class solution (i.e., the number of subgroups).

Structural brain characteristics

To investigate subgroup differences in grey matter, we extracted grey matter volumes for each of the 418 ROIs that were included in our main analysis and subsequently averaged the grey matter volumes within each module. The two participants with the missing T1-scan at Stage III were excluded from this analysis, resulting in a sample of 111 participants for the grey matter data.

To investigate subgroup differences in white matter microstructure, we used the diffusion data to estimate mean kurtosis. Mean kurtosis is influenced by changes in organelles, cell membranes and the ratio of intracellular to extracellular water compartments (Falangola et al., 2008). It provides a sensitive metric to determine how aging affects the complexity of white matter microstructure, and typically decreases in late-life (Benitez et al., 2018).

Diffusion data were pre-processed and analysed as described in a previous paper (Geerligs et al., 2018). Briefly, the data were co-registered, normalized to MNI space and smoothed with a 1-mm FWHM Gaussian kernel to reduce residual interpolation errors. Subsequently, we calculated the average mean kurtosis values for 18 tract-based regions of interest defined by the Johns Hopkins University white matter tractography atlas (Hua et al., 2008). These included the uncinate fasciculus, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, anterior thalamic radiations, forceps minor, forceps major, cerebrospinal tract, the inferior longitudinal fasciculus, ventral cingulate gyrus, and the dorsal cingulate gyrus. All tracts were split into their left and right hemisphere sections, except for the forceps minor and forceps major.

Participants with severe head motion during the DWI scan, as revealed by an automated striping detection method on the diffusion data, were excluded (Neto Henriques and Correia, 2015). In addition, for each tract, participants with mean kurtosis values of 3 SDs above or below the group average were excluded. This resulted in a final sample of 96 participants for all tracts, except for the inferior longitudinal fasciculus (n = 95), superior longitudinal fasciculus (n = 95), cerebrospinal tract (n = 94), and ventral cingulate gyrus (n = 86).

Statistical tests

All statistical tests were performed using R (version 4.3.1).

Given that overall responsivity (i.e., average activity across all included ROIs) explained most of the variability in brain module activity, we first explored how

this factor related to age and task performance using Pearson correlations. To investigate whether associations between overall responsivity and task performance were age-independent, we additionally calculated the partial correlations between these two variables while accounting for age.

Next, we performed several between-group comparisons to better understand the diverse brain activity profiles associates with the VSTM task that were identified with the latent profile analysis. To assess which brain modules showed the most pronounced differences across subgroups we statistically compared brain module activity between groups. We also tested whether subgroups differed in demographic characteristics (age, sex, educational attainment), VSTM task performance (the number and precision of items in memory at load 3), grey matter volumes (i.e., average grey matter volumes in each of the brain modules), and white matter microstructure (i.e., average mean kurtosis in each of the 18 tracts). These comparisons were performed to understand which factors contributed to the differences in brain activity profiles.

We applied a two-step approach to determine between-group differences. First, Welch's ANOVA was used to determine if there were differences between subgroups in the variable of interest. This was used instead of the regular Fisher's one-way ANOVA because of unequal sizes and variances between groups. Second, each significant ANOVA was followed by pairwise Welch's t-tests between groups (i.e., using non-pooled standard deviations to consider the unequal variances between groups). Chi-squared tests were used in case of categorical data (i.e., comparing sex or educational attainment across groups). As educational attainment had less than < 5 observations in certain categories, this variable was split into a dichotomous category prior to performing the comparisons (university level vs. other educational categories), however for descriptive purposes all categories are reported.

Analyses on grey matter volumes were corrected for intracranial volume. All analyses were repeated while additionally correcting for the effects of age, except for the comparisons on demographic characteristics. Specifically, we regressed the covariate(s) on the variable of interest and used the residuals of that regression for the ANOVA and subsequent t-tests.

To further investigate the extent to which different neural routes facilitated successful VSTM performance, we investigated the associations between brain module activity and task performance within each subgroup. If certain

associations are present in one subgroup but not in another, this could suggest that these subgroups relied on different cognitive operations to successfully complete the task. To test this, we calculated Pearson correlations between brain module activity and task performance within each subgroup, adjusting for the effects of age (i.e., partial correlations). The difference between coefficients were statistically compared using Fisher's z-tests.

We used false discovery rate (FDR) corrections (Benjamini & Hochberg, 1995) to adjust for multiple comparisons across different brain modules, white matter tracts or pairwise tests. In addition to reporting (FDR-corrected) p-values, we computed Bayes Factors (BF) for the alternative hypothesis using the *BayesFactor* package (https://cran.r-project.org/web/packages/BayesFactor/index.html). Effects were considered as strongly supported in case of both FDR-adjusted $p < 0.05$ and $BF > 3$ (Buades-Rotger et al., 2023; Driessen et al., 2018). In addition, we calculated Bayesian R^2 to evaluate the fit of each model (Gelman et al., 2019), using the *performance* package (https://easystats.github.io/performance/index.html).

Results

Brain modules with similar brain activity patterns across participants

We identified seven distinct modules of brain regions with similar patterns of inter-individual variability in terms of their brain activity while performing the VSTM task (Figure 2). The brain activity metric utilized to define these modules (and used in all subsequent analyses) is based on load 3 vs. load 1 during the maintenance period.

The modules included a frontal control module (FCM), which overlapped largely with the traditional fronto-parietal control network. This module encompasses the lateral prefrontal cortex and the anterior cingulate but did not include parietal areas. A distinct temporo- parietal module (TPM) included parietal areas that typically fall within the default mode and fronto-parietal control network, predominantly in the left hemisphere, but also included temporal areas. The cerebellum and thalamus module (CTM) covered the cerebellum and thalamus, and the visual module (VM) included the occipital cortex. Another module overlapped with the dorsal attention network, covering the frontal eye fields and the intraparietal sulcus, which we refer to as the dorsal attention module (DAM). The motor module (MM) covered the bilateral precentral gyrus but also extended into the right posterior temporal cortex. Lastly, one module largely overlapped with the default mode network, covering the medial prefrontal cortex, precuneus, and temporal areas, which we refer to as the default mode module (DMM).

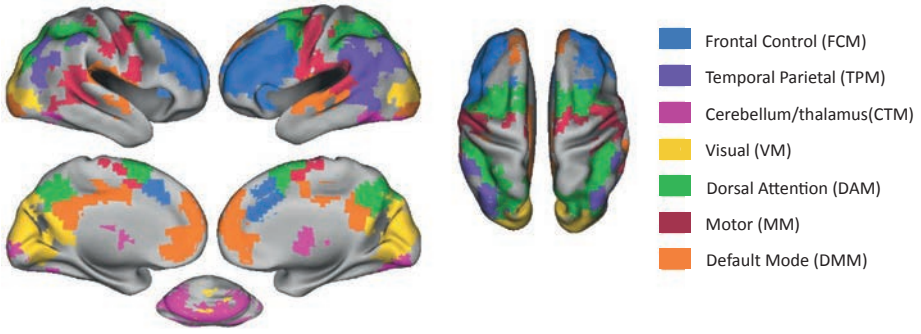


Figure 2. An illustration of the seven brain modules we identified.

Overall responsivity increases with age and accounts for module-specific brain activity

As previously described, the average activity across all included ROIs explained a substantial proportion of the variance in brain activity within each module (R^2 = 0.61-0.75).

We explored how the overall responsiveness related to age and task performance. Average activity across all brain modules increased with age (r = 0.37, 95% CI = [0.19; 0.52], uncorrected p < 0.001, BF = 338.96). However, we did not observe significant associations between overall activity and memory precision (r = 0.04, uncorrected p = 0.688, BF = 0.15) or number of items in memory (r = -0.07, uncorrected p = 0.460, BF = 0.18).

Latent profile analysis identifies subgroups with distinct activation signature across modules

To look beyond overall responsivity, this factor was regressed out of the seven identified brain networks. To account for all variance in brain activity, the LPA grouped participants based on the residual brain activity within each brain network, in addition to the overall responsivity across all ROIs. The BIC and ICL values suggested that the most optimal fit was acquired with a model of four latent subgroups with equal shape, variable volume and assumed diagonal covariance matrix (n = 35, n = 24, n = 42, and n = 12 in groups 1-4, respectively). The distributions of BIC and ICL values for the different latent profile models are shown in Supplementary Figure B and C. A more detailed description of the decision on the number of classes, as well as the corresponding fit indices, is provided in Supplementary Methods.

An overview of the brain module activation profiles across subgroups is displayed in Figure 3. To investigate which networks were the strongest drivers of the subgroup differences, we statistically compared the brain activity profiles across subgroups (Table 1). It should be noted that the LPA was designed to produce subgroups with distinct brain activity profiles. Therefore, these significance values are only meaningful in relation to each other as a comparison of the relative contributions of different modules and subgroups, but not in isolation. A complete overview of the between-group statistics for the brain module activity is depicted in Supplementary Table A.

The most substantial differences in residual brain activity were observed for the FCM, VM, DAM, and DMM, as reflected by the corresponding Bayes Factors and

values of Bayesian R^2 (all ≥ 0.26, indicating substantial effect size; Cohen, 2013). Focusing on four most influential modules, subgroup 1 is characterized by less FCM activity compared to subgroups 3 and 4, the lowest DAM activity across all groups, and the least DMM deactivity. Subgroup 2 demonstrates the least FCM activity but the highest VM activity across all subgroups. In contrast, group 3 shows higher FCM activity than subgroups 1 and 2, but lower VM activation than subgroup 2. Subgroup 4 shows a similar pattern as subgroup 3 with even higher FCM and lower VM activity. We observed no significant differences for the TPM and overall responsivity of brain activity to the task load manipulation. These results remained consistent after applying age corrections.

In summary, while subgroup 2 exhibited the lowest frontal activation paired with higher visual activation, subgroups 3 and 4 displayed the opposite pattern. In contrast, subgroup 1 was characterized by having the least DAM activity and DMM deactivation. This may suggest that different neural mechanisms were used to complete the VSTM task.

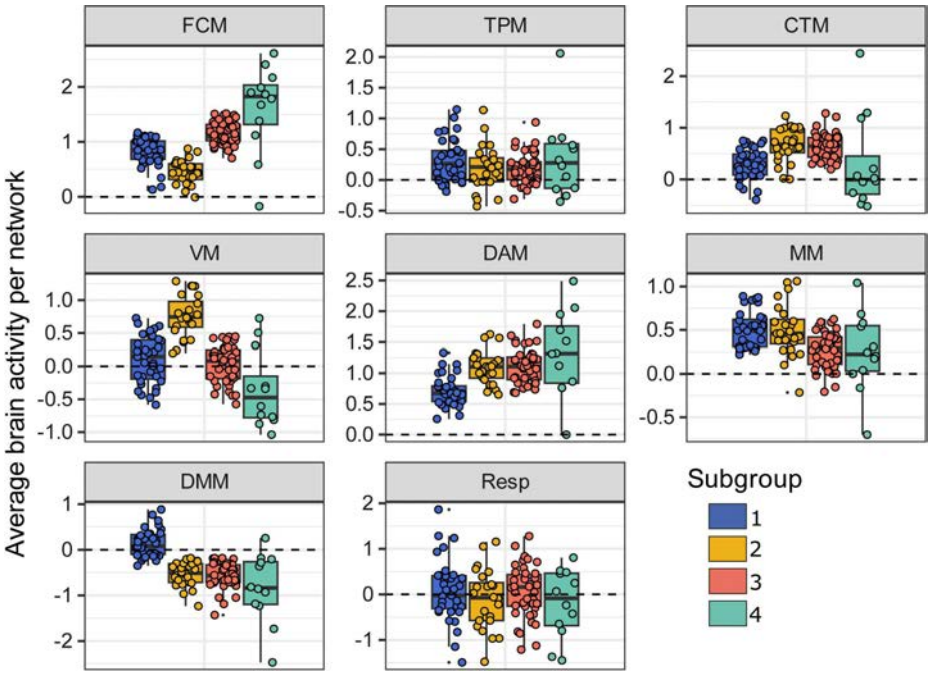


Figure 3. For each of the four identified subgroups this figure shows the mean-regressed average brain activity in each of the seven identified brain networks as well as the overall responsivity across all ROIs (Resp). The most influential brain modules were the FCM, VM, DAM, and DMM. FCM = frontal control module; TPM = temporal parietal module; CTM = cerebellum/thalamus module; VM = visual module; DAM = dorsal attention module; MM = motor module; DMM = default mode module.

Table 1. Comparing residual network activity across subgroups

	F	Bayesian R^2	t 2>1	t 3>1	t 4>1	t 3>2	t 4>2	t 4>3
FCM	54.29**	0.51†	-5.37**	4.82**	3.43**	12.45**	4.98**	2.00
TPM	1.05	0.00						
CTM	10.92**	0.15	4.42**	5.33**	-0.03	-0.45	-1.42	-1.32
VM	33.93**	0.46†	7.48**	-0.89	-2.54*	-9.43**	-6.22**	-2.23
DAM	20.00**	0.28†	5.69**	7.01**	3.06*	0.30	1.11	1.03
MM	9.45**	0.15	-0.05	-4.97**	-1.91	-3.29*	-1.75	-0.17
DMM	42.56**	0.47†	-8.99**	-10.49**	-4.32*	-0.37	-1.31	-1.21
Resp	0.77	0.00						

*FDR-corrected p-value < 0.05 & BR > 3; **=FDR-corrected p-value < 0.001 & BR > 3. †$R^2 \geq 0.26$.

Subgroups showed no differences in demographics or VSTM task performance

Subgroup characteristics are displayed in Table 2. No significant between-group differences were found for age, sex, education (all $p > 0.05$, BF < 3). We found a trend level age difference between the subgroups ($F_{3,40.8}$=2.79, p = 0.053, BF = 0.43), with subgroup 4 tended to be younger than the other participant groups (subgroup 1: $t_{23.6}$ = 2.83, p = 0.009, BF = 3.70; subgroup 2: $t_{27.7}$ = 2.29, p = 0.030, BF = 1.74; subgroup 3: t_{18} = 2.01, p = 0.059, BF = 1.49). VSTM performance did not significantly differ across subgroups (precision and number of items in memory at load 3, all $p > 0.05$, BF < 3). These results were unaffected by age corrections. A complete overview of the between-group statistics for the subgroup characteristics can be found in Supplementary Table B.

Table 2. Subgroup characteristics

	All participants	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4
N	**113**	**35**	**24**	**42**	**12**
Age, mean (SD)	53 (18.0)	57 (19.1)	55 (19.8)	51 (15.6)	41 (15.4)
Sex					
Male, n (%)	59 (52%)	14 (40%)	15 (63%)	24 (57%)	6 (50%)
Female, n (%)	54 (48%)	21 (60%)	9 (38%)	18 (43%)	6 (50%)
Highest education					
University, n (%)	82 (73%)	21 (60%)	19 (79%)	32 (76%)	10 (83%)
A' levels, n (%)	17 (15%)	6 (17%)	3 (13%)	7 (17%)	1 (8.3%)
GCSE grade, n (%)	9 (8%)	4 (11%)	1 (4.2%)	3 (7.1%)	1 (8.3%)
None > 16, n (%)	5 (4.4%)	4 (11%)	1 (4.2%)	0 (0%)	0 (0%)
Number of items in memory (load 3), mean (SD)	2.40 (0.46)	2.35 (0.50)	2.38 (0.47)	2.43 (0.47)	2.49 (0.34)
Memory precision (load 3), mean (SD)	0.12 (0.05)	0.10 (0.04)	0.12 (0.04)	0.12 (0.05)	0.13 (0.04)

Subgroups revealed distinct associations between brain activity and VSTM task performance

Next, we investigated the association between brain activity and task performance within each subgroup, while correcting for age. Since this concerned within-group analyses, we excluded subgroup 4 because of its small number of participants (n = 12). To limit the number of comparisons, we focused on the brain modules with the most pronounced differences between the subgroups: the FCM, VM, DAM, and DMM. A complete overview of the associations between brain module activity and performance on the VSTM task for each of the subgroups is displayed in Supplementary Table C.

For the FCM, we found that the subgroups 1 and 2 showed negative associations between FCM activity and memory precision (subgroup 1: r = −0.37, 95% CI = [−0.62; −0.04], uncorrected p = 0.030, BF = 2.36; subgroup 2: r = −0.41, 95% CI = [−0.70; 0.01], uncorrected p = 0.045, BF = 1.93, see Figure 4A). However, this association was absent in subgroup 3 (r = 0.11, uncorrected p = 0.465, BF = 0.30). When we compared the slopes between subgroups 1 and 3, we found that they were significantly different (z = -2.11, 95% CI = [-0.87; -0.03], uncorrected p = 0.035), the same was true for the comparison between subgroups 2 and 3 (z = -2.05, 95% CI = [-0.94; -0.02], uncorrected p = 0.040). Notably, subgroups 1 and 2 were characterized by having relatively low FCM recruitment than subgroup 3 and 4. Therefore, these results suggest that the low recruitment of the FCM within subgroups 1 and 2 may have been beneficial to their memory precision. No association was observed between FCM activity and number of items in memory in any of the subgroups.

For the VM, no significant associations with items in memory or memory precision were observed.

In the DAM, we observed that subgroup 1 demonstrated a positive association between DAM activity and memory precision (r = 0.42, 95% CI = [0.10; 0.66], uncorrected p = 0.012, BF = 4.97, see Figure 4B). In subgroup 2, this association tended in a similar direction; however, this was not significant (r = 0.30, uncorrected p = 0.15). The slope from subgroup 1 significantly differed from subgroup 3 (z = 2.14, 95% CI = [0.04; 0.86], uncorrected p = 0.032). Subgroup 1 was characterized by having the least DAM recruitment. This suggests that for subgroup 1, their low DAM activity may have negatively impacted their memory precision. There were no significant associations between DAM activity and number of items in memory.

In the DMM, no associations were observed between DMM activity and memory precision. A negative association was observed between reduced DMM deactivation and the number of items in memory in subgroup 1 (r = -0.38, 95% CI = [-0.63; -0.05], uncorrected p = 0.026, BF = 2.65), however no associations were found in subgroup 2 (r = -0.11, p = 0.597, BF = 0.35) or subgroup 3 (r = 0.01, p = 0.942, BF = 0.23; see Figure 4C). The slopes did not significantly differ between groups. These results suggest that the increased activity (or reduced suppression) of the DMM in subgroup 1 may have hindered the number of items participants in that subgroup could recall.

Taken together, we observed several unique associations between brain module activity and VSTM performance that were subgroup-specific, even though task performance did not differ across groups. This further supports the notion that these distinct brain activity profiles reflect different yet equally effective pathways to perform the task. It should be noted that after applying FDR-corrections for multiple testing across the three subgroups and four networks, none of these associations remained significant, and therefore should be interpreted with caution.

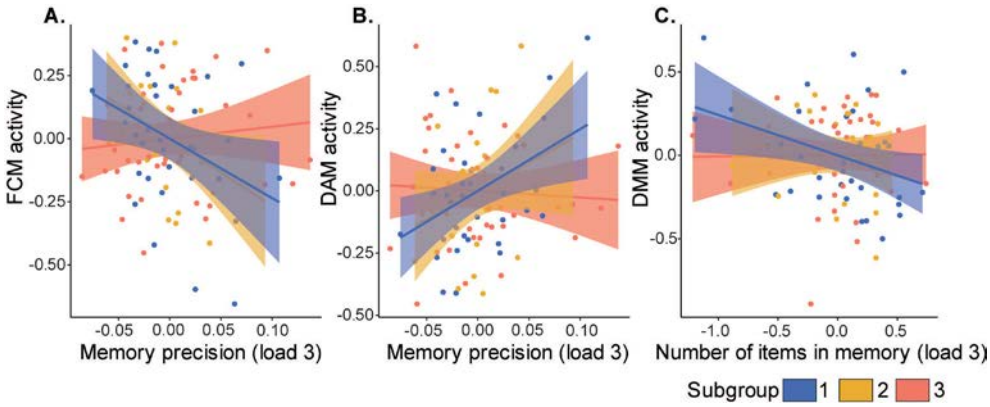


Figure 4. Associations between brain module activity in the frontal control module (FCM), visual module (VM), dorsal attention module (DAM), and default mode module (DMM) and performance on the visual short-term memory task. All analyses were corrected for age. **A.** Subgroups 1 and 2 showed negative associations between FCM activity and memory precision (uncorrected p = 0.030, uncorrected p = 0.045). **B.** Subgroup 1 demonstrated a positive association between DAM activity and memory precision (uncorrected p = 0.012). **C.** Subgroup 1 demonstrated a negative association between reduced DMM suppression and the number of items in memory (uncorrected p = 0.026).

Subgroups differ in white matter integrity

Next, we investigated whether structural brain characteristics differed between groups. First, we compared grey matter volumes within each of the modules between groups while correcting for total intracranial volume. Grey matter volume in the TPM significantly differed across subgroups ($F_{3,39.84}$ = 5.67, FDR-adjusted p = 0.017, BF = 5.10), however this effect disappeared after additionally correcting for age (unadjusted p = 0.048; BF = 0.72).

We also investigated whether the different subgroups showed significant differences in white matter microstructure, as measured by mean kurtosis (MK). We found significant differences between subgroups for four white matter tracts (see Figure 5). These included the left inferior frontal occipital fasciculus (IFOF; F3,37.8 = 4.73, FDR-adjusted p = 0.030, BF = 5.04), right IFOF ($F_{3,36.10}$ = 4.08, FDR-adjusted p = 0.049, BF = 3.49), left inferior longitudinal fasciculus ($F_{3,35.09}$ = 6.71, FDR-adjusted p = 0.011, BF = 28.10) and the left uncinate fasciculus (F3,35.43 = 6.60, FDR- adjusted p = 0.011, BF = 16.93).

Only the effects in the left inferior longitudinal fasciculus and the left uncinate fasciculus remained significant after correcting for age ($F_{3,34.8}$ = 5.42, FDR-adjusted p = 0.033, BF = 5.81; F3,35.4 = 6.64, FDR-adjusted p = 0.020, BF = 17.32, respectively). The left inferior fasciculus showed lower MK in subgroup 2 relatively to subgroup 3 ($t_{53.56}$ = 3.71, FDR-adjusted p = 0.003, BF = 30.24) and subgroup 4 ($t_{13.37}$ = 2.65, unadjusted p = 0.019, BF = 11.23), however the latter effect did not survive FDR-corrections.

The left uncinate fasciculus showed lower mean kurtosis in subgroup 2 relatively to subgroup 1 ($t_{45.50}$ = 2.58, FDR-adjusted p = 0.039, BF = 3.49), subgroup 3 ($t_{50.46}$ = 4.37, FDR-adjusted p <0.001, BF > 100), and subgroup 4 ($t_{15.49}$ = 2.60, FDR-adjusted p = 0.039, BF = 6.62). So, subgroup 2, which is the subgroup with the least FCM activity but the highest VM activity across all subgroups, specifically shows lower MK in the left uncinate fasciculus and the left inferior longitudinal fasciculus. Notably, the low recruitment of the FCM within this subgroup appeared to be beneficial to their memory precision.

A complete overview of the between-group statistics for grey matter volumes and MK is provided in Supplementary Tables D and E.

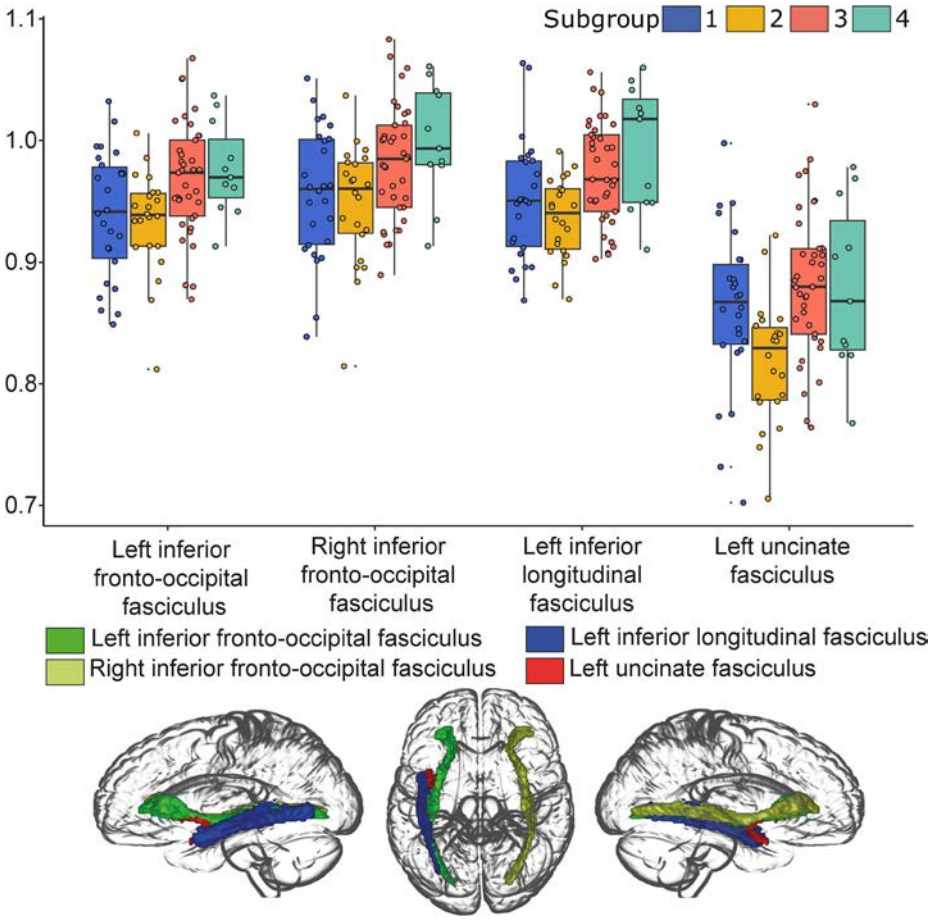


Figure 5. The upper part of the figure shows the average mean kurtosis values in each subgroup for the white matter tracts that displayed significant between-group differences (FDR-corrected p-value < 0.05 and Bayes Factor > 3). The bottom part visualizes the white matter tracts in a glass brain, generated with MRIcroGL (https://www.nitrc.org/projects/mricrogl). Only the effects in the left inferior longitudinal fasciculus and left uncinate fasciculus survived additional age corrections.

Discussion

While we often assume that similar patterns of neural activity are engaged to complete a cognitive task across individuals, accumulating evidence suggests that this is not necessarily the case, even in the absence of brain injury or disease (Noppeney et al., 2004; Price & Friston, 2002; Seghier & Price, 2018). Instead of discarding inter-individual variability in task-related functional activity, we leveraged it in our analyses to investigate brain degeneracy or many-to-one mapping in the context of VSTM performance. We identified four participant subgroups with distinct brain activity profiles, particularly within the FCM, VM, DAM, and DMM. Despite substantial differences in brain activity, these subgroups showed no difference in task performance or age, suggesting that these profiles may reflect different yet equally effective pathways to perform the task. This was further supported by the small, albeit distinct associations between task performance and brain modular activity across subgroups. Individual differences in brain structure may partly account for differences in brain activity, as subgroups showed age-independent differences in white matter integrity for the left inferior longitudinal fasciculus and the left uncinate fasciculus. Here, we first discuss our findings in relation to many-to-one mapping. Subsequently, we describe the modules and subgroups that we identified in more detail as well as the role of global versus local inter-individual variability in brain activity. Finally, we highlight the factors that contributed to subgroup variations in brain activity.

Degeneracy suggests that there can be multiple neural pathways leading to the same behavioural outcome (Edelman & Gally, 2001; Mason et al., 2015; Price & Friston, 2002; Westlin et al., 2023). We identified four subgroups with marked differences in recruitment of various brain modules during the VSTM task, after accounting for differences in overall network activity. These results add to previous studies that revealed subgroups with distinct profiles of task-related functional activity (Cerliani et al., 2017; Fischer-Baum et al., 2018; Kherif et al., 2009; Noppeney et al., 2006; Noppeney et al., 2005; Seghier et al., 2008; Seghier & Price, 2016). Similarly to previous findings (Fischer-Baum et al., 2018; Noppeney et al., 2006), these subgroups demonstrated similar levels of performance. These findings illustrate how different patterns of brain activity can lead to the same functional outcome, providing support for the notion of brain degeneracy. Additionally, we observed several unique associations between brain modular activity and task performance. This finding suggests that there is not a single route to successful cognitive performance, and the optimal route may vary from person to person. This finding highlights the individual-specific

nature of brain-cognition relationship, where diverse neural mechanisms can yield similar outcomes (Noppeney et al., 2006; Seghier & Price, 2018).

As a first step toward identifying subgroups, we reduced the dimensionality of our data, identifying seven brain modules that showed similar between-participant variability in their activity patterns during the maintenance period of the VSTM task (load 3 vs. load 1). Strikingly, these modules show strong correspondence to brain networks that are typically identified using functional connectivity analyses, such as the frontoparietal control network and default mode network (Power et al., 2011; Yeo et al., 2011). This happens even though functional connectivity is typically based on temporal correlations in activity within participants while we investigated correlations in activity between participants, suggesting that there is a shared underlying source. These results corroborate the idea that there is a stable intrinsic network architecture that is largely uniform across individuals but also shows reliable individual differences (Finn et al., 2015; Fox & Raichle, 2007; Gratton et al., 2018). This intrinsic architecture manifests itself both in how networks are functionally connected within a single person (within-subject) and in the differences in network activity among individuals (between- subjects). In line with this, previous studies demonstrated that functional connectivity can be used to predict task-activation, and that individual differences in connectivity are related to variability in task-related activation (Cole et al., 2014; Cole et al., 2021; Finn et al., 2015; Tavor et al., 2016).

We observed that the brain activity across the seven brain modules was highly correlated, corroborating previous findings where the global recruitment of task-related functional activity explained most inter-individual variability, both in relation to performance and age (Chen et al., 2022; Mitchell et al., 2023; Samu et al., 2017). Consistent with prior studies, the average activity across all modules explained 60-75% of the variability in activity observed within each brain module. To be able to look beyond this general factor, we used module-specific activity for our subsequent analysis, where the average activity within each module was corrected for the average activity across all modules. Results from the latent profile analysis suggests that there is meaningful inter-individual variability beyond this general factor, by revealing subgroups with differences in white matter integrity and unique associations between brain activity and performance. These findings illustrate how individual differences in task-related brain activation arise from both overall responsivity to the task (Samu et al., 2017), and the specific recruitment patterns of brain regions,

highlighting the importance of individual-specific factors in shaping task-related brain activity (Cole et al., 2021; Finn et al., 2015; Gratton et al., 2018).

Of the seven modules we identified, four showed the most significant differences in activity across subgroups: the FCM, VM, DAM, and DMM. These brain modules largely overlap with the frontoparietal network, visual network, dorsal attention network, and default mode network, respectively (Power et al., 2011; Yeo et al., 2011). With increasing task load, activity typically increases in the frontoparietal and dorsal attention networks, whereas the default mode network becomes more suppressed (Huang et al., 2016; Nagel et al., 2009; Salami et al., 2019; Salami et al., 2018; Zuo et al., 2019). This reflects a shift away from internally focused processes to task-oriented activity (Fox et al., 2005; Seeley et al., 2007; Smith et al., 2009). Notably, this pattern was weaker for subgroup 1, suggesting that this subgroup might have been less attentive during the maintenance phase (Anticevic et al., 2012; Berry et al., 2017). Surprisingly, this subgroup showed task performance comparable to the other subgroups, despite the positive association between DAM activity and memory precision, and the negative association between DMM activity and the number of items in memory. One possibility is that VSTM performance was sustained in this subgroup through increased engagement during the encoding or retrieval phase (Linke et al., 2011; Magen, 2017). Stimulus information might also have been preserved in a passive state, where maintenance is facilitated by neural mechanisms not characterized by increased activity (i.e., activity-silent mechanisms), such as short-term synaptic plasticity (Lewis-Peacock et al., 2014; Stokes, 2015).

Successful VSTM performance is further facilitated through interactions between the frontoparietal and visual networks (D'Esposito & Postle, 2015; Eriksson et al., 2015; Scimeca et al., 2018). The sensory recruitment hypothesis of working memory suggests that the same brain regions responsible for encoding the stimulus are also essential for maintaining this information (D'Esposito, 2007; D'Esposito & Postle, 2015). In line with this, in the context of VSTM, visual regions have been shown to maintain detailed sensory representations of the stimuli (Emrich et al., 2013; Postle, 2015; Serences, 2016). The frontoparietal network is thought to exert top-down control over these areas and support the maintenance of more abstract representations of the stimuli, such as verbal descriptions (Christophel et al., 2017; Gayet et al., 2018; Scimeca et al., 2018; Serences, 2016). Interestingly, subgroup 2 demonstrated the highest VM activity and lowest FCM activity. The reduced

FCM recruitment in this subgroup was beneficial to VSTM performance, as reflected by the negative associations between FCM activity and memory precision in these participants. In contrast, subgroups 3 and 4 demonstrated relatively high FCM activity and lower VM activity. The use of different strategies to complete the task is an important source of variability for task-related brain activity (Miller et al., 2012; Sanfratello et al., 2014). Consistently, previous studies that identified subgroups with distinct brain activity profiles during task engagement attributed this variability to the adoption of different strategies (Kherif et al., 2009). It is possible that subgroup 2 might have relied more on visual representations, while subgroup 3 and 4 maintained stimulus information through more abstract forms, thereby relying more on the FCM. This would also align with the two most commonly reported strategies to perform VSTM tasks: maintaining visual representations of the stimuli (e.g., picturing the red dots moving to the left corner) and translating salient stimuli features into verbal representations (e.g., mentally repeating "the red dots moved to the left corner") (Berger & Gaunitz, 1979; Pearson & Keogh, 2019).

Subgroup 2 also showed decreased white matter integrity in the inferior longitudinal fasciculus and the uncinate fasciculus, whereas this was preserved in subgroups 3 and 4. The inferior longitudinal fasciculus is involved in modulating visual information and semantic-lexical processing (Herbet et al., 2018; Shekari & Nozari, 2023). The uncinate fasciculus is associated with associative learning and semantic retrieval (Olson et al., 2015; Von Der Heide et al., 2013). This suggests that the use of a visually oriented strategy in subgroup 2 may be linked to the reduced microstructural integrity in two white matter tracts that play a role in creating and retrieving verbal representations (Duffau et al., 2013; Herbet et al., 2018; Shekari & Nozari, 2023). However, we did not find any direct association between brain activity and performance in subgroup 3, which makes it challenging to interpret how this brain activity profile precisely facilitated task performance in this group.

The age-independent differences in white matter integrity across subgroups were consistent with our expectation that structural brain characteristics would contribute to the variability in brain activity among the subgroups (or vice versa). This also aligns with previous research linking white matter microstructure to the recruitment of different brain regions during task performance (Burzynska et al., 2013; Burzynska et al., 2015). We did not observe any differences in grey matter across subgroups, suggesting that white matter integrity may be relatively more important to explain inter-individual

variability in brain activity in our sample (Miller et al., 2012). Typically, white matter degradation is associated with declines in cognitive performance, including working memory (Bennett & Madden, 2014; Oschwald et al., 2020). Our results suggest that this is not necessarily the case when different neural pathways can be used to perform a task (Madden et al., 2009), corresponding to the notion of brain degeneracy (Noppeney et al., 2004; Price & Friston, 2002). It should be noted that the differences in white matter integrity between subgroups were relatively small, emphasizing the need to further investigate these associations in future studies. Nevertheless, our findings underscore that individual differences in structural brain characteristics are an important source of variability in brain activity and cognitive performance (Genon et al., 2022; Kanai & Rees, 2011; Miller et al., 2012; Seghier & Price, 2018).

Although prior research has demonstrated strong age-related differences in brain activity and performance during VSTM tasks, including the one used here (Lugtmeijer et al., 2023; Morcom & Henson, 2018; Sander et al., 2012), we did not observe any differences in age or performance between the subgroups. This suggests that other factors beyond age or task performance were the primary drivers behind the distinct brain activation patterns observed across subgroups (Finn et al., 2015; Gratton et al., 2018). These factors may have included the extent to which participants were engaged throughout the task (Linke et al., 2011; Magen, 2017; Rose, 2020), the strategies adopted to complete the task (Kherif et al., 2009; Miller et al., 2012), and variations in white matter integrity (Burzynska et al., 2013; Burzynska et al., 2015), as discussed above. Nonetheless, age was positively correlated with the global recruitment of brain activity, consistent with prior research showing that that variability in overall responsivity was primarily due to age-differences (Mitchell et al., 2023; Samu et al., 2017). Therefore, the lack of age differences between subgroups might also be explained by our approach of clustering participants based on the residual brain activity in each module (i.e., after regressing out the overall responsiveness). In contrast, task performance was not associated with overall responsivity, suggesting that this factor is not the most substantial driver of inter-individual variability in brain activity. Therefore, studies that are interested in explaining performance metrics would benefit from distinguishing individuals based on performance itself rather than brain activity (e.g., Lövden et al., 2018; Salami et al., 2018).

There are several limitations that should be considered when interpreting these findings. First, we explored how the brain activity differences across

subgroups may be associated with different cognitive processes. Although the use of different strategies has been recognized an important source of task-related functional activity (Kherif et al., 2009; Miller et al., 2012; Noppeney et al., 2006; Sanfratello et al., 2014), we note that this interpretation remains speculative as we do not have any information about which strategies participants used when they performed the task. Therefore, the evidence here should be taken as proof of principle, showing that when we use a different approach to look at task-related brain activity, interesting dimensions of inter-individual variability are revealed that may otherwise remain hidden (Cerliani et al., 2017; Fischer-Baum et al., 2018; Kherif et al., 2009; Noppeney et al., 2006; Seghier et al., 2008; Seghier & Price, 2016; Seghier & Price, 2018). Second, our dataset consists of a relatively small number of participants, which may have limited our ability to observe within-group associations with performance. Lastly, although we have discussed the role of several factors in explaining the variability in brain activity between subgroups, this does not rule out the possibility that other variables that were not considered here could also contribute, such as other early-life factors, genetic factors or brain development (Walhovd et al., 2023). We hope that future studies focusing on this subject will include larger samples and a more extensive characterization of individual-specific factors that could further explain this variability.

Taken together, the novel approach introduced here allowed us to uncover distinct subgroups with marked differences in neural activity during the VSTM task, associations between brain module activity and VSTM performance, and white matter microstructural properties. However, these subgroups did not significantly differ in their demographic characteristics or VSTM performance. The identification of distinct subgroups illustrates how multiple neural pathways may underlie successful VSTM performance. This further highlights the importance of considering brain degeneracy to understand variability in brain-cognition associations (Edelman & Gally, 2001; Mason et al., 2015; Price & Friston, 2002; Westlin et al., 2023). Recognizing this possibility provides us with a more comprehensive understanding of the different ways in which our brains support cognitive functions and how this may vary from person to person. Consequently, these insights may help to unravel new ways in which structure and function interact, and how complementary routes can lead to the same cognitive outcomes.

Acknowledgments

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Data and code availability

Data availability is provided via the Cam-CAN data portal (https://camcan-archive.mrc-cbu.cam.ac.uk/dataaccess/). The scripts and analysis pipeline are made available via Github (https://github.com/michellegjansen/neural_pathways_VSTM).

Supplements

Supplementary methods

Selecting the most optimal latent profile model and number of classes

First, we compared the latent profile models based on their Bayesian Information Criterion (BIC) and Integrated Completed Likelihood (ICL) values, specifying between 1 and 5 classes (i.e., subgroups). In this context, larger BIC and ICL values indicate a better model fit (Scrucca, Fop, Murphy, & Raftery, 2016). To assume that any correlation between modules must be causes by participants with different brain activity profiles, we only considered models where the model space was restricted to models that did not allow for covariance between modules within subgroups of participants. Both the BIC and ICL suggested that the model with equal shape, variable volume, and assumed diagonal covariance ("VEI" model) provided the most optimal fit (see also Supplementary Figures 2 and 3).

Subsequently, to select the number of classes, we compared the BIC and ICL values, as well as the bootstrapped Likelihood Ratio Test (LRT) results. The BIC and ICL both indicated that the solution with 4 classes provided the most optimal fit (BIC = -1028, ICL = -1047.89). However, the LRT remained significant for 5 classes, suggesting that the addition of another class continued to improve the model fit. Further LRT analyses resulted in a non-significant result only at 8 classes (p = 0.422), suggesting that a model with 7 classes concurred with the best model fit. However, the BIC and ICL continued to show the most optimal fit at 4 classes. As we aimed for a parsimonious solution, we therefore opted for the solution with 4 subgroups. A complete overview of the model fit indices for 1-8 classes is provided in the table below.

Number of classes	df	BIC	ICL	LRT	p-value
1	16	-1121.36	-1121.36		
2	26	-1072.37	-1080.84	96.26	0.001
3	36	-1054.57	-1080.66	65.08	0.001
4	46	**-1028.00**	**-1047.89**	73.85	0.001
5	56	-1037.85	-1054.45	37.42	0.003
6	66	-1047.51	-1065.71	37.61	0.009
7	76	-1049.46	-1064.24	45.33	0.001
8	86	-1077.12	-1093.73	19.61	**0.422**

Abbreviations: BIC = Bayesian Information Criterion; ICL = Integrated Completed Likelihood; LRT = Likelihood Ratio Test.

Scrucca, L., Fop, M., Murphy, T. B., & Raftery, A. E. (2016). mclust 5: Clustering, Classification and *Density Estimation Using Gaussian Finite Mixture Models. R j, 8(1), 289-317.*

Supplementary Table A. Between-group comparisons of brain module activity

Brain module	N	No correction applied					Corrected for age				
		F-statistic	p-value	q-value	BF	R^2	F-statistic	p-value	q-value	BF	R^2
FCM	**113**	**54.29***	**< 0.001**	**< 0.001**	**3.00e+14**	**0.51†**	**36.92***	**< 0.001**	**< 0.001**	**3.52e+12**	**0.46†**
TPM	113	1.05	0.383	0.44	1.00e-01	0.00	36.79	0.425	0.4859	1.27e-01	0.00
CTM	113	10.92*	< 0.001	< 0.001	1.59e+02	0.15	35.76*	< 0.001	< 0.001	1.78e+02	0.15
VM	**113**	**33.93***	**< 0.001**	**< 0.001**	**2.80e+12**	**0.46†**	**37.23***	**< 0.001**	**< 0.001**	**4.26e+11**	**0.44†**
DAM	**113**	**20.00***	**< 0.001**	**< 0.001**	**8.16e+05**	**0.28†**	**36.58***	**< 0.001**	**< 0.001**	**6.37e+04**	**0.24**
MM	113	9.45*	< 0.001	< 0.001	2.36e+02	0.15	36.38*	< 0.001	<0.001	1.27e+02	0.14
DMM	**113**	**42.56***	**< 0.001**	**< 0.001**	**1.38e+13**	**0.47†**	**37.13***	**< 0.001**	**< 0.001**	**4.72e+11**	**0.44†**
Resp	113	0.77	0.517	0.517	7.00e-02	0.00	38.19	0.512	0.512	6.40e-02	0.00

Abbreviations: BF = Bayes Factor; FCM = frontal control module; TPM = temporal parietal module; CTM = cerebellum/thalamus module; VM = visual module; DAM = dorsal attention module; MM = motor module; DMM = default mode module. Results from the Welch's ANOVA and corresponding Bayes Factor (BF) for the alternative hypothesis and Bayesian R^2. Results were considered as significant if both FDR-corrected q-value < 0.05 and BF > 3. Differences were most pronounced for the frontal control module (FCM), visual module (VM), dorsal attention module (DAM), and default mode module (DMM), as reflected by the corresponding values of BF and Bayesian R^2. Results were not affected by age corrections.

*= FDR-corrected q-value < 0.001 & BF > 100.

†$R^2 \geq 0.26$.

Supplementary Table B. Between-group comparisons of participant characteristics

Continuous variables	N	Df	Df error	F-statistic	p-value	BF	R^2
Age	113	3	40.77	2.79	0.05	0.43	0.00
Number of items in memory (load 3)	113	3	44.12	0.45	0.72	0.04	0.00
Memory precision (load 3)	113	3	43.36	1.98	0.13	0.18	0.00
Categorical variables	N	Df	χ^2-statistic	95% CI	p-value	BF	Cramer's V
Sex	113	3	3.43	0.00-1.00	0.32	0.16	0.07
Educational attainment	113	3	4.28	0.00-0.30	0.23	0.26	0.11

BF = Bayes Factor. Upper part displays the results from the Welch's ANOVA and corresponding Bayes Factor (BF) for the alternative hypothesis and Bayesian R^2. Lower part displays results from the Chi- squared test and corresponding Bayes Factor (BF) for the alternative hypothesis. Results were considered as significant if both FDR-corrected q-value < 0.05 and BF > 3. Notably, educational attainment was statistically compared after dichotomizing the four corresponding categories (university as highest level education vs. the other catgories; A' levels, GCSE grade, none above 16). The between-group comparisons of memory performance were not affected by age corrections.

Supplementary Table C. Within-group associations between task performance and brain module activity

	Subgroup 1			Subgroup 2			Subgroup 3		
	***N* = 35**			***N* = 24**			***N* = 42**		
	r	**95% CI**	**p**	**r**	**95% CI**	**p**	**r**	**95% CI**	**p**
Memory precision (load 3)									
FCM	-0.37	-0.62 – -0.04	0.030*	-0.41	-0.70 – 0.01	0.045	0.12	-0.19 – 0.41	0.465
VM	-0.06	-0.38 – 0.28	0.742	0.28	-0.14 – 0.61	0.191	-0.15	-0.43 – 0.16	0.341
DAM	0.42	0.10 – 0.66	0.012*	0.30	-0.12 – 0.63	0.152	-0.06	-0.36 – 0.25	0.696
DMM	0.08	-0.26 – 0.40	0.637	-0.14	-0.52 – 0.27	0.498	0.11	-0.20 – 0.40	0.472
Number of items in memory (load 3)									
FCM	0.24	-0.10 – 0.53	0.167	0.17	-0.24 – 0.54	0.418	-0.10	-0.39 – 0.21	0.531
VM	0.11	-0.23 – 0.42	0.541	-0.09	-0.32 – 0.42	0.679	-0.02	-0.32 – 0.29	0.917
DAM	0.19	-0.15 – 0.50	0.264	0.18	-0.24 – 0.55	0.390	0.01	-0.29 – 0.31	0.941
DMM	-0.38	-0.63 – -0.05	0.026*	-0.11	-0.50 – 0.30	0.597	0.01	-0.29 – 0.31	0.942

Abbreviations: CI = confidence interval; FCM = frontal control module; VM = visual module; DAM = dorsal attention module; DMM = default mode module.Pearson correlations the associations between visual short-term memory task performance and brain module activity, for each subgroup and corrected for age (i.e., partial correlations). Confidence intervals are standardized.

*= p-value < 0.05.

Supplementary Table D. Between-group comparisons of grey matter volumes in each brain module

Grey matter volume	N	Corrected for total intracranial volume					Corrected for total intracranial volume and age				
		F	p	q	BF	R^2	F	p	q	BF	R^2
FCM	113	0.90	0.45	0.45	0.06	0.00	0.15	0.93	0.93	0.03	0.00
TPM	113	5.67**	0.002	0.02	5.10	0.08	2.87*	0.05	0.34	0.72	0.00
CTM	113	3.54*	0.02	0.08	0.89	0.00	2.04	0.12	0.43	0.11	0.00
VM	113	2.97*	0.04	0.08	0.57	0.00	1.04	0.39	0.67	0.07	0.00
DAM	113	2.62	0.06	0.09	0.20	0.00	0.71	0.55	0.77	0.06	0.00
MM	113	3.08	0.04	0.08	0.26	0.00	1.14	0.34	0.67	0.06	0.00
DMM	113	1.78	0.17	0.19	0.13	0.00	0.32	0.81	0.93	0.04	0.00

Abbreviations: BF = Bayes Factor; FCM = frontal control module; TPM = temporal parietal module; CTM = cerebellum/thalamus module; VM = visual module; DAM = dorsal attention module; MM = motor module; DMM = default mode module. Results from the Welch's ANOVA and corresponding Bayes Factor (BF) for the alternative hypothesis and Bayesian R^2, corrected for total intracranial volume or additionally for age. To correct for these effects, we regressed the covariate(s) on the variable of interest and used the residuals of that regression. Results were considered as significant if both FDR- corrected q-value < 0.05 and BF > 3. The between-group differences of grey matter volume in the temporal parietal module (TPM) did not remain significant after applying additional age corrections.

*=uncorrected p-value < 0.05.

**=FDR-corrected q-value < 0.05 & BF > 3.

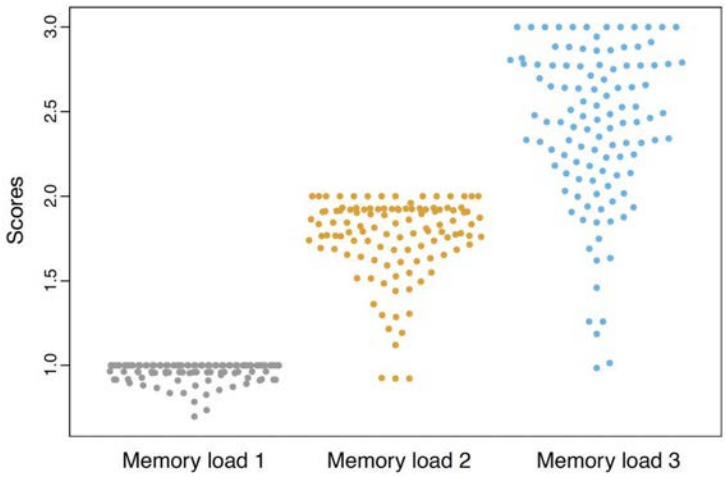
Supplementary Table E. Between-group comparisons of mean kurtosis in each white matter tract

Mean kurtosis	N	No covariates					Corrected for age				
		F	p-value	q-value	BF	R^2	F	p-value	q-value	BF	R^2
Left anterior thalamic radiation	96	2.95	0.05	0.07	0.88	0.00	1.89	0.15	0.22	0.27	
Right anterior thalamic radiation	96	1.80	0.16	0.21	0.22	0.00	1.28	0.30	0.41	0.10	0.00
Left dorsal cingulate gyrus	96	3.57	0.02	0.06	2.69	0.07	2.69	0.06	0.22	0.92	0.00
Right dorsal cingulate gyrus	95	0.71	0.55	0.58	0.07	0.00	0.49	0.69	0.73	0.05	0.00
Left ventral cingulate gyrus	86	0.12	0.95	0.95	0.04	0.00	0.33	0.81	0.81	0.05	0.00
Right ventral cingulate gyrus	94	1.13	0.35	0.40	0.12	0.00	1.21	0.32	0.41	0.12	0.00
Left cerebrospinal tract	95	5.57**	0.00	0.02	0.84	0.00	2.06	0.12	0.22	0.15	0.00
Right cerebrospinal tract	94	3.18	0.04	0.07	1.37	0.04	2.81	0.05	0.22	0.56	0.00
Forceps major	96	2.73	0.06	0.09	0.80	0.00	2.13	0.11	0.22	0.32	0.00
Forceps minor	96	3.81	0.02	0.05	1.02	0.01	2.05	0.12	0.22	0.30	0.00
Left inferior frontal- occipital fasciculus	96	4.73***	0.01	0.03	5.04	0.09	3.02*	0.04	0.22	1.16	0.02
Right inferior frontal- occipital fasciculus	96	4.08***	0.01	0.05	3.49	0.08	2.36	0.09	0.22	0.60	0.00
Left inferiorlongitudinal fasciculus	**96**	**6.71*** **	**0.00**	**0.00***	**28.10**	**0.14**	**5.42*** **	**0.00**	**0.03**	**5.81**	**0.10**
Right inferior longitudinal fasciculus	95	3.40*	0.03*	0.06	2.18	0.06	2.54	0.07	0.22	0.69	0.00
Left superior longitudinal fasciculus	95	1.91	0.15	0.20	0.23	0.00	1.12	0.36	0.41	0.11	0.00
Right superior longitudinal fasciculus	96	3.18	0.03	0.07	1.00	0.00	1.09	0.37	0.41	0.13	0.00
Left uncinatefasciculus	**96**	**6.60*** **	**0.00**	**0.01**	**16.93**	**0.13**	**6.64*** **	**0.00**	**0.02**	**17.32**	**0.13**
Right uncinate fasciculus	96	1.60	0.21	0.25	0.20	0.00	1.89	0.15	0.22	0.28	0.00

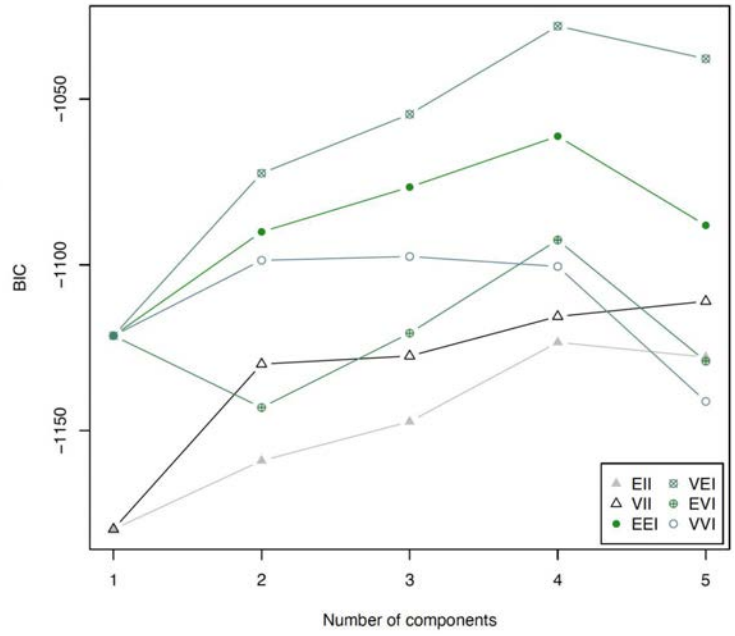
BF = Bayes Factor. Results from the Welch's ANOVA and corresponding Bayes Factor (BF) for the alternative hypothesis and Bayesian R^2, with and without additional corrections for age and average mean kurtosis across all tracts. To correct for these effects, we regressed the covariate(s) on the variable of interest and used the residuals of that regression. Results were considered as significant if both FDR-corrected q-value < 0.05 and BF > 3. Only the left inferior longitudinal fasciculus and left uncinate fasciculus demonstrated significant differences between-groups after age corrections.

*= uncorrected p-value < 0.05; **=FDR-corrected q-value < 0.05.

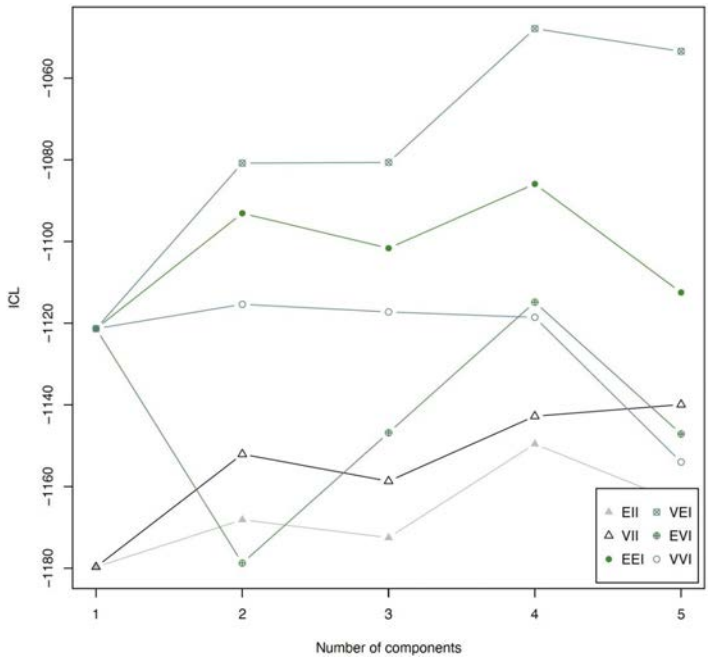
***=FDR-corrected q-value < 0.05 & BF > 3.



Supplementary Figure A. The distribution of the number of items in memory at each memory load (load 1-3) as illustrated with beeswarm plots. The number of items in memory for load 1 displayed a ceiling effect, where many participants achieved high performance. This was also present to some extent at load 2. Therefore, the analyses in this manuscript focused on load 3, where the data demonstrated more variation.



Supplementary Figure B. Distribution of Bayesian Information Criterion (BIC) values for the different latent-profile models (1-5 clusters) estimated based on the residual activity in each brain network as well as the overall responsivity across all networks. The most optimal BIC value (BIC = -1028) corresponded to a model with 4 latent subgroups of equal shape, variable volume, and a diagonal distribution ("VEI").



Supplementary Figure C. Distribution of Integrated Completed Likelihood (ICL) values for the different latent-profile models (1-5 clusters) estimated based on the residual activity in each brain network as well as the overall responsivity across all networks. The most optimal ICL value (ICL = -1048) corresponded to a model with 4 latent subgroups of equal shape, variable volume, and a diagonal distribution ("VEI")

Chapter 7

Classification Of MeMory InTerventions: Rationale and developmental process of the COMMIT tool

Published as
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Abstract

Over the last decades, numerous memory interventions have been developed to mitigate memory decline in normal ageing. However, there is a large variability in the success of memory interventions, and it remains poorly understood which memory intervention programs are most effective and for whom. This is partially explained by the heterogeneity of memory intervention protocols across studies as well as often poor reporting of the study design. To facilitate a reporting framework that enables researchers to systemize the content and design of memory intervention paradigms, we developed the Classification Of MeMory InTerventions (COMMIT) tool using a 3-stage developmental process. Briefly, COMMIT was based on qualitative content analysis of already existing memory intervention studies published between April 1983 and July 2020, and iteratively validated by both internal and external expert panels. COMMIT provides an easily-applicable interactive tool that enables systematic description of memory intervention studies, together with instructions on how to use this classification tool. Our main goal is to provide a tool that enables the reporting and classification of memory interventions in a transparent, comprehensible, and complete manner, to ensure a better comparability between memory interventions, and, to ultimately contribute to the question which memory intervention shows the greatest benefits.

Introduction

Ageing is characterized by a decline in various cognitive domains, such as episodic memory, executive function, and processing speed (Salthouse, 2019), posing a threat to functional independence, autonomy, and quality of life in older age (Missotten et al., 2008). However, the process of cognitive ageing is highly heterogeneous. Individuals not only differ in their susceptibility to age-related cognitive decline and underlying neural changes, but also in the cognitive domains that are being affected (Cabeza et al., 2018). Together with the notion that cognitive and neural processes have the potential to be altered at advanced age (i.e., cognitive and neural plasticity, respectively), this suggests that optimizing cognitive functions may still be possible in the ageing population (Lövdén et al., 2010).

Various interventions have been developed to maintain or improve cognitive functions in older age (Kivipelto et al., 2018). While pharmacological interventions have not been effective in reducing ageing-related memory decline, non-pharmacological interventions (e.g., physical exercise, diet adjustments, cognitive trainings) have yielded more promising results (Cotelli et al., 2012; Yao et al., 2020). Long-term memory function is considered to be a major criterion for successful ageing (Depp & Jeste, 2006; Nyberg & Pudas, 2019). This cognitive domain is also particularly susceptible to the effects of advanced age and the accumulation of neuropathology, and therefore predominantly affected by ageing-related pathologies such as Alzheimer's disease (Hedden et al., 2013; Qiu et al., 2019; Salthouse, 2019). One of the most commonly applied cognitive rehabilitation approaches therefore aims at improving memory functions. Memory interventions typically comprise two types of rehabilitation approaches: *a restorative approach*, consisting of exercises and/or training paradigms specifically designed to improve memory function (i.e., memory function training), and *a compensatory approach* which focuses on acquiring and applying compensatory strategies (i.e., memory strategy training). Both intervention approaches have been used to target cognitive decline in both healthy and pathological ageing (Gates et al., 2011; Lampit, Hallock, Moss et al., 2014; Mowszowski et al., 2010).

Increasing evidence suggests that memory interventions indeed could be successful in improving memory functions across diverse populations (Gates et al., 2011; Gross et al., 2012; N. T. Hill et al., 2017; Lampit, Hallock, & Valenzuela, 2014; Leung et al., 2015). However, the efficacy of these

interventions varies greatly across studies (Eikelboom, Bertens, & Kessels, 2020; Gross et al., 2012; Mewborn et al., 2017; Zelinski, 2009). These mixed results may be partially explained by heterogeneity in study paradigms, for example, in terms of the applied setting (e.g., single vs. group trainings), materials used (e.g., digital vs. paper-pencil trainings), or content of the particular intervention (e.g., strategy training vs. memory exercises; Kelly et al., 2014; Lampit, Hallock, & Valenzuela, 2014; Mewborn et al., 2017). In addition, individual characteristics may also influence intervention success, such as cognitive status (e.g., presence of mild cognitive impairment), baseline performance (e.g., on memory), or sociodemographic variables such as age, sex, and education (Mewborn et al., 2017; Roheger et al., 2020a).

Nevertheless, systematic reviews and meta-analyses focusing on the overall effects of memory interventions or potential individual variables that influence the performance of memory interventions experienced difficulties and/or were unable to perform a proper evidence synthesis (Kueider et al., 2012; Roheger et al., 2020b; Traut et al., 2021; Zehnder et al., 2009; Zhu et al., 2016). These difficulties were not only attributed to the aforementioned variability in memory intervention components of the studies itself, but also to insufficient reporting of memory intervention studies, making it difficult to categorize such components for further analysis (Green et al., 2014; Eikelboom et al., 2020; Roheger et al., 2020a).

Considering the potential impact of memory interventions in preserving or improving healthy ageing (Gross et al., 2012; Kueider et al., 2012; Mewborn et al., 2017), the reporting of memory interventions should facilitate transparency and allow researchers to critically appraise the methodological design and results. To our knowledge, however, none of the existing guidelines cover the specific aspects of memory intervention studies, such as the applied setting, materials used, or content of the particular intervention (see, e.g., the Enhancing the QUAlity and Transparency Of health Research [EQUATOR] network guidelines; Altman & Simera, 2016; Simera et al., 2010).

Consequently, we developed COMMIT (*C*lassification *O*f *Me*M*o*ry *I*n*T*erventions), a standardized scoring tool together with instructions for detailed reporting of memory interventions to facilitate a comprehensive reporting framework. The COMMIT tool specifically incorporates the diversity in intervention components that have been used across memory interventions to describe and classify the varying components of such intervention

studies. COMMIT aims to: 1) systematically classify the content of memory interventions, and 2) assist authors to present their memory intervention studies in a transparent, comprehensible, and complete manner. Therefore, COMMIT enables researchers to accurately describe their own memory intervention studies, while also allowing researchers and publishers to critically appraise such studies and extract data for systematic reviews, meta-analyses, and mega-analyses.

Materials and methods

The development of COMMIT was based on the following 3-stage approach: 1) a systematic search for all memory intervention studies conducted among healthy ageing individuals published until January 2021; 2) a qualitative data analysis to derive a classification system of memory intervention studies of the methods section of each memory intervention in a stratified sample; 3) translation of the classification system into the COMMIT tool. For a flowchart of this process, see Figure 1.

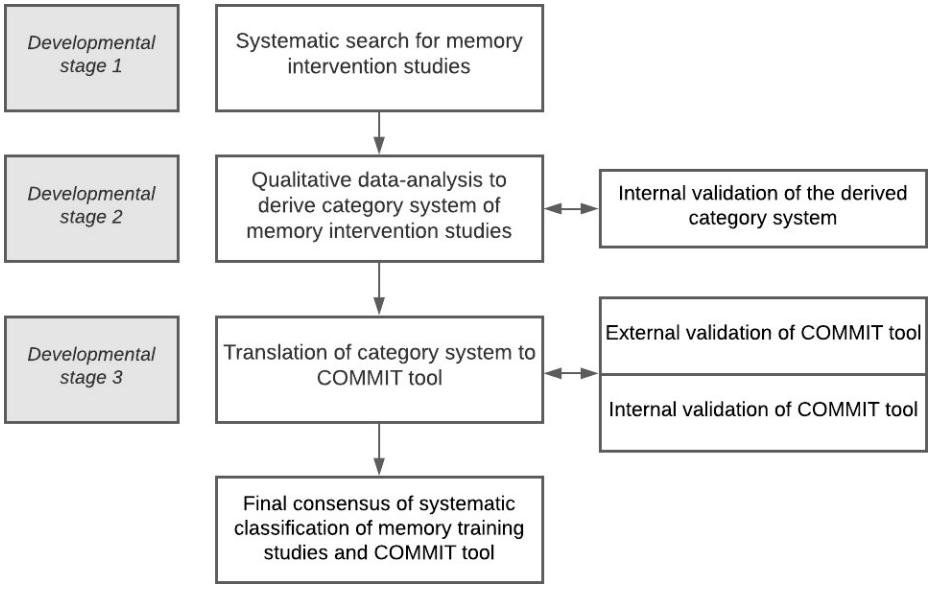

Figure 1. Description of the different developmental stages of the COMMIT tool

Development Stage 1: Systematic search for memory intervention studies

Search and study selection: We performed the systematic search and study selection as a follow-up on a previously published review focusing on prognostic factors for change in memory functioning after a memory intervention among healthy older adults ≥ 55 years (Roheger et al., 2020a). Briefly, we performed a systematic search across MEDLINE, Web of Science Core Collection, CENTRAL, and PsycInfo until November 2019, and updated our search for the present study until January, 2021. We additionally searched the reference lists of all identified trials, relevant review articles, and current treatment guidelines for relevant content. When no full text was readily available, we contacted the authors to ask for the full text publications within a 2-week time frame. The systematic search and full search strings for each database are presented in Supplementary Meth ods ("Overview of systematic search strings").

Two authors initially screened the titles and abstracts in accordance with predefined eligibility criteria (MR and AKF) with the Covidence Software (Veritas Health Innovation). Full-text articles of the research papers were subsequently screened for inclusion in the present study by two authors (MGJ and MR). In case of uncertainty about inclusion, final consensus about particular studies was reached during consensus meetings with co-authors (AKF, JMO, EK).

Inclusion criteria: We included memory intervention studies with a minimum of two sessions focusing on healthy older adults from peer-reviewed journals, written in English. More specifically, we defined memory interventions as cognitive rehabilitation techniques with a clearly defined long-term memory intervention component, specifically incorporated to target memory-related outcomes (e.g., episodic memory, prospective memory or semantic memory). We excluded working memory interventions, as this cognitive domain more closely aligns with executive functions, and research on working memory intervention has become a field on its own (Gathercole et al., 2019; Oberauer et al., 2018; Soveri et al., 2017).

Our inclusion was not limited to studies that solely focused on memory interventions, but also covered those that combined memory interventions with other types of cognitive, pharmacological, or physical training. Furthermore, we put no restrictions in terms of the applied setting (e.g., individual or group setting) or materials used for the intervention (e.g., computerized and/or paper-pencil tasks). We also included pilot studies

and study protocols. In this way, we were hoping to cover the whole range of memory intervention paradigms that have been used throughout time within our study. Nevertheless, the methodological description of a study needed to be available; if a study referred to a protocol paper for its design, we included the protocol paper instead. We excluded books, book chapters, abstracts, and conference papers.

Stratified sub-sample selection: We created a stratified sub-sample of all eligible studies (n = 274; see results section), as evaluation of the complete study sample is not required to obtain saturation (Morse, 1995). This resulted in a sub-sample of n = 40 studies. The stratified sub-sample was acquired using a three-step process. First, we arranged all eligible studies according to their publication date in 5-year time frames, starting from 1975 up until 1980, and counted the number of studies published in each time frame. Second, we calculated the relative amount of studies per time frame, and converted this number to our corresponding sample of 40 studies. For example, if n = 24 studies were published between 1996 and 2000, the relative contribution of these studies to the total sample n = 274 was 8.78%. Subsequently, among our sub-sample of n = 40 studies, we then randomly selected n = 4 studies that were published between 1996 and 2000, as this reflected the above calculated 8.78%. The selection of the studies within the stratified time blocks was achieved using R (https://www.R-project.org/).

Development Stage 2: Qualitative data analysis to derive initial category system

We used the qualitative data analysis software MaxQDA2020 (https://www.maxqda.com/) to apply qualitative content analysis to the method sections derived from the sub-sample of memory intervention studies, according to Kuckartz (2014). Research was performed in accordance to the Consolidated Criteria for Reporting Qualitative Studies (COREQ; Tong et al., 2007). The quality of this process was additionally monitored by one author (DC) experienced in qualitative research and content analysis. Two authors (MR, MGJ) developed an initial category system, using both deductive and inductive categorizations as recommended in previous literature (Kuckartz, 2014). Deductive categories were derived using existing literature (Bamidis et al., 2014; Gates et al., 2011; Gross et al., 2012; Lampit, Hallock, & Valenzuela, 2014; Roheger et al., 2020a; Sitzer et al., 2006). The derived categories were subsequently revised during consensus meetings with co-authors (AKF, EK, JMO, RPCK) experienced in the field of memory intervention research, covering various specializations and

subdomains relevant to disentangle memory intervention components (e.g., strategy-oriented and process-oriented memory interventions, utilization of training paradigms in healthy and/or pathological ageing, and both online and offline intervention application settings). New deductive and inductive categories were generated from the data during the content analysis of the stratified sample, where two authors (MR, MGJ) worked independently on the coding of this sample.

Two authors (MR, MGJ) subsequently discussed and harmonized the newly derived main and sub-categories, as well as on the individual coding of categories per study after each phase of independent coding, herewith optimizing the reliability and validity of the process. Whenever possible, subordinate categories were merged as long as this did not lead to loss of meaningful information during the process. Potential discrepancies were solved by consulting co-authors (AFK, EK, JMO, RPCK).

After we reached saturation on the stratified sub-sample (i.e., when no new main or sub-categories arose; Morse, 1995), a consensus meeting was organized to further refine the category system among all co-authors experienced in cognitive and/or memory intervention design (MR, MGJ, AFK, EK, JMO, RPCK; Eikelboom et al., 2020; Folkerts et al., 2017; Frankenmolen et al., 2018; Kalbe et al., 2020; Karssemeijer et al., 2017; Roheger et al., 2020b). Notably, if saturation was reached before finalizing the coding of the stratified sub-sample, we continued with processing this sample until completion. After this process, we extracted another stratified sub-sample (n = 5) among all memory intervention studies to test the newly derived category system to ensure quality and allow for potential further revision of categories. The latter process was repeated until no other revisions of the category system occurred. For a flowchart of the complete content analysis, see Figure 2.

Development Stage 3: Translation of category system into COMMIT tool

Based on the initial categorization system, we developed a first version of the COMMIT tool. During this developmental process, we aimed to make the COMMIT tool as comprehensive as possible while also maintaining an easily-applicable interface. We additionally developed detailed instructions (Table 1; see end of results section), describing each item and how to use the COMMIT tool.

In order to improve and validate the COMMIT tool and corresponding instructions, we first acquired feedback from all co-authors with experience

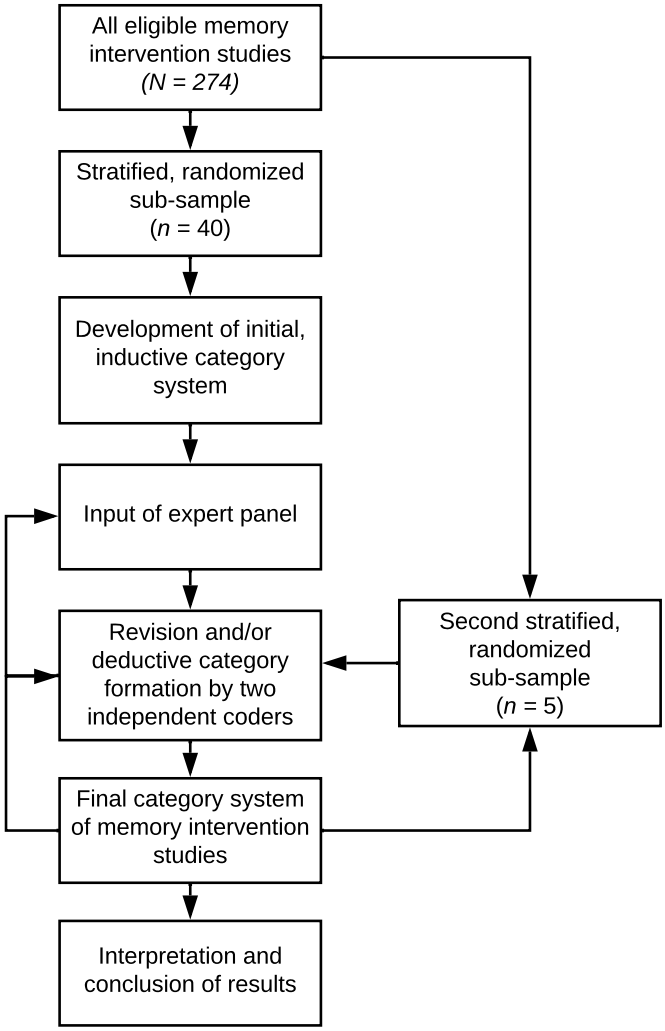

Figure 2. Process flowchart of qualitative content analysis

in memory intervention studies for internal validation (internal expert panel; MR, MGJ, AFK, EK, JMO, RPCK). For external validation, we reached out to 20 external investigators active in the field of memory intervention studies by them or by qualified members of their research groups. More specifically, we asked them about their willingness to help with the evaluation of COMMIT, together with a brief description of the purpose of COMMIT and how the evaluation process would work. Researchers were requested to fill in the COMMIT tool with the help of the instructions table (Table 1) for a memory intervention study conducted by themselves and to evaluate this process based

on several aspects. These aspects included how practical it was to use the tool and corresponding guidelines, whether any categories or items were missing to correctly describe memory interventions, and whether there were any additional comments or suggestions to further improve the COMMIT tool. Once the researcher agreed with this procedure, we sent all relevant documents to facilitate their participation in our external expert panel. After receiving feedback, we revised the COMMIT tool accordingly and consulted both the internal and external expert panels for any further enquiries or revisions. Of the 20 researchers that were approached by us, five researchers replied and assisted in the evaluation of COMMIT. After processing the feedback from all parties involved, we send the revised COMMIT tool for any further feedback and/or approval.

Results

Systematic search of memory intervention studies

A complete overview of the included and excluded studies, together with reasons for exclusion, is presented in the flowchart in Supplementary Figure A. Our database search and search of included studies in previously published systematic reviews and meta-analysis on memory interventions, revealed a total of 12,975 studies. An updated search revealed 154 additional results in January 2021. After duplicate removal, we screened a total of 10,133 studies for eligibility based on predefined criteria. From the remaining articles (n = 692), we finally included 274 memory intervention studies.

Subsequently, the randomized, stratified sample of 40 studies was obtained for further analysis (see Materials and Methods). After the coding of 34 studies of the initial stratified sub-sample was completed, saturation was reached; however, we also coded the remaining 6 studies. Our category system was further refined during a consensus meeting with all co- authors. Subsequently, we derived a second stratified sub-sample of 5 studies. During coding of the latter sample, no new categories were established, indicating that saturation was sustained, and therefore we did not incorporate another stratified sub-sample. Our final stratified sample included memory intervention studies that were published between 1983 and 2020.

The main characteristics of the sub-sample of memory intervention studies are displayed in Supplementary Table A, including the sample size of the study,

design, duration, and brief memory intervention description. Sample sizes of the intervention groups varied between *n* = 9 to *n* = 620 participants. Most of the studies included in this stratified sample involved randomized controlled trials (*n* = 36). We also included quasi-randomized controlled trails (*n* = 6), and (longitudinal) cohort studies (*n* = 3). Duration of conducted memory interventions was either self-paced (e.g., Lampit, Hallock, Moss et al., 2014), and varied from 20 minutes (e.g., Bureš et al., 2016) to 3 hours per session (Chapman et al., 2016). In addition, a high heterogeneity regarding training frequency was found, varying from 1 session per week (e.g., Wiegand et al., 2013) to daily sessions (e.g., Antonenko et al., 2018). With regards to the duration of the training, this varied from 3 consecutive days (e.g., Antonenko et al., 2017) to 2 years (e.g., Buiza et al., 2008).

With regard to the conducted memory intervention paradigms, descriptions were very heterogeneous, such as the naming and definition of the memory interventions (e.g., "number-consonant mnemonic training", Hill et al., 1997; "imagery-based strategy training", Carretti et al., 2007; "multi-factorial training program focusing on memory", West et al., 2008; "multi-domain memory and ageing program", Wiegand et al., 2013; "cognitive restructuring memory intervention", Caprio-Prevette & Fry, 1996). Accordingly, not only the memory intervention content differed across studies, but also additional training components varied greatly, such as educational support, supervision of the trainings, other cognitive domains that were trained within the memory intervention, and home exercises. Altogether, these findings further emphasize the need to classify memory intervention paradigms in a more systematic manner.

Memory intervention classification system

An overview of the final category system is given in Figure 3. The coding system follows a hierarchical design with the main categories displayed on the left side of the Figure (level 1), and the sub-categories on the right side, comprising increasingly more details with every step in the hierarchy (levels 2-4).

Our analysis showed that the training content of memory intervention studies could be broadly divided into two main categories (level 1). The first category involves *memory intervention components* and describes all training components that have been incorporated within an intervention paradigm with the direct goal to improve memory performance. The second category involves *additional components of intervention*. Although the elements described in the latter category are not directly incorporated to improve memory functions, these components play

an important role with regards to the intervention design and conduction of the memory intervention, and may conversely also influence training efficacy (e.g., executive function training and personalized training approaches).

Memory intervention components (level 1) can be further subdivided into *content of memory intervention* and *educative components* (all level 2). Regarding the *content of memory intervention* (level 2), a distinction can be made between *internally applied memory strategies, externally applied memory strategies*, and *practicing distinct memory tasks* (all level 3). *Internally applied memory strategies* (level 3) are defined as memory strategies that do not need any external help or anchor in their execution, and involve mental manipulations to facilitate memory of targeted stimuli such as chunking (i.e., taking individual pieces of information and grouping them into larger units), associations (i.e., making an association between items), categorizations (i.e., grouping items together based on common features), use of rhymes and patterns to memorize information (i.e., creating a rhyme that involves several stimuli), and mental imagery (i.e., eliciting a perceptual experience that occurs mentally in the absence of the appropriate external stimuli; all level 4). *Externally applied memory strategies* (level 3), on the contrary, actively help and/or cue an individual with the information that has to be memorized. This may involve, e.g., using external aids like shopping notes, calendars, placing things in conspicuous places, and asking someone to help you remember (all level 4). *Practicing distinct memory tasks* (level 3) refers to the repetitive execution of diverse standardized tasks with the sole aim to practice and stimulate the function that is probed in that task, for example, by practicing list- or location learning, spaced repetition, or transfer tasks where participants are stimulated to actively practice in everyday situations (all level 4).

Educative components (level 2) is the second sub-category of memory intervention components. Here, we can distinguish between the *material* (level 3) that is used to facilitate transfer of knowledge (e.g., lectures that were given, homework material, self-study material; all level 4), and the *content* of the education (level 3), such as psychoeducation, experiential learning of training content (i.e., learning through exercises that actively facilitate experience with the topic), or traditional learning of training content (i.e., learning course concepts through lectures and reading material; all level 4).

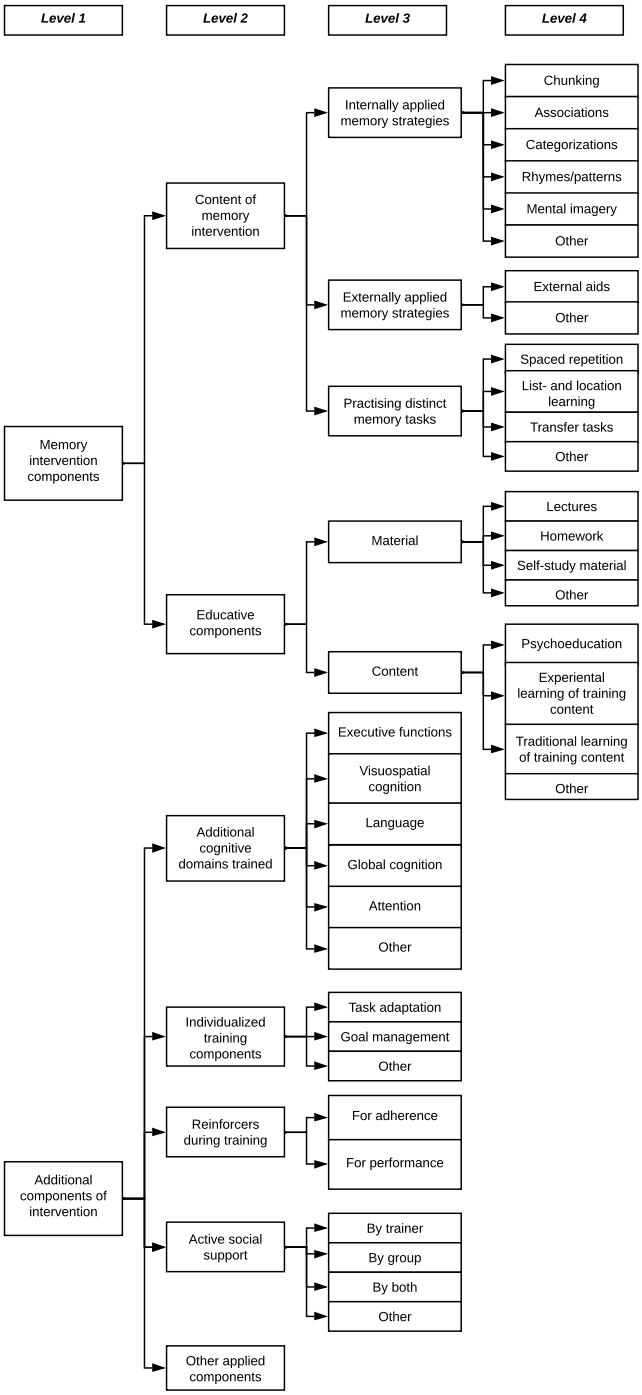

Figure 3. Hierarchical structure of memory intervention components

Additional components of intervention (level 1) can be further classified into *additional cognitive domains trained* (level 2), such as executive functions, visuo-cognition, language, global cognition, attention or other cognitive domains (all level 3), *individualized training components* (level 2), such as individual training task adaptation and individual goal management (level 3), and *reinforcers during training* (level 2), either provided for adherence or for performance at the training (level 3). Furthermore, these additional intervention components could involve *active social support* (level 2), either by the trainer, the group, or both (level 3), and *other additional applied components* (level 2, e.g., physical exercise, medication, reminiscence therapy, etc.).

Translation of category system to COMMIT tool

After transforming the initial category system to the PDF format, we consulted the internal expert panel for feedback. Subsequently, we revised of the COMMIT tool primarily in terms of its lay-out, user-friendliness, and practical aspects. For example, we included sections that allowed for the specification of "title", "goal", "setting" and "description of duration" of the performed intervention. We also included the sections: "trainer and/or therapist qualifications", "training manual", "target group(s)", "language(s) of training", and a section to describe a typical memory intervention session. Although the classification system of COMMIT originates from memory interventions among healthy older adults, the latter sections were incorporated to enable the description of more clinically oriented work. Besides this, to emphasize the relative contribution of different memory intervention components, we incorporated a section that allows to rank these various aspects relatively to each other.

The external validation procedures resulted in feedback from five different external researchers (see Acknowledgments for an overview of the researchers involved). All researchers noted that the COMMIT tool was overall easily-applicable and practical to use. Furthermore, the tool was described to be comprehensive, and the initial classification system remained undisputed. With regards to the adjustment or addition of content, the researchers noted that the duration, reward, and feedback sections could be more thoroughly described, and, therefore, we revised these sections accordingly, for example, by adding the possibility to describe for which measurement instruments feedback was provided. We also clarified the instructions for the corresponding items. Furthermore, to allow for any further comments about the intervention for potential aspects or specifications that were not covered by the previous sections, we added an "other comments" section. As some researchers noted

that they preferred more detailed examples with regards to using COMMIT, we created examples based on existing memory intervention studies. The subsequent version was approved by all involved researchers (internal and external).

The resulting COMMIT tool comprises an interactive PDF with 26 items, some of which include sub-items (Supplementary Material, "COMMIT tool"). In addition, we provide detailed instructions with regards to how each item should be effectively incorporated within the tool (see Table 1). To facilitate the use of the COMMIT, we make the tool, corresponding instructions, and pre-filled examples openly available via OSF (https://osf.io/bg9q8/).

Table 1. Guidelines to fill in the COMMIT tool

Section / Topic	Item	Checklist Item Explanation
Title		
Title	1	Clearly identify your study as a **memory** intervention, directly targeting memory-related outcomes *(instead of, e.g., multidomain cognitive training, working memory intervention, brain training etc.)*.
Goal		
Goal	2	Briefly describe the overall goal of the memory intervention: Which domains are aimed to be improved with the intervention? In which population do you want to use the memory intervention? *[e.g., "improve/maintain verbal long-term memory in healthy older participants"]*
Target group(s)	3	Identify which patient / participant target group the intervention is administered to. *[e.g., "healthy older adults aged > 50 years", "patients with Parkinson's disease"]*
Description of training length		
Description of duration	4	Identify **how many minutes each memory intervention session** lasts**, how many sessions** your intervention consists of per week, **the total duration of all sessions in minutes,** and **the total duration in weeks.** In case the intervention is conducted by the participants in their own speed and time, please tick "self-paced". Note that if an intervention is not provided on a weekly basis, you could calculate the number of sessions per week by dividing the total number of sessions by the total duration of trainings per week to acquire the number of sessions per week (e.g., 6 sessions in total provided every other week for 12 weeks would result in 0.5 sessions per week [6 / 12 = 0.5]). A similar calculation could be made if the duration of each session differs across various sessions.
Booster training	5	Indicate whether your training includes a booster session (tick "booster training" in case it does), and specify the number of booster training sessions in total and the total duration in minutes.

Table 1. Continued

Section / Topic	Item	Checklist Item Explanation
		A booster session aims to review and/or re fresh the content or skills provided throughout an intervention.
Other characteristics	6	Please identify any other characteristics of the training duration that are not covered by the aforementioned duration categories.
Trainer and/ or therapist qualifications	7	Tick "trainer/therapist" if your training is administered by a specific trainer or therapist (rather than self-applied by the participants) and specify the qualification of the trainer *(e.g., "certified trainer", "psychology student with Bachelor degree trained for six weeks")*. Also indicate whether supervision or guidance of the trainers takes place. If a learning tool or training is available for the trainer and/or therapist to perform this particular memory intervention, please indicate this too.
Training manual	8	Indicate whether the training manual is in the developmental stage or already in clinical use (tick the applicable box). Further, specify whether and where the training manual you used is available for use by others, e.g., published and available for clinicians.
Language(s) of training	9	Specify in which language(s) the training is available.
Setting		
Group setting	10	Identify whether the training is performed in an individual setting (single icon), in a group-based setting (several icons), or in a combined setting (single icon + several icon). In case the setting is combined, describe how many minutes per session are conducted in each different setting at the "Other characteristics" of the "Description of duration"-section. *[e.g., mixed setting, first 3 sessions á 60 minutes each in individual settings, 6 sessions á 60 minutes each in group setting]*
Application setting	11	Identify whether the training is home-based (home icon), or performed at a clinical or institutional setting (hospital icon), or in a combined setting (home icon + hospital icon). In case the setting is combined, describe how many minutes per session are conducted in each different setting at the "Other characteristics" of the "Description of duration"-section. *[e.g., mixed setting, first 3 sessions á 60 minutes each in clinical/ institutional setting, 6 sessions á 60 minutes each in home-based setting]*
Application mode	12	Identify whether the training is computerized (computer-icon), or in paper-pencil application modus (book icon), or in a combined application form (computer icon + book icon). In case the setting is combined, describe how many minutes per session are conducted in each different setting at the "Other characteristics" of the "Description of duration"-section.
		[e.g., mixed setting, first 20 minutes of each session in paper-pencil form, 30 minutes of each session computerized]
Supervision of training	13	Identify whether the training is self-administered, or supervised, or in a combined application form. In case the setting is combined, describe how many minutes per session are conducted in each different setting at the "Other characteristics" of the "Description of duration"-section. *[e.g., mixed setting, 20 minutes self-administered preparatory assignments prior to each session, 40 minutes supervised session]*

Table 1. Continued

Section / Topic	Item	Checklist Item Explanation
Memory intervention components		
Ranking of relative contribution of components	14	Provide the relative contribution of the memory intervention components that are included in the memory intervention. The higher the contribution of a particular component, the lower the rank number (i.e., "1." indicates the memory component that was most central in the intervention). If the memory intervention consists only of one memory intervention component, it suffices to only specify the first rank.
Internally applied memory strategies	15	Identify, which **internally applied memory strategies** are part of the memory intervention. You can tick internal memory strategies that are used in the present study, and further specify these in the box below. Note that this is only applicable if the memory intervention incorporates internally applied memory strategies. *[e.g,. "Categorization", Specify: Participants received a list of words and were asked to categorize the words, e.g., "animals", "tools"]*
Externally applied memory strategies	16	Identify, which **externally applied memory strategies** are part of the memory intervention. You can tick external memory strategies that are used in the present study, and further specify these in the box below. Note that this is only applicable if the memory intervention incorporates externally applied memory strategies. *[e.g,. "external memory aids", Specify: Participants were asked to create diary entries about specific events to help them memorize]*
Practicing distinct memory tasks	17	Identify which **distinct memory tasks are practiced** in the memory intervention. You can tick distinct tasks that are used in the present study, and further specify these in the box below. Note that this is only applicable if distinct memory tasks are practiced in the memory intervention. *[e.g., "transfer task", Specify: Participants trained abstract word list learning and were then asked to learn a list of supermarket items]*
Educative component Material/ Content	18	Identify the **content of the educative component(s)** throughout your memory intervention and what **materials are used**. Specify how long the participants approximately spent on the educative component of your training. You can tick contents and materials that are used in the present study, and further specify these in the box below. Note that this is only applicable if the memory intervention contains an educative component. *[e.g,. "Psychoeducation" "Lectures", Specify: Participants received 4 hours of psychoeducation on ageing and memory processes in form of lecturers taught by the training supervisor]*
Additional components of training		
Additional cognitive components trained	19	Identify, which **additional cognitive components are trained** during the memory intervention. Specify which tasks are used to train these components. You can tick the additional cognitive components that are used in the present study, and further specify these in the box below. Note that this is only applicable if the memory intervention contains additional components. *[e.g., "attention", Specify: Attention was trained with a specific version of the Example-Task by Example et al..]*

Table 1. Continued

Section / Topic	Item	Checklist Item Explanation
Individualized	20	Specify whether the training is individualized in any form, e.g. by goal management or task adaptation strategies. *[e.g., the task XY was adaptive, so that it increased its difficulty by one level in case the participant answered correctly]*
Reinforcers during training	21	Specify whether any reinforcers were given during the training. In addition, indicate whether reinforcers were provided for adherence or performance. *[e.g., for each successful training session, participants received a token]*
Active social support	22	Specify whether any active social support is provided during the memory intervention, either by the trainer, the group, both, or other. *[e.g., at the end of each session, participants shared their experiences of the training with the group; the trainer send motivational tips via an online platform]*
Specify other applied components		
Specify other applied components	23	Indicate, whether there are any other additional, non-cognitive training components either simultaneously and/or before/after the memory intervention, such as physical exercise, relaxation training, non-invasive brain stimulation etc. Specify details about frequency, duration, and content of the additional training. *[e.g., the first 20 minutes of each memory intervention session were accompanied by anodal transcranial direct current stimulation.]*
Feedback during the intervention		
Feedback provided during intervention	24	Indicate whether any feedback to the patient or participant was provided during the intervention on adherence or performance. Feedback may have been provided on several outcome types, including near-transfer outcomes, far transfer outcomes, and patient- or subject-reported outcomes. *[e.g., the outcomes of a custom-made progress questionnaire were used to provide feedback on adherence; episodic memory test XY was used to provide feedback on performance]*
Briefly describe a typical memory intervention session		
Briefly describe a typical memory intervention session	25	Provide a brief description of the content covered in a typical memory intervention session. This provides the reader with more contextual information with regards to the organization of the sessions. If appropriate, also indicate how much time was planned for specific tasks. *[e.g,. the memory intervention typically starts with a 15-minute discussion about the homework assignments that were given in theprevious session, subsequently ...]*
Other comments		
Other comments	26	This section may be used for any additional comments about the memory intervention study that were not addressed in any of the other sections and/or to further specify certain components.

Discussion

COMMIT was developed as an easily-applicable interactive tool with detailed instructions and examples, to facilitate a reporting framework that enables researchers to systemize the content and structural aspects of memory interventions. COMMIT is the first tool that takes the heterogeneous nature in the content of memory interventions into account, as its classification system is based on qualitative content analysis of a stratified sub-sample of previously published memory interventions. The studies included in this sub-sample were highly variable in sample size, design, and memory intervention components described, further emphasizing the need for more systematic categorization of such studies. Together with incomplete reporting of memory intervention paradigms, this heterogeneity has led to methodological limitations in determining the efficacy and efficiency of memory interventions in previous studies (Green et al., 2014; Eikelboom et al., 2020; Roheger et al., 2020a). COMMIT aims to tackle these difficulties by providing a categorization system for standardized reporting of memory interventions.

We propose that all memory classification components as listed in COMMIT need to be separately addressed in the main report of memory intervention studies. We additionally encourage to upload the filled-in COMMIT tool as additional material either in the supplementary material or in open data registries (such as OSF; https://osf.io/). A link or reference to the checklist can be provided in the main paper. If it is not possible to describe all memory classification components in the main text (e.g., due to word count restrictions), we recommend uploading the filled-in COMMIT tool as an online supplement. In this way, COMMIT continues to assist researchers in describing all crucial components of a memory intervention study and ensures that other researchers can still easily appraise the memory intervention. Furthermore, we strongly encourage using the instructions and examples in conjunction with the checklist to foster complete, coherent, and transparent reporting.

Although COMMIT addresses the diverse approaches that were incorporated in previous memory interventions, it does not include recommendations for designing, conducting, and analysing trials. Therefore, this tool should be used as an addition to previously established reporting guidelines from the EQUATOR network, for example, the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials (Schulz et al., 2010) and the Strengthening the Reporting of Observational Studies in Epidemiology

(STROBE) statement for observational studies (von Elm et al., 2007). Nevertheless, COMMIT does provide a template for standardized reporting of memory intervention studies which eases the comparison between studies and may also identify missing aspects in the design and/or conduct of a particular study. Potential users of COMMIT thus may not only include researchers and clinicians who conduct memory interventions or who want to synthesize evidence on different memory interventions, but also organizations offering memory interventions, journal editors, manuscript reviewers, and readers who want to get a detailed insight in memory intervention studies. Therefore, COMMIT could serve multiple purposes in the scientific community, not only allowing authors to present memory intervention studies in a transparent yet comprehensible manner, but also by aiding in the critical appraisal of the content of such studies and hence extracting useful information for proper data synthesis in systematic reviews and meta-analyses. In this way, COMMIT may also complement the recently developed Cognition-oriented Treatments Article Library and Evaluation (CogTale), an online repository for cognitive intervention trials which directly facilitates the performance of meta- analyses through its own platform (Sabates et al., 2021).

Although COMMIT focuses on the reporting of memory interventions in cognitive ageing, these interventions are also highly relevant to improve memory functioning in, for example, traumatic brain injury, stroke, multiple sclerosis, and Parkinson's disease (Elliott & Parente, 2014; Taylor et al., 2021; Leung et al., 2015; Kalbe et al., 2020). Furthermore, memory interventions are only one part of the huge range of cognitive training approaches which target, amongst others, the domains of working memory, attention, visuo-cognitive or a mix of all or of some of these domains (Jiang et al., 2017; Mewborn et al., 2017; Parsons et al., 2016; Soveri et al., 2017). COMMIT can be seen as a starting point for the development of classification and reporting recommendations for cognitive trainings across diverse populations, as this research field is embossed with high heterogeneity and complexity (Butler et al., 2018; Roheger et al., 2021; Shani et al., 2021; Traut et al., 2021). Besides this, we emphasize that the COMMIT tool represents an evolving recommendation, which still requires perpetual reappraisal and, if necessary, modifications. Therefore, we would like to encourage the scientific community to focus their future efforts in revising COMMIT.

Taken together, we present an interactive tool that allows for the systematic classification and description of memory interventions: COMMIT - a reporting

framework that enables researchers to report and systemize the content and structural aspects of memory intervention paradigms.

Acknowledgments

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Data availability statement

The latest version of the COMMIT tool is accessible through OSF (https://osf.io/bg9q8/). The version of the COMMIT tool used at the time of publishing is provided in our Supplementary Material. For further details about the total amount of the different memory intervention categories and coding for each individual included study (i.e., code book of qualitative analysis in MaxQDA), please send an e-mail to: Mandy.Roheger@uni-oldenburg.de.

Supplements

Supplementary Methods

Overview of systematic search string

A systematic search was conducted in MEDLINE Ovid, Web of Science Core Collection, CENTRAL, and PsycInfo until 12th November 2019. An updated search was conducted until January, 2021.

Source	Search strings
CENTRAL	"healthy older adults": ti, ab, kw "healthy elderly": ti, ab, kw MeSH descriptor: [Healthy aging] "older adults": ti, ab, kw MeSH descriptor: [Aged] MeSH descriptor: [Aged, 80 and over"] "elderly individuals", ti, ab, kw "cognitive aging": ti, ab, kw "cognitive intervention": ti, ab, kw "cognitive training": ti, ab, kw "brain training": ti, ab, kw "memory training": ti, ab, kw "reasoning training": ti, ab, kw "mnemonic training": ti, ab, kw "training": ti, ab, kw "intervention": ti, ab, kw MeSH descriptor: [Memory] "memory": ti, ab, kw {or #1-#8} {or #9-#16} #17 or #18 #19 and #20 and #21
Medline Ovid	"healthy older adults" [All fields] "healthy elderly" [All fields] "Healthy aging" [MeSh] "older adults" [All fields] "Aged" [Mesh:NoExp] "Aged, 80 and over" [MeSh] "elderly individuals" [All fields] "cognitive aging" [All fields] 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 "cognitive intervention" [All fields] "cognitive training" [All fields] "brain training" [All fields] "memory training" [All fields] "reasoning training" [All fields] "mnemonic training" [All fields] "training" [All fields] "intervention" [All fields] 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17

Source	Search strings
	"memory" [MeSh] "memory" [all fields] 19 OR 20 9 AND 18 AND 21
PsycInfo	exp memory/ exp Aging/ "healthy older adults".mp. "healthy elderly".mp. "older adults".mp. "cognitive aging".mp. "aged (attitudes toward)"/ "cognitive intervention".mp. "cognitive training".mp. "brain training".mp. "memory training".mp. "reasoning training".mp. "mnemonic training".mp. "training".mp. "intervention".mp. exp brain stimulation/ or exp brain training/ 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 2 or 3 or 4 or 5 or 6 or 7 1 and 17 and 18
Web of Science Core Collection	"healthy older adults" [All fields] "healthy elderly" [All fields] "Healthy aging" [MeSh] "older adults" [All fields] "Aged" [Mesh:NoExp] "Aged, 80 and over" [MeSh] "elderly individuals" [All fields] "cognitive aging" [All fields] 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 "cognitive intervention" [All fields] "cognitive training" [All fields] "brain training" [All fields] "memory training" [All fields] "reasoning training" [All fields] "mnemonic training" [All fields] "training" [All fields] "intervention" [All fields] 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 "memory" [MeSh] "memory" [all fields] 19 OR 20 9 AND 18 AND 21

Supplementary Table A. Overview of included studies

	Author	Year	N of the intervention group	Design	Duration of memory intervention	Memory intervention description
1	Yesavage et al.	1983	*n* = 25	Randomized controlled trial with active control.	1.5 hours per session, 2 times a week for 3 weeks.	Face-name mnenomic vs. its combination with initial learning of techniques to improve visual imagery abilities.
2	Flynn and Storandt	1990	*n* = 21	Randomized controlled trial with active and passive control group.	1.5 hours per session, 1 session per week for 4 weeks; completion of manual within 6 weeks.	Self-paced training via bibliotherapy as compared to its combination with participation in supplementary discussion groups.
3	Neely and Backman	1993	*n = 11*	Randomized controlled trial with active and passive control group.	1.5 hours per session, 1 session per week for 10 weeks.	Effects of a multifactorial memory training program (encoding operations, attentional functions, and relaxation) as compared to an unifactorial program (encoding operations).
4	De Vreese et al.	1996	*n* = 9	Randomized controlled trial with active and passive control groups.	1.5 hours per session, 1 session per week for 12 weeks.	The influence of single therapy (drug vs. memory) as compared to combined therapy.
5	Caprio-Prevette & Fry	1996	*n* = 77	Randomized controlled trial with an active control group.	2 hours per session, 1 session per week for 10 weeks.	Cognitive restructuring memory training and traditional memory training, both with additional educational components.
6	Hill et al.	1997	*n* = 17	Randomized controlled trial with placebo control group.	1-1.5 hours per session, 3 sessions over a 2-week interval.	Number-consonant mnenomic provided with a take-home manual and tutor- guided group training sessions.
7	Troyer	2001	*n* = 36	Quasi-experimental with passive control condition.	2 hours per session, 1 session per week for 5 weeks.	Memory education and intervention program with particular focus on everyday memory, in large-group lectures and smaller group discussions.
8	Jobe et al.	2001	*n* = 620*	Randomized controlled trial with active and passive control groups.	1-1.25 hours per session, 10 sessions within a 6-week interval.	Cognitive training, including targeted training on memory functions, reasoning, and speed of information processing.

Supplementary Table A. Continued

	Author	Year	N of the intervention group	Design	Duration of memory intervention	Memory intervention description
9	Woolverton et al.	2001	*n* = 27	Randomized controlled trial with active and waitlist control groups.	4 weeks to complete the program.	Testing the effects of a shorter version of a self- taught memory training program.
10	Dunlosky et al.	2003	*n* = 33	Randomized controlled with active and waitlist control groups.	2 hours per session, 1 session per week for 2 weeks.	Training of self-testing together with sentence generation and interactive imagery (memory mnemonics).
11	O'Hara et al.	2007	*n* = 118**	Randomized controlled trial with active control.**	8 sessions within a 2-week interval.	Mnenomic training, including method-of- loci for recall of a word list and a name association technique. Provided in either a standard or comprehensive version.
12	Hohaus	2007	*n* = 20	Quasi- experimental with passive control group.	3 hours per session, 1 session per week for 5 weeks.	The Optimizing Memory Program (memory training and education) as compared to the Use It or Lose It (active control) program.
13	Carretti et al.	2007	*n* = 13	Randomized controlled trial with active control.	0.5-1 hours per session, 5 sessions within a 2-week interval (fixed interval between sessions of 2 days).	Imagery-based strategy training.
14	Bagwell and West	2008	*n* = 115	Randomized controlled trial with passive and partial control.	2 hours per session, 4 sessions within a 9-week interval, self-completion of homework	Multi-factorial training program focusing on self-efficacy and memory.
15	Buiza et al.	2008	*n* = 153	Quasi- experimental, double-blind design with passive control.	±2 sessions per week for 2 years (total of 180 sessions).	Cognitive training including major memory training component (execution memory, recent word list memory, short-term memory, working memory, learning potential).

Supplementary Table A. Continued

	Author	Year	N of the intervention group	Design	Duration of memory intervention	Memory intervention description
16	West et al.	2008	*n* = 42	Randomized controlled trial with wait-list control.	2 hours per session, 1 session per week for 6 weeks, self- completion of homework.	Multi-factorial training program focusing on self-efficacy and memory.
17	Becker et al.	2008	*n* = 27	Randomized controlled trial with active control.	1-1.5 hours per session, 2 sessions per week for 2 weeks (6 hours in total).	The Cognitive Behavioral Model of Everyday Memory in either or 8 or 4 sessions.
18	Preiss et al.	2010	*n* = 77	Quasi- experimental with passive control.	1 hour per session, 9 sessions within a 6-week interval.	Composite memory intervention program, including learning of mnemonic strategies.
19	Lima-Silva et al.	2010	*n* = 37	Randomized controlled trial with passive control.	1.5 hours per session, 5 sessions.	Cognitive training based on the creation of mental images and changes in metamemory.
20	Gajewski and Falkenstein	2012	*n* = 32	Randomized controlled trial with passive and active control groups.	1.5 hours per session, 2 sessions per week for a period of 4 months.	Different types of group-based and trainer-guided interventions, including a cognitive training with memory component.
21	Cheng et al.	2012	*n* = 33	Randomized controlled trial with active and wait-list control groups.	1 hour per session, 2 sessions per week for 12- weeks.	Multi-domain cognitive training with strategies or techniques to improve memory (e.g., loci memory training, face/name memory training).
22	Wiegand et al.	2013	*n* = 21	Randomized controlled trial with waitlist control.	2 hours per session, 1 session per week for 5 weeks.	The Memory and Aging Program, multi-dimensional training including training and education with regards to memory.

Supplementary Table A. Continued

	Author	Year	N of the intervention group	Design	Duration of memory intervention	Memory intervention description
23	Kwok et al.	2013	*n* = 86	Randomized controlled trial with passive control.	1 session per week for 8 weeks.	The Active Mind training program, including memory training (e.g., mnenomics, method of loci, memory aids).
24	Feng et al.	2014	*n* = 90	Quasi experimental with passive control group.	1 hour per session, 2 sessions per week for 12 weeks.	Cognitive training which targeted multiple domains, including memory (memorizing pictures and words).
25	Engvig et al.	2014	*n* = 22	Randomized controlled trial with passive control group.	1.5 hours per session, 1 session per week for 8 weeks.	Memory training with main focus on improving verbal recall memory with method of loci.
26	Lampit et al.	2014	*n* = 38	Randomized controlled trial with active control group.	0-0.75 hours per session, 36 sessions in a period of 3 months.	A supervised, group- based, multi-domain cognitive training, including a memory component. Based on COGPACK package.
27	Zanjani et al.	2015	*n* = 72	Cohort study.	1-1.5 hours per week, 1 session per week for 4 weeks.	Feasibility of memory banking, a life story development intervention.
28	Candela et al.	2015	*n* = 24	Randomized controlled trial with one active and one passive control group.	1.5 hours per session, 1 session per week for 12 weeks.	Cognitive Training: "Lab I – cognitive empowerment" was designed to increase memory ability in training memory strategies and education on memory impairments.
29	Cavallini et al.	2015	*n* = 16	Randomized controlled trial with an active control group.	5 sessions in a period over 3 weeks.	Self-help memory training program: each participant received a manual with detailed explanations and exercises on the use of mnemonics and memory strategies.
30	Giuli et al.	2016	*n* = 55	Randomized controlled trial with passive control group.	1.5 hours per session, 1 session per week for 10 weeks.	Cognitive enhancement training, including learning and practicing memory strategies for several situations.

Supplementary Table A. Continued

	Author	Year	N of the intervention group	Design	Duration of memory intervention	Memory intervention description
31	Zimmermann et al.	2016	*n* = 36	Randomized controlled trial with active control group.	2 times 15 sessions that had to be completed in 3 weeks.	Process-based object- location memory training in which participants learned object-location tasks.
32	De Lange et al.	2016	*n* = 94	Randomized controlled trial with active and passive control group, cross- over design.	1 session for 10 weeks per group.	Memory training with focus on method of loci, introduction of different memory strategies and learning of word-list tasks.
33	Chapman et al.	2016	*n* = 18	Randomized controlled trial with active control group.	3 hours per week for 12 weeks.	Strategic Memory Advanced Reasoning Training "SMART" trains metacognitive strategies using three core cognitive control functions: attention, integrative reasoning, innovation.
34	Barban et al.	2016	*n* = 384	Randomized controlled trial in a crossover design.	1 hour per session, 2 sessions per week, for 3 months.	Process-based cognitive training combined with reminiscence therapy using a software called SOCIABLE.
35	Bureš et al.	2016	*n* = 37	Randomized controlled trial with active control group.	20-30 minutes per session, 3 sessions per week for 8 weeks.	Cognitive training with focus on memory tasks such as remembering word lists.
36	Bellander et al.	2017	*n* = 19	Randomized controlled trial with active control group.	4 sessions per week for 6 weeks.	Associate memory training including the practice of three different memory tasks.
37	Golino et al.	2017	*n* = 47	Semi- randomized controlled trial with waitlist control.	1-1.5 hours per session, 1 session per week for 12 weeks.	Multi-domain cognitive training with strategies or techniques to improve memory (e.g., visual imagery, face/name memory training).

Supplementary Table A. Continued

	Author	Year	N of the intervention group	Design	Duration of memory intervention	Memory intervention description
38	Unkenstein et al.	2017	*n* = 32	Longitudinal cohort study.	2 hours per session, 2 sessions per week for 4 weeks.	LaTCH Memory Strategies program consisted of group discussions and education on memory and memory problems.
39	Antonenko et al.	2018	*n* = 40	Randomized controlled study with sham-stimulation as control group.	3 sessions on consecutive days.	Visuo-spatial memory training with combined tDCS.
40	Brathen et al.	2018	*n* = 126	Cohort study comparing two groups (young vs. old adults).	1 session per week for 10 weeks and 8 weekly online home assignments.	Memory training involved learning the method of loci to improve episodic memory performance.
41	Ihle et al.	2018	*n* = 126	Randomized controlled study with active control group.	2 sessions per week for 4 weeks.	Imagery training targeted the encoding of the prospective memory intention in the intention-formation phase. Rehearsal training targeted the maintenance of the prospective memory intention in the intention-retention phase.
42	Deng et al.	2019	*n* = 26	Randomized controlled trial with active and passive control groups.	1 hour per session, 2 sessions per week for 12 weeks.	Multi-domain cognitive training with strategies or techniques to improve memory (e.g., loci memory training, face/name memory training).
43	Imaoka et al.	2019	*n* = 31	Randomized controlled trial with active control group.	1 session per week for 12 weeks.	Memory training and additional exercise, focusing on repetition of stories.

N of the memory training group displays the number of subjects that were in the group(s) of interest of a particular memory training study after exclusion or drop-out. *As we used the protocol paper to describe the design, the final number of participants was derived from Willis et al. (2006). **This information was acquired from the parent study as described in Brooks et al. (1993)

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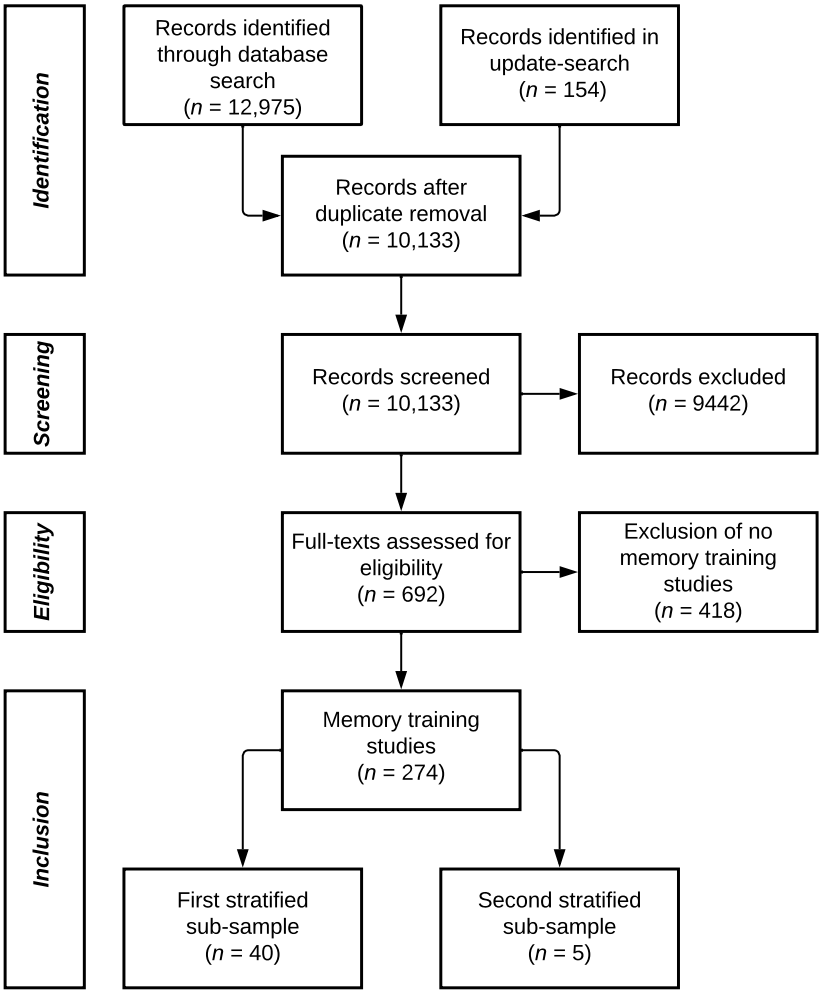


Supplementary Figure A. Flowchart of study inclusion

Supplementary Material. The COMMIT tool

COMMIT

CLASSIFICATION OF MEMORY INTERVENTIONS

"Any cognitive training with a clearly defined memory intervention component, specifically targeting memory-related outcomes"

Scan for examples

Title of memory intervention

Goal

Target group(s)

Setting

Individual vs. Group vs. Combined

Home-based vs. Clinical/institutional vs. Combined

Computerized vs. Paper-pencil vs. Combined

Self-administered vs. Supervised vs. Combined

Description of duration

Self-paced ☐
Number of sessions per week:
Total duration of one session (minutes):
Total duration of all sessions (minutes):
Total duration of training (weeks):

Booster training ☐ Number of sessions in total:
Duration in minutes:
Interval initial training to booster sessions (weeks):

Other characteristics:

Trainer and/or therapist qualifications

Self-administration ☐ Supervision or guidance of trainers ☐
Trainer/therapist ☐ Use of learning tool or training ☐
Specify qualification below:

Training manual

In development ☐
Clinical use ☐
Availability:

Language(s) of training

Memory intervention components

Ranking of relative contribution of components: *e.g., 1) Internally applied; 2) Externally applied; 3)practising distinct tasks etc;* 1. 2. 3. 4. 5.

Internally applied memory strategies

Most commonly used in literature:

Chunking ☐ Rhymes and patterns ☐ Associations ☐
Categorizations ☐ Mental imagery ☐ Other ☐

Specify:

Externally applied memory strategies

Most commonly used in literature:

External memory aids *(e.g. use of lists)* ☐
Other ☐

Specify:

Practicing distinct memory tasks

Most commonly used in literature:

Rehearsal of tasks *(e.g. object-list learning)* ☐ Transfer tasks *(e.g. practice in daily life)* ☐
Spaced repetition *(e.g. spaced retrieval)* ☐ Other ☐

Specify:

Educative component

Material

Lectures ☐ Self-study material ☐
Homework ☐ Other ☐

Specify:

Content

Experimental learning of content *(e.g. group exercises)* ☐ Psychoeducation *(e.g. on aging/memory)* ☐
Traditional learning of content *(e.g. lecture by trainer)* ☐ Other ☐

Specify:

Additional components of intervention

Additional cognitive components trained

Most commonly used in literature:

Executive functions ☐ Language ☐ Attention ☐
Visuospatial cognition ☐ Global cognition ☐ ☐

Specify:

Individualized

Task adaptation ☐ Other ☐
Goal management ☐

Specify:

Reinforcers during training

For adherence ☐
For performance ☐

Specify (e.g., tokens, etc.):

Active social support

By trainer ☐ By both ☐
By group ☐ Other ☐

Specify:

Other applied components (e.g. physical exercise, medication, TMS, reminiscence therapy, etc.)

Specify:

CLASSIFICATION OF MEMORY INTERVENTIONS

Feedback provided during intervention

On adherence ☐

On performance ☐

Specify outcomes and measurement instruments that were used to provide feedback on:

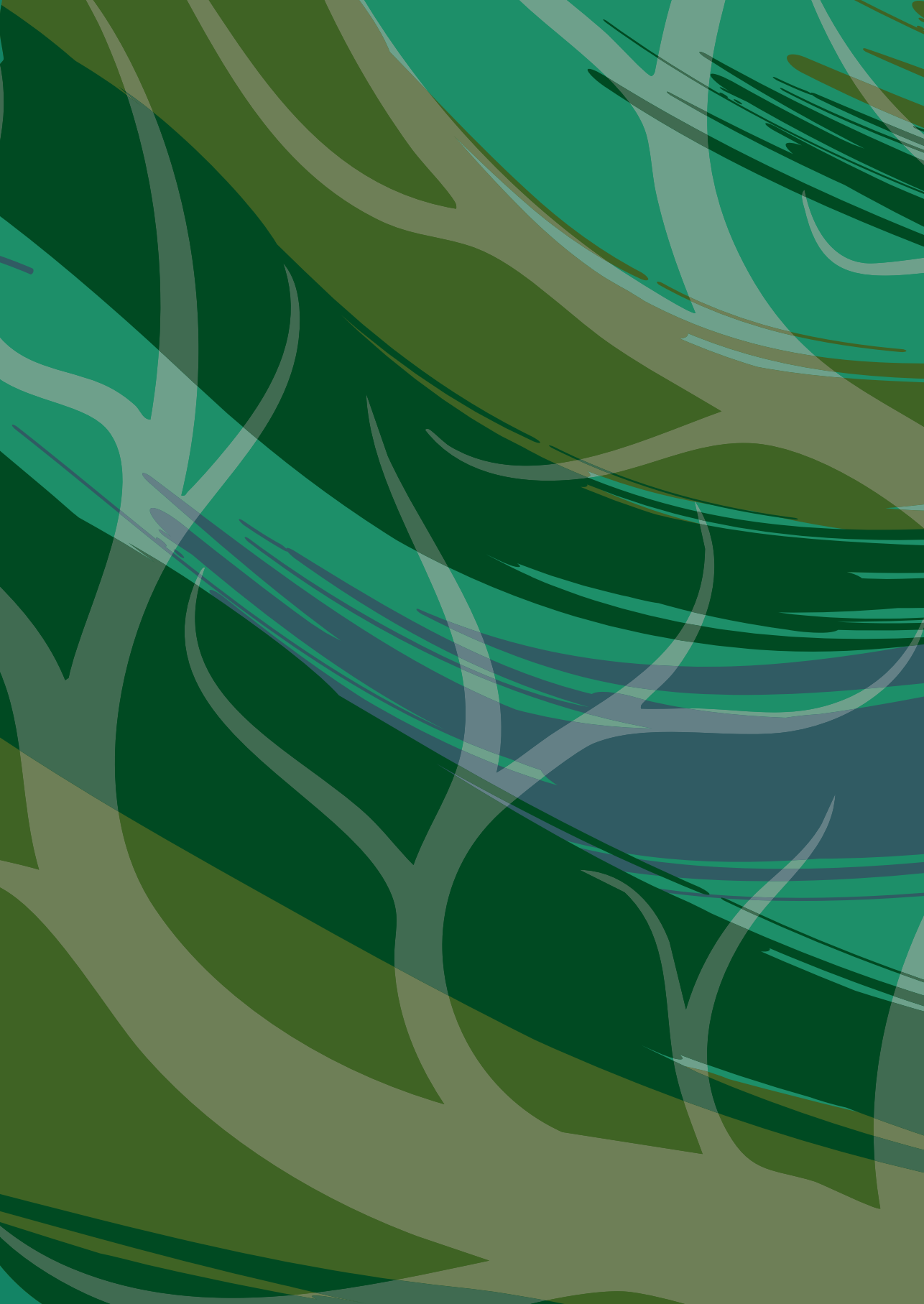
Near-transfer outcomes:

Far transfer outcomes:

Patient- or subject-reported outcomes:

Briefly describe a typical memory intervention session
If appropriate, please indicate how much time is planned for specific tasks

Other comments



General discussion

Chapter 8

Summary and discussion

Cognitive functioning is a key determinant of healthy ageing, and exhibits marked variability across both normal and pathological ageing. The present thesis used this heterogeneity to increase our understanding of cognitive ageing, focusing on the interplay between cognitive functions, brain health, and potentially modifiable factors contributing to risk and resilience (socio-behavioural or lifestyle-related factors). Additionally, this thesis aimed to further advance research on cognitive ageing. An open dataset was introduced to study the underlying mechanisms of risk and resilience in cognitive ageing, an innovative method was employed to better utilize inter-individual variability in the context of fMRI studies, and the standardized reporting of memory interventions was facilitated with an online tool. Reflecting the multifaceted nature of cognitive ageing research, the presented studies considered various study populations (e.g., normal ageing vs. Alzheimer's disease dementia), and applied a wide range of methods (e.g., qualitative content analysis vs. quantitative MRI). This final chapter summarizes the main findings of the presented studies, followed by a discussion on their implications for optimizing cognitive ageing as well as methodological considerations. Finally, an outlook for the future of cognitive ageing research is provided.

Main findings

Part I. Understanding heterogeneity in cognitive ageing

To explain discrepancies in cognitive performance among individuals with similar ageing- related brain changes or neuropathology, it has been suggested that individuals with higher levels of cognitive reserve are less susceptible to the negative effects of these brain alterations. I investigated whether such protective effects persist in advanced age in **chapter 2**. This cross-sectional study included 83 adults between 71-94 years of age that resided in homes for older adults. A composite score of verbal intelligence and educational attainment was used as proxy measure of cognitive reserve. The moderation analyses revealed that with advancing age, performance on the flexibility and fluency tasks decreased, but only among those with relatively low levels of cognitive reserve. In contrast, individuals with average or high levels of cognitive reserve showed no significant effects of age on performance. In conclusion, in the old-old, verbal intelligence and educational attainment exert protective effects on cognitive functions, particularly executive functioning.

In **chapter 3**, I examined whether associations between educational attainment and cognitive functioning varied across several clinical diagnoses, and with

varying degrees of neuropathological burden within a particular diagnosis. Patients with SCD (*n* = 108), MCI (*n* = 190) and Alzheimer's disease dementia (*n* = 245) were included from a cross-sectional memory clinic study. As diagnostic severity increased, the positive effects of education on global cognitive functioning and executive functions decreased. For episodic memory, positive associations were only found in SCD. Additionally, the effects of education on cognitive functioning varied across different degrees of neuropathological burden within specific diagnoses. However, these effects did not survive corrections for multiple comparisons and should be interpreted with caution. Nonetheless, these findings provide a more extensive characterization of the extent to which education positively affects cognitive functioning across various disease states.

Chapter 4 focuses on the dynamics between cognitive functioning, brain health and vascular risk factors. Specifically, I focused on cerebral small vessel disease (SVD) in 623 participants from the Whitehall II Imaging sub-study. SVD severity scores were derived from several MRI markers, including white matter hyperintensities, cerebral microbleeds, lacunes, and enlarged perivascular spaces. Subsequently, SVD burden in late life (mean age 70) was retrospectively related to measures of vascular risk and cognitive functioning obtained at 5-year intervals for up to 25 years prior to the MRI scan. The findings revealed that severe SVD burden in late life was associated with higher mean arterial pressure already in midlife, as well as accelerated trajectories of cognitive decline from mid-to-late life. SVD burden also related to other concurrent measures of brain health, including widespread reductions in grey matter volumes and reduced white matter microstructural integrity. These findings indicate that managing vascular risk in midlife may be a viable target for intervention studies aimed at optimizing healthy ageing.

Part II. Advancing research on cognitive ageing

To better understand cognitive ageing, an extensive characterization of the brain is needed, along with other factors related to risk and resilience, such as socio-behavioural and lifestyle-related factors. Several large neuroimaging datasets have been publicly released, further accelerating this line of research. **Chapter 5** aimed to add to these existing datasets with the Advanced BRain Imaging on ageing and Memory (ABRIM) study. ABRIM provides a cross-sectional database of 295 adults between 18-80 years of age, evenly distributed in age and sex. Beyond conventional neuroimaging sequences, several quantitative imaging methods were included for a more

comprehensive characterization of the ageing brain, such as quantifying myelination and iron depositions. Participants also underwent comprehensive cognitive and behavioural assessments, covering different cognitive domains and other factors relevant to understand resilience in ageing (e.g., depressive symptoms, educational attainment, occupational complexity, leisure activities). Actigraphy data was included from a sub-sample (n = 120), measuring sleep-wake rhythms. As part of the ABRIM MRI collection, the pseudonymized MRI data were released, including raw and pre-processed images, derivatives, quality metrics, as well as the corresponding code. The ABRIM behavioural collection will be made available in the future, including the cognitive, behavioural and actigraphy measures. The publicly shared ABRIM data repositories will hopefully support researchers in further elucidating the underlying mechanisms of heterogeneity in cognitive ageing across the adult lifespan.

When investigating the relationship between functional activity and cognitive outcomes, it is typically assumed that most individuals recruit comparable brain regions while performing a certain task (one-to-one mapping). In **chapter 6**, I revisited this assumption by exploring the possibility that cognitive performance may be supported through multiple neural pathways, also referred to as brain degeneracy. This study focused on visual-short term memory (VSTM) in 113 participants, between 23-87 years of age, from stage III of the Cam-CAN study. First, seven groups of brain regions (i.e., brain modules) were identified with similar inter-individual variability during the task. Subsequently, latent profile analysis was applied, identifying four subgroups with different recruitment patterns of these brain modules. While these subgroups did not differ in age or task performance, several distinct associations between brain modular activity and task performance were observed across the subgroups. This suggests that there indeed may be multiple routes towards successful cognitive performance, corroborating the concept of brain degeneracy. Additionally, white matter integrity differed across subgroups, suggesting that differences in brain morphology might be related to this variability in brain activity.

While memory interventions have been frequently studied in the context of both normal and pathological ageing, their efficacy has proven to be difficult to determine, partially due to the diverse protocols and inconsistent study reports. **Chapter 7** addressed this issue by introducing the Classification Of MeMory InTerventions (COMMIT) tool. To derive a categorization system of

the different memory intervention components, qualitative content analysis was applied on a stratified sample of memory intervention studies published between April 1983 and July 2020. This approach allowed us to capture memory intervention components used in previous studies in all their diversity. The categorization system was then converted into an interactive format and further refined through internal and external validation procedures. The resulting COMMIT tool comprises a standardized reporting framework for memory intervention studies as well as a comprehensive guide on its use. Therefore, COMMIT facilitates standardized reporting of memory intervention studies, which could also ease the systematic comparisons of these studies.

Understanding cognitive ageing

Normal versus pathological ageing

Inter-individual variability in cognitive ageing is partly attributed to differences in brain health (Nyberg & Pudas, 2019; Turrini et al., 2023). Brain health is influenced by multiple factors, including normal ageing-related changes, neurodegenerative disease, and cerebrovascular disease, which rarely occur in isolation (Boyle et al., 2018; Wilson et al., 2023). This co-occurrence was also evident in our studies. For example, in chapter 3, medial temporal lobe atrophy, global atrophy, as well as white matter hyperintensities frequently co-occurred in SCD, MCI and probable Alzheimer's disease dementia. In chapter 4, severe SVD burden was prevalent in approximately 10% of a sample of community-dwelling older adults and concurred with reduced white matter integrity as well as grey matter volumes, a finding that is consistent with previous studies (Heinen et al., 2020; Muñoz Maniega et al., 2017; Wardlaw et al., 2019). In turn, these structural brain changes overlap with those that are typically associated with older age itself (Bethlehem et al., 2022; MacDonald & Pike, 2021). Given that brain regions prone to ageing-related changes are also those that are more vulnerable for pathological processes, it has proven to be difficult to distinguish normal ageing-related brain changes from pathology (Fjell et al., 2014). Therefore, brain health may be better understood as a spectrum, where there is not a clear-cut boundary between "normal" and "pathological" (Woodward et al., 2024).

Although the severity of brain atrophy is typically linked to neurodegenerative disease, such as Alzheimer's disease (Fjell et al., 2014; Pini et al., 2016), SVD is increasingly recognized as an independent contributor (Duering et al., 2023). Brain regions affected by SVD and Alzheimer's disease show considerable

overlap, including the medial temporal lobes (Jokinen et al., 2020), although some variations have been reported across studies (Heinen et al., 2020; Lambert et al., 2016). Chapter 4 demonstrated that the association between SVD burden and reduced white matter integrity was more pronounced in individuals with cognitive impairments, whereas the negative relationship between SVD burden and grey matter volume did not vary depending on cognitive status. This underscores the importance of white matter integrity in explaining cognitive deficits in the context of SVD (Pasi et al., 2016; Tuladhar et al., 2015), even beyond conventional MRI markers of SVD, such as white matter hyperintensities, cerebral microbleeds, and lacunes (Konieczny et al., 2021).

Nonetheless, this does not imply that brain atrophy is irrelevant for SVD-related cognitive decline. On the contrary, brain atrophy has been consistently shown to be a key contributor to cognitive dysfunctions in SVD (De Guio et al., 2020; Jokinen et al., 2020). However, as brain atrophy results from both SVD and Alzheimer's disease, the effects of brain atrophy on cognitive functioning may be better understood when considered in the context of both conditions, rather than in relation to SVD burden alone (De Guio et al., 2020). The precise relationship between Alzheimer's disease and SVD, as well as their concurrent impact on the brain and cognitive functioning is a topic of further investigation (Koncz & Sachdev, 2018; Roseborough et al., 2017). For example, it has been suggested that SVD-related damage and Alzheimer's disease synergistically affect cognitive functioning (Dupont et al., 2020; van Leijsen et al., 2019). However, several studies merely identified additive or independent effects of these conditions on cognition (Legdeur et al., 2019; Roseborough et al., 2017; Vemuri et al., 2015). This emphasizes the need to study how these different dimensions of brain health are interrelated and precisely affect cognitive outcomes. This approach also has been embraced by the recently revised National Institute on Ageing and Alzheimer's Association (NIA-AA) framework, which now emphasizes the need to study Alzheimer's disease in the context of co-pathologies, including vascular injury (Jack Jr. et al., 2024).

From brain structure to function

Another important dimension of heterogeneity in cognitive ageing involves the functional organization of the brain, which is characterized by a stable intrinsic architecture where functional networks, such as the frontoparietal control network and default mode network, support cognitive functioning (Power et al., 2011; Raichle, 2015; Yeo et al., 2011). Chapter 6 identified subgroups of participants with varying recruitment patterns of these networks during a VSTM

task. This aligns with previous research that demonstrated consistent inter-individual differences within this robust functional architecture (Finn et al., 2015; Gratton et al., 2018; Seitzman et al., 2019). Despite these different brain activity profiles, no differences were observed in VSTM task performance. This supports the notion of brain degeneracy, where multiple neural routes can lead to similar behavioural outcomes (Edelman & Gally, 2001; Price & Friston, 2002). While performance was equal across subgroups, there were several subgroup-specific associations between network activity and task performance, suggesting that the recruitment of specific brain networks benefited some subgroups but not others. This contrasts with the common assumption in most fMRI studies that most individuals demonstrate similar recruitment patterns during a given task, where brain activity patterns are averaged across groups of participants (Poldrack et al., 2017). As the proportion of individuals with specific brain-cognition associations may vary across studies, averaging these patterns across participants could contribute to inconsistencies in study findings (Seghier & Price, 2018; Westlin et al., 2023).

The use of different neural pathways during task performance may be partially shaped by individual variations in the structural architecture of the brain, as this is largely intertwined with its functional organization (Fotiadis et al., 2024; Park & Friston, 2013; Suárez et al., 2020). In line with this, ageing has been associated with differences in task-related functional activity (Cabeza et al., 2018; Grady, 2012), which in turn have been attributed to ageing-related changes in brain structure (Burzynska et al., 2015; Capogna et al., 2022; Jauny et al., 2024; Salami et al., 2012). In chapter 6, several subgroup differences were observed for white matter integrity, suggesting that this factor contributed to the variability in brain activity profiles. However, no subgroup differences were observed in terms of age. It should be noted that previous studies revealed that age differences are more strongly linked to the overall responsiveness of the brain rather than network-specific activity (Mitchell et al., 2023; Samu et al., 2017). As the study in this thesis specifically focused on network-specific activity, this might explain why no age differences were found between subgroups. Importantly, this does not rule out ageing as a contributor to the use of different neural pathways to complete a certain task; rather, this simply may have been overlooked in the current analysis.

From a theoretical perspective, there are multiple ways in which brain degeneracy could take form in older age that also align with existing models of cognitive ageing. Some older individuals may use neural mechanisms that

more closely resemble those of younger adults, consistent with the notion of brain maintenance (Nyberg et al., 2012). In contrast, others may achieve similar cognitive outcomes through the use of alternative neural pathways when the primary circuit is disrupted (Seghier & Price, 2018), aligning with the revised Scaffolding Theory of Ageing and Cognition (STAC-R) or cognitive reserve theory (Oosterhuis et al., 2022; Reuter-Lorenz & Park, 2014; Stern et al., 2023). Importantly, the precise neural pathway used to support cognitive performance can vary from person to person, as well as their efficacy. The identification of other individual-specific factors that drive the use of different neural pathways beyond brain structural differences could provide additional insights into these processes, especially as the correspondence between brain structure and function has been shown to decrease with advancing age (Liu et al., 2024). Examples of these factors may include differences in strategies (Miller et al., 2012; Sanfratello et al., 2014), or task engagement (Magen, 2017; Rose, 2020). While chapter 6 illustrates how brain degeneracy provides valuable insights into variability in brain-cognition associations in a broad sense, this concept could certainly help to understand heterogeneity in cognitive ageing.

The role of potentially modifiable factors

Another central theme in this thesis involved increasing our knowledge of the role of potentially modifiable factors in cognitive ageing, offering insights that could aid in the development of intervention or prevention strategies. In chapter 4, higher mean arterial pressure was linked to greater burden of SVD in late life; however, this was not the case for other vascular risk factors (i.e., body mass index or the Framingham Stroke Risk score). This aligns with the notion that hypertension in particular contributes to SVD-related damage (Wardlaw et al., 2013). Hypertension also has been identified as an aggravator of Alzheimer's disease pathology (Iadecola & Gottesman, 2019). The underlying mechanisms of these effects include dysregulated cerebral blood flow, causing alterations in the microvasculature of the brain as well as disruptions of the blood-brain barrier (Pacholko & Iadecola, 2024; Ungvari et al., 2021). Given the substantial impact of hypertension on brain health, this factor is considered as one of the most important risk factors for cognitive decline (Iadecola et al., 2016; Livingston et al., 2024; Norton et al., 2014).

The findings from chapters 2 and 3 align with prior research showing that educational attainment and verbal intelligence are associated with better cognitive outcomes overall, even at advanced age or in the presence

of neurodegenerative disease (Boyle et al., 2021; Seblova et al., 2020; Staekenborg et al., 2020). While chapter 2 showed that the protective effects of a composite measure of educational attainment and verbal intelligence on cognitive functioning was still evident in advanced age, chapter 3 focused on the extent to which such effects are sustained depending on underlying disease severity. It has been hypothesized that some degree of neuropathological burden should be present for protective effects or compensatory processes to occur (Barulli & Stern, 2013; Gregory et al., 2017; Stern, 2009). As neurodegeneration continues to progress, the protective effects eventually reach their limit and subsequently start to diminish, reflecting an inverted U-shaped relationship (Gregory et al., 2017; Staekenborg et al., 2020). While neuropathological burden strongly correlates with age and the severity of cognitive impairments, this varies considerably across individuals with the same clinical diagnosis (Kapasi et al., 2017; Power et al., 2018), as well as study cohorts (e.g., community-based vs. clinical cohorts) (Schneider et al., 2009). In our study, the positive effects of educational attainment decreased or even completely disappeared with increasing severity of clinical diagnosis (i.e., SCD, MCI and Alzheimer's disease dementia). Within SCD and MCI, the effects of educational attainment on cognitive functioning were differentially moderated by the degree of neuropathological burden. Collectively, these findings suggest that the effects of education on cognitive performance depends on clinical status and neuropathological severity. This supports the idea that socio-behavioural factors – such as educational attainment – contribute to reducing the negative effects of ageing or neuropathology on cognitive functioning only under specific circumstances (Gregory et al., 2017; Nyberg et al., 2020; Staekenborg et al., 2020). Therefore, it is important to consider the underlying disease severity to understand contradictory findings regarding the role of educational attainment in cognitive performance (Groot et al., 2018; Staekenborg et al., 2020), as well as differences in trajectories of cognitive decline (Seblova et al., 2020).

It is evident that these socio-behavioural and lifestyle-related factors are useful in understanding why cognitive ageing is highly variable. However, determining the way in which such factors should be addressed in intervention (or prevention) strategies to optimize cognitive ageing is a different question. One possibility involves "simply" increasing the factors that contribute to cognitive maintenance (e.g., educational attainment), while decreasing those that elevate the risk of cognitive decline (e.g., hypertension). Besides from considering the extent to which these factors are truly modifiable

(e.g., and not genetically determined) (Harris & Deary, 2011; Krapohl et al., 2014; Loeffler, 2021), it is important to establish the optimal timing of such interventions (Kivipelto et al., 2018). For example, educational attainment and crystallized intelligence are predominantly shaped in early life (Deary et al., 2012; Ritchie & Tucker-Drob, 2018), suggesting that these are less viable targets for interventions later in life. In contrast, lifestyle-related factors evolve more dynamically throughout the adult lifespan, such as blood pressure (Ji et al., 2020). Notably, cognitive impairments in older age have been shown to relate more strongly to midlife than late-life blood pressure (Iadecola & Gottesman, 2019; Ungvari et al., 2021). In line with this, chapter 4 showed that the association between severe SVD burden and elevated mean arterial pressure was present from midlife onwards, while SVD burden also related to steeper rates of cognitive decline. Similar results have been found for other vascular risk factors, including obesity (Fitzpatrick et al., 2009; Singh-Manoux et al., 2012) and hypercholesteremia (Benito-León et al., 2015; Iwagami et al., 2021; Solomon et al., 2009). This suggests these lifestyle-related factors should ideally be addressed in midlife to reduce the risk of cognitive decline and dementia (Iadecola et al., 2016; Livingston et al., 2024), if not earlier (Walhovd et al., 2023).

It should be noted that evaluating the effectiveness of interventions applied in midlife is extremely challenging as this would involve decades of longitudinal data, ideally acquired in the context of a randomized-controlled trial, which is not ethically feasible (Suresh, 2011). Additionally, prior research has shown that multi-domain lifestyle interventions and cognitive rehabilitation applied later in life can positively affect cognitive functioning (Gavelin et al., 2021; Kelly et al., 2014; Noach et al., 2023), and reduce the risk of dementia (Bott et al., 2019; Meng et al., 2022). This suggests that interventions in late life do have potential to optimize cognitive ageing. However, their efficacy may be limited to specific subgroups of participants. For instance, the positive effects of multi-domain lifestyle interventions have been established among individuals at risk of cognitive decline (Chhetri et al., 2018; Kivipelto et al., 2018) or those with untreated hypertension prior to the intervention (Moll van Charante et al., 2016). Furthermore, the benefits of cognitive rehabilitation approaches have been linked to differences in baseline cognitive resources (Cavallini et al., 2019; Guye et al., 2017). However, whether individuals with lower or higher cognitive resources demonstrate the greatest benefits may depend on the specific type of intervention (e.g., strategy-based vs. process-

oriented approaches) and warrants further investigation (Cavallini et al., 2019; Lövdén et al., 2012; Traut et al., 2021).

Consequently, another possibility to address socio-behavioural and lifestyle-related factors in intervention strategies to optimize cognitive ageing involves investigating the extent to which such factors could be used to determine which intervention works best and for whom. In this context, chapter 7 introduced the COMMIT tool to provide a framework of standardized reporting for memory interventions. This makes it easier to aggregate findings from different studies and thereby could aid in conducting systematic review and meta-analyses focusing on the role of these individual-specific factors in intervention success. To fully leverage the potential of personalized interventions, this also requires an understanding of the underlying mechanisms of intervention efficacy (Fuellen et al., 2015). Additionally, tailoring interventions to an individual's needs or goals may help to increase intervention engagement, which in itself is a major criterion of success (Li et al., 2024; Ngandu et al., 2022).

Methodological considerations

To investigate inter-individual variability in cognitive ageing, rigorous methodological choices are instrumental to balance the validity and reliability of research with its feasibility, inevitably imposing constraints on the study design, analyses, and interpretation of findings. For example, the use of neuropsychological tests is crucial to obtain valid measures of cognitive functioning (Kessels & Hendriks, 2023; Lezak et al., 2012). In this thesis – as in most research – decisions to incorporate specific tests were not only based on their validity, but also involved practical considerations, such as the time to administer the test, availability of normative data, and access to the test itself. While neuropsychological assessments involve the use of multiple tests for a detailed evaluation of different cognitive domains, cognitive screening tests allow for the rapid assessment of global cognitive functioning (Kessels & Hendriks, 2023). For example, in chapter 4, the MoCA was used to detect the presence of cognitive impairments, following the conventional cut-off score (MoCA < 26) (Nasreddine et al., 2005). The MoCA has been shown to outperform other cognitive screening tests in detecting cognitive impairments, including the Mini-Mental State Examination (Siqueira et al., 2018; Tsoi et al., 2015). However, it should be noted that the conventional cut-off does not adequately correct for the effects of demographic variables, such as age or educational attainment (Kessels et al., 2022). Therefore, the lower MoCA scores in this sample of relatively older adults may be better explained by age

itself rather than the presence of actual cognitive impairments (Engedal et al., 2022; Kessels et al., 2022). This emphasizes the need to replicate the findings of chapter 4 in the context of appropriate normative data, as well as using multiple neuropsychological tests to more comprehensively capture SVD-related cognitive decline (Hamilton et al., 2021; Salvadori et al., 2023).

The concept of cognitive reserve has facilitated numerous studies that improved our understanding of variability in cognitive ageing (Chapko et al., 2018; Nelson et al., 2021; Opdebeeck et al., 2016; Pinto et al., 2024). In chapter 2, a composite measure of verbal intelligence and educational attainment was considered as a proxy measure for the concept of cognitive reserve, similarly to prior research (Harrison et al., 2015; Opdebeeck et al., 2016; Pinto et al., 2024). Despite several consensus meetings (Stern et al., 2023; Stern et al., 2020), it remains controversial how the concept of cognitive reserve should be operationalized in research (Elman et al., 2022; Kremen et al., 2022; Pinto et al., 2024). One important consideration is that the procedure of grouping factors such as educational attainment and verbal intelligence together under the umbrella of cognitive reserve could obscure the nuances in how these might differentially contribute to cognitive aging. For example, it has been suggested that verbal intelligence may more closely reflect the capacities of an individual to counteract ageing-related brain changes or neuropathology than other commonly used proxy measures of cognitive reserve, such as educational attainment (Malek-Ahmadi et al., 2017; van Loenhoud et al., 2020), occupational complexity, leisure activities, and physical activity (Boyle et al., 2021). Our understanding of cognitive ageing is reflected by our ability to predict cognitive functioning; however, improving the predictive value of socio-behavioural or lifestyle-related factors involves acknowledging that these represent distinct characteristics (e.g., verbal intelligence ≠ educational attainment), modelling their individual contributions to cognitive functioning, as well as examining how these effects depend on other factors, such as age or brain health (Elman et al., 2022).

This thesis primarily used cross-sectional studies to investigate heterogeneity in cognitive ageing. There are several advantages associated with the use of cross-sectional study designs over longitudinal ones (Mann, 2003). As participants are only tested once, cross-sectional studies are more feasible to conduct, especially when this concerns comprehensive assessment procedures among large samples. Additionally, there is an absence of practice effects, whereas in longitudinal studies repeated testing could mask the true

cognitive decline due to familiarity with the tests or test procedures in general (Wilson et al., 2002). It also has been suggested that cross-sectional studies may more closely capture the true pattern of ageing-related cognitive decline than longitudinal studies (Salthouse, 2019). However, it should be noted that findings from cross-sectional studies are influenced by cohort effects, where variability in cognitive functions results from generational factors rather than ageing- related cognitive decline (e.g., differences in educational opportunities or healthcare access) (Merten et al., 2022; Salthouse, 2014). Additionally, cross-sectional studies merely inform on the correlation between variables at a specific timepoint. Although this has proven to be valuable in informing on the mechanisms of effects and potential interventions (Spector, 2019), longitudinal designs are warranted for to obtain a comprehensive picture of cognitive ageing. For example, only multiple measurements in time allow us to distinguish overall levels of brain or cognitive health from their maintenance or decline, dissect the temporal dynamics between potentially modifiable risk factors, brain health and cognitive functioning; and evaluate the effectiveness of interventions (Livingston et al., 2024; Nyberg & Pudas, 2019; Walhovd et al., 2023).

The need to replicate the presented results to ensure their reliability has been emphasized throughout this thesis (Pashler & Wagenmakers, 2012; Poldrack et al., 2017). To enhance the reproducibility of the presented studies, availability to the original data and code is provided wherever possible, as guided by the FAIR (Findability, Accessibility, Interoperability, and Reusability) principles (Wilkinson et al., 2016) (see Research Data Management for more details). Asides from increasing the sample size to ensure sufficient power to detect true effects (Button et al., 2013), this should also involve enhancing the representativeness of the population (Kopal et al., 2023; Wig et al., 2024). The present studies focused on participants that were included from Western, Educated, IndustRialized, and Democratic (WEIRD) societies, these findings are not generalizable to non-WEIRD populations (Henrich et al., 2010). Within the context of WEIRD societies, the representativeness of the study samples is also questionable. For example, the exclusion criteria of the ABRIM study (chapter 5) likely have resulted in the recruitment of relatively more healthy participants (e.g., no MRI contraindications or presence of psychiatric or neurological disorders). Beyond these formal criteria, informal barriers or constraints could also refrain an individual from participating (e.g., time availability or mobility restrictions). As the recruitment strategy in ABRIM largely relied on convenience sampling, these effects were likely

amplified, further compromising the representativeness of the study (Brodaty et al., 2014; Pruchno et al., 2008). As illustrated in this thesis, sufficient inter-individual differences are crucial to understand cognitive ageing. Therefore, focusing on narrow populations does not only limit the generalizability of study findings but also restricts our ability to uncover the underlying mechanisms of cognitive ageing (Wig et al., 2024).

An outlook for the future of cognitive ageing research

This thesis aimed to increase our understanding of cognitive ageing by focusing on the role of brain health, lifestyle-related variables, and socio-behavioural factors in explaining variability in cognitive functioning. As discussed in the previous sections, the impact of these variables on cognitive functioning could depend on each other, vary substantially from person to person, and may change across the lifespan itself. This multifaceted nature of cognitive ageing as well as the complex dynamics between these diverse factors has been acknowledged by the life course model of STAC-R (Reuter-Lorenz & Park, 2024). Briefly, this model suggests that throughout our lives (i.e., life course experience), we are subjected to different factors that either enrich or deplete neural resources, which in turn influence cognitive performance through their effects on brain health (i.e., brain structure and function), and compensatory scaffolding (i.e., adaptability of the brain in the face of cognitive challenges). Examples of such factors include genetics, educational opportunities, physical activity, and neurodegenerative disease, and their impact may vary across the lifespan (Reuter-Lorenz & Park, 2014, 2024).

The life course model of STAC-R from Reuter-Lorenz and Park (2024) is displayed in Figure 1, highlighting the key findings of the present thesis. Briefly, chapters 2 and 3 demonstrated that higher educational attainment and verbal intelligence were linked to improved cognitive outcomes, even among individuals of advanced age. However, the extent to which such protective effects are sustained depends on the severity of cognitive deterioration and neuropathology. Additionally, chapter 4 demonstrated that elevated blood pressure – already from midlife onwards – was linked to more severe SVD burden later in life, as well as reduced white matter integrity and grey matter volumes. Collectively, these findings highlight the interrelatedness of brain health, life course experience (e.g., educational attainment or blood pressure), and cognitive functioning, as outlined in the STAC-R model.

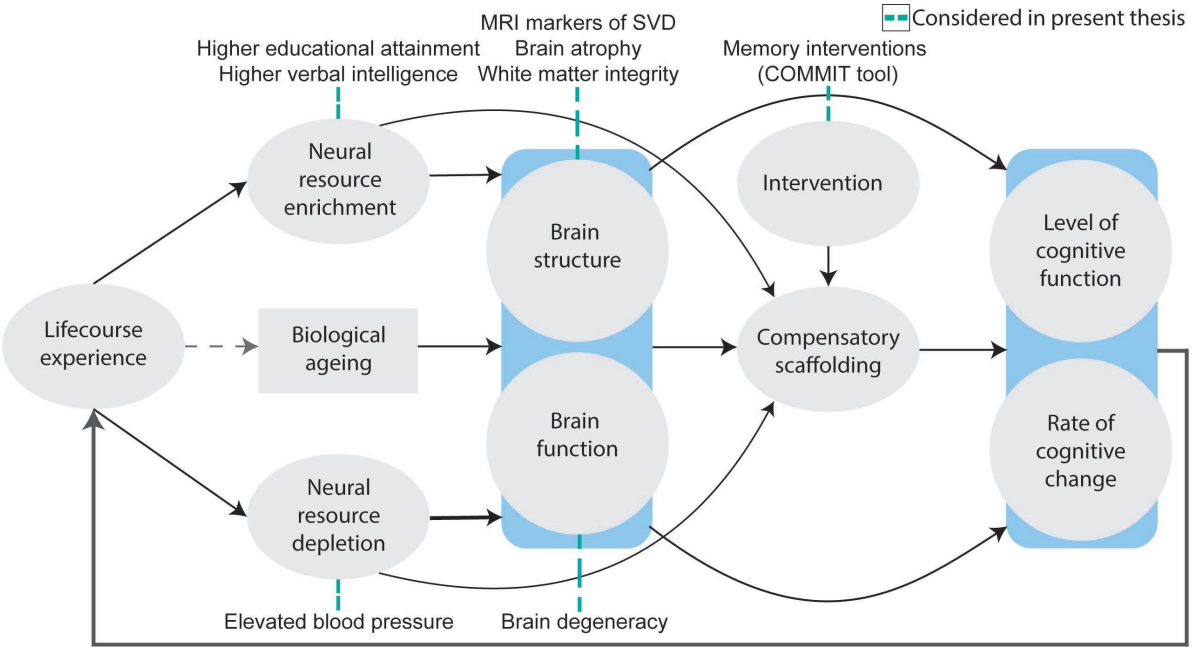


Figure 1. The life course model of the Scaffolding Theory of Aging and Cognition (adapted from Reuter- Lorenz and Park, 2024). The green dotted lines indicate the topics that were highlighted in the present thesis. Life course experience (e.g., exposure to genes, socio-behavioural and lifestyle-related factors) influences brain health and compensatory scaffolding through neural resource enrichment or depletion. Together, these variables shape cognitive performance. This thesis aligns with the STAC-R framework by showing that higher educational attainment and verbal intelligence are linked to improved cognitive outcomes, even in the old-old. However, the extent to which these effects are sustained depends on the severity of cognitive deterioration and neuropathology, which could vary considerably across populations (e.g., normal ageing versus Alzheimer's dementia). In contrast, elevated blood pressure was linked to increased SVD burden and compromised white matter integrity and grey matter volumes. This thesis also showed that different neural activity patterns, thereby reflecting brain function, could underlie successful visual short-term memory performance. Additionally, the use of these distinct activity patterns related to differences in white matter integrity. Lastly, the COMMIT tool that was introduced in this thesis could be used to investigate the effectiveness of memory interventions within this framework.

It could be argued that STAC-R also allows for the possibility that successful cognitive performance could be supported through multiple neural pathways (i.e., brain degeneracy). First, the model suggests that brain function underlies cognitive functioning, relates to brain structure, and is influenced by life course experience. This also implies that variations in life course experience could contribute to differences in neural activity patterns to complete a certain task. Supporting this, chapter 6 showed that different neural activity patterns (i.e., brain function) could underlie visual short-term memory performance, which in turn related to differences in white matter integrity. Second, brain degeneracy can also be reflected through compensatory scaffolding, as the use of different neural routes may become evident when the primary circuit is compromised by ageing-related brain changes or neural damage (Seghier & Price, 2018). As discussed previously, although this thesis did not directly address compensatory processes in cognitive ageing, recognizing that these processes could vary from person to person could provide further insights into cognitive ageing. Beyond the recruitment of alternative neural pathways, STAC-R suggests that compensatory scaffolding can also involve other processes, such as enhanced recruitment of existing neural pathways or neurogenesis. Furthermore, compensatory scaffolding is shaped by individual variations in brain health (e.g., white matter integrity) and life course experience (educational attainment), as well as intervention paradigms. In this context, the COMMIT tool, as introduced in chapter 7, can also be used to investigate the effectiveness of memory interventions from a more mechanistic perspective. For example, specific intervention components (e.g., strategy-based versus process-based approaches) may differentially support compensatory scaffolding, with some contributing to increased engagement of the frontoparietal regions (e.g., Simon et al., 2020) and others enhancing hippocampal volumes (e.g., Bråthen et al., 2022). Additionally, life course experience may also shape how interventions influence compensatory scaffolding, such as the severity of neurodegenerative disease (van Balkom et al., 2020).

Taken together, the life course model of STAC-R provides a valuable framework to advance the study on cognitive ageing. It allows researchers to investigate the diverse factors contributing to risk and resilience from a dynamic perspective and recognizes that "one-size- fits-all" is not applicable when it comes to cognitive ageing. However, in practice, investigating the complex dynamics among multiple variables requires the use of large datasets to ensure sufficient statistical power (Button et al., 2013; Bzdok & Yeo, 2017; Genon et al., 2022; Marek et al., 2022). Ideally, this would also concern longitudinal

studies to dissect how the interactions between life course experience, brain health, compensatory scaffolding, and cognitive functioning unfold over time (Livingston et al., 2024; Walhovd et al., 2023).

The availability of neuroimaging datasets that can be used to study cognitive ageing research has rapidly grown in the past decades, although this primarily concerns cross-sectional studies (Madan, 2022; Niso et al., 2022). These data sharing initiatives have substantially contributed to cognitive ageing research, providing researchers with direct access to large datasets as well as with the possibility to the aggregate data across multiple studies (Laird, 2021; Madan, 2022). To complement already existing databases that could be used to dissect the neurocognitive mechanisms of ageing, chapter 5 introduced the ABRIM study. However, data sharing comes with its own challenges. For example, what is the optimal balance between data sharing, privacy legislations, and ethical considerations? Which infrastructure should be used for data management and sharing? How to ensure that the dataset truly adheres to the FAIR principles? How can I sufficiently address these questions while I am busy with unravelling the building blocks of cognitive ageing itself? Although the ABRIM MRI collection has been a collaborative effort between a multidisciplinary team of researchers, data stewards, local privacy officer, these questions remained imperative. This illustrates that the adoption of open science goes beyond acknowledging its importance for scientific progress; it requires addressing technical and legal challenges, as well as recognizing that data sharing in itself is a valuable scientific endeavour (Allen & Mehler, 2019; Giehl et al., 2024).

Effectively using open datasets also comes with its own challenges (Horien et al., 2021). For example, structural brain health is most frequently characterized with measures derived from conventional MRI scans (e.g., T1-weighted images) (Blinkouskaya et al., 2021; MacDonald & Pike, 2021; Oschwald et al., 2020). However, the parameters of the MRI scanner largely influence the signal intensity of these images (Hagiwara et al., 2020), challenging the comparison and aggregation of results across different scanners or protocols (Huppertz et al., 2010; Medawar et al., 2021). One solution involves the application of harmonisation strategies, which reduce the variability of MRI measures across studies through standardized pre-processing steps and modelling techniques (Bordin et al., 2021; Tax et al., 2019). Another option involves using measures derived from quantitative imaging, as these provide a more absolute characterization of various tissue properties in the brain and are less influenced

by scanner parameters (Buonincontri et al., 2019; Hagiwara et al., 2020), such as in the ABRIM MRI collection. The implementation and validation of these techniques is crucial to fully harness the potential of open datasets and ensure reproducibility of findings (Gebre et al., 2023; Walhovd et al., 2018).

On a final note, I do not want to convey that "the bigger, the better" should be the new mantra to advance research in cognitive ageing. If anything, the chapters in this thesis illustrate how the use of different study paradigms, methodologies and populations can offer important insights into heterogeneity in cognitive ageing. Given our limited resources, it is important to carefully consider what is needed to adequately address the research question of interest, while maintaining sufficient methodological rigor (Spector, 2019; Tibon et al., 2022). Therefore, decisions on the sample size, number of measurements, and population of interest should be driven by the objectives of the study, not by trends or buzzwords. For example, in the context of cognitive neuropsychology, single case studies have substantially contributed to our understanding of cognitive processes (Medina & Fischer-Baum, 2017). As with any scientific challenge, understanding cognitive ageing is a collaborative effort, with each study providing an important piece of the puzzle of this complex yet dynamic process.

Conclusion

Cognitive ageing is a dynamic process shaped by a multitude of factors including, among others, brain health, socio-behavioural factors, as well as lifestyle-related factors. These factors exert varying influences throughout the lifespan and can also interact with each other. To fully understand why cognitive ageing varies from person to person, it is important to leverage inter-individual variability in these factors rather than discarding it. The potential of intervention strategies to promote healthy ageing may be maximized by focusing on how their effectiveness depends on individual-specific factors, as well as the timing at which these should be ideally applied. The scientific community increasingly embraces inclusive, collaborative, and open research, providing an optimal environment to further study cognitive ageing from this dynamic perspective.

8

Chapter 9

Dutch summary

Wat komt er in jou op als je nadenkt over gezond ouder worden? De kans is groot dat er verschillende gedachten voorbijkomen, die illustreren wat voor jou op latere leeftijd een betekenisvolle en vervullende manier van leven zou zijn. Bijvoorbeeld het doorbrengen van kostbare tijd met dierbaren, in staat zijn om te genieten van je favoriete maaltijd of simpelweg nog steeds nieuwsgierig zijn naar de wereld om je heen. Hoewel we steeds ouder worden, gaat dit niet gepaard met een vergelijkbare toename in het aantal jaren die in goede gezondheid worden doorgebracht. In het licht van de dubbele vergrijzing is het daarom van groot belang om de bouwstenen van gezonde veroudering beter te begrijpen.

Een van de belangrijkste voorwaarden van gezonde veroudering is het behoud van ons denkvermogen of cognitief functioneren. Hieronder valt bijvoorbeeld het geheugen en de executieve functies, zoals flexibiliteit. De mate van cognitieve veranderingen gedurende de levensloop verschilt aanzienlijk van persoon tot persoon, zowel in de context van normale als pathologische veroudering (bijvoorbeeld bij de ziekte van Alzheimer). Een beter begrip van waar deze interindividuele variabiliteit vandaan komt kan waardevolle handvatten bieden voor het ontwikkelen van interventie- of preventiestrategieën, die gezonde veroudering bevorderen. Het primaire doel van dit proefschrift is daarom het vergroten van ons begrip van cognitieve veroudering. Hiervoor wordt enerzijds verder ingezoomd op interindividuele variabiliteit in cognitief functioneren bij normale en pathologische veroudering ("Deel I. Het begrijpen van heterogeniteit in cognitieve veroudering). Specifiek richt het onderzoek zich op de dynamieken tussen hersengezondheid, cognitief functioneren en sociaal-gedragsmatige factoren (bijvoorbeeld verbale intelligentie) of leefstijlfactoren (bijvoorbeeld bloeddruk), die mogelijk gedurende de levensloop beïnvloed kunnen worden. Anderzijds wordt er gefocust op het avanceren van onderzoek naar cognitieve veroudering op zichzelf (Deel II. Het avanceren van onderzoek naar cognitieve veroudering).

Deel I. Het begrijpen van heterogeniteit in cognitieve veroudering

Een van de theoretische concepten die veel wordt gebruikt om verschillen tussen mensen in cognitieve veroudering te begrijpen is cognitieve reserve. Het idee is dat mensen met een hogere cognitieve reserve betere cognitieve prestaties laten zien dan zou worden verwacht op basis van hun leeftijd of de aanwezige hersenschade. In **hoofdstuk 2** is onderzocht in hoeverre de positieve effecten van cognitieve reserve nog steeds aanwezig zijn op een zeer hoge leeftijd. Deze cross-sectionele studie richtte zich op 83 ouderen met leeftijden tussen de 71 en 94 jaar oud, woonachtig in verzorgingstehuizen.

Cognitieve reserve werd geschat door middel van een gecombineerde maat van opleidingsniveau en verbale intelligentie. De resultaten lieten zien dat de negatieve relatie tussen leeftijd en woordvloeiendheid (*fluency*) of flexibiliteit alleen werden waargenomen bij mensen met een relatief lage cognitieve reserve, maar niet bij mensen met een gemiddelde of hoge cognitieve reserve. Dit laat zien dat factoren als verbale intelligentie en opleidingsniveau zelfs op zeer hoge leeftijd nog een positieve invloed kunnen uitoefenen op het cognitief functioneren, in het bijzonder voor de executieve functies.

Hoewel opleidingsniveau een positieve invloed heeft op cognitieve prestaties, is het onduidelijk in hoeverre dit voordeel behouden blijft naarmate de ernst van de diagnose of hersenschade toeneemt. Zo is in **hoofdstuk 3** onderzocht in hoeverre de relatie tussen opleidingsniveau en cognitief functioneren verschilt tussen mensen met subjectieve cognitieve stoornissen (n = 108), lichte cognitieve stoornissen (mild cognitive impairment; MCI, n = 190) en alzheimerdementie (n = 245). De positieve effecten van opleidingsniveau op de cognitieve prestaties namen af met de toenemende ernst van de diagnose. Bij mensen met subjectieve cognitieve stoornissen en MCI werd deze relatie eveneens beïnvloed door de ernst van hersenschade, bepaald aan de hand van de mate van hippocampale atrofie, globale atrofie en wittestofafwijkingen. Deze effecten waren echter klein en vergen meer onderzoek. Desondanks illustreert deze studie hoe de effecten van opleidingsniveau op cognitief functioneren beter kunnen worden beschreven in het licht van de onderliggende ziekten, zowel in de mate van klinische symptomatologie als van de ernst van hersenschade.

In **hoofdstuk 4** zijn de relaties tussen leefstijlfactoren, hersengezondheid en cognitief functioneren verder onderzocht. Het onderzoek richtte zich op *cerebral small vessel disease* (SVD), een veelvoorkomende aandoening op latere leeftijd die de kleinste bloedvaten in de hersenen aantast. Een eerder verzamelde dataset, bevatte gegevens van 623 deelnemers die allemaal een MRI-scan ondergingen toen zij gemiddeld 70 jaar oud waren. Metingen van leefstijlfactoren en cognitieve prestaties werden met tussenpozen van 5 jaar uitgevoerd, 5 tot 25 jaar voorafgaand aan de MRI-scan. De eerste metingen van leefstijlfactoren en cognitieve prestaties werden verkregen toen de deelnemers gemiddeld 48 jaar oud waren. Met behulp van verschillende MRI maten van SVD-gerelateerde schade werd een totaalscore berekend om de ernst van de schade te meten. Vervolgens werd er onderzocht hoe de ernst van SVD op latere leeftijd samenhing met leefstijlfactoren en cognitieve prestaties

uit eerdere metingen. De resultaten toonden aan dat mensen met ernstige SVD-gerelateerde schade op latere leeftijd een relatief hogere bloeddruk hadden, waarbij deze verschillen al aanwezig waren op middelbare leeftijd. Ook lieten mensen met ernstige SVD een snellere cognitieve achteruitgang zien in de jaren voorafgaand aan de MRI-scan. Verder was de ernst van SVD ook gerelateerd aan andere maten voor hersengezondheid, zoals een kleiner volume van de grijze stof en een afname van de integriteit van de witte stof. Deze bevindingen ondersteunen het idee dat interventies gericht op het bevorderen van gezond ouder worden zich zouden moeten richten op de middelbare leeftijd.

Deel II. Het avanceren van onderzoek naar cognitieve veroudering

Het begrijpen van cognitieve veroudering vergt een uitgebreide karakterisering van de hersenen en andere factoren die verschillen in veerkracht bij cognitieve veroudering kunnen verklaren. In de afgelopen jaren zijn er verscheidene grootschalige MRI-datasets beschikbaar gesteld om dergelijke onderzoeken te ondersteunen. Het primaire doel van **hoofdstuk 5** is om een bijdrage te leveren aan deze bestaande datasets met de Advanced BRain Imaging on ageing and Memory (ABRIM) studie. ABRIM is een cross-sectionele database van 295 volwassenen in de leeftijd van 18-80 jaar, met een gelijke verdeling van leeftijd en geslacht. Naast het gebruik van conventionele MRI-technieken hebben wij ook kwantitatieve MRI toegepast om een uitgebreidere karakterisering van hersengezondheid mogelijk te maken, bijvoorbeeld door het meten van myelinisatie en ijzerafzettingen in de hersenen. Het onderzoeksprotocol richtte zich daarnaast op het meten van cognitieve prestaties op verschillende domeinen en het in kaart brengen van andere factoren die relevant zijn voor het begrijpen van cognitieve veroudering, zoals depressieve klachten, opleidingsniveau en vrijetijdsactiviteiten. Bij een subgroep van deelnemers (n = 120) is ook actigrafie-data verzameld, waarmee slaappatronen kunnen worden gemeten. De ABRIM *MRI collection* bestaat uit de gepseudonimiseerde MRI-data, inclusief de originele en geanalyseerde MRI-scans, afgeleide data en de bijbehorende code om de analyses te reproduceren. De overige data zullen in de toekomst met de ABRIM *behavioural collection* worden vrijgegeven. Met deze openbaar beschikbare datasets hopen we onderzoekers te ondersteunen bij het verder ontrafelen van de onderliggende mechanismen van interindividuele verschillen in cognitieve veroudering gedurende de levensloop.

Onderzoek naar de relatie tussen hersenactiviteit en cognitieve prestaties wordt vaak gedaan onder de assumptie dat de meeste mensen dezelfde

hersengebieden gebruiken om een bepaalde taak uit te voeren (*one-to-one mapping*). In **hoofdstuk 6** hebben wij deze aanname herzien door de mogelijkheid te onderzoeken of het visueel korte-termijn geheugen (VSTM) door verschillende neurale systemen kan worden ondersteund. Dit fenomeen wordt ook wel *brain degeneracy* of *many-to-one mapping* genoemd. Dit onderzoek werd gedaan met behulp van 113 deelnemers van de Cam-CAN studie, met leeftijden tussen de 22 en 87 jaar oud. Alle deelnemers voerden een taak uit om het VSTM te meten, terwijl hun hersenactiviteit werd gemeten in een MRI-scanner. Eerst werden er zeven groepen van hersengebieden – of hersenmodules – geïdentificeerd die vergelijkbare activatiepatronen vertoonden bij de deelnemers tijdens het uitvoeren van de VSTM-taak. Vervolgens zijn er met behulp van latente klassenanalyse vier subgroepen van deelnemers ontdekt, die werden gekenmerkt door verschillende activatiepatronen van de hersenmodules. Hoewel deze subgroepen niet verschilden in leeftijd of taakprestaties, hadden verschillende subgroepen andere relaties tussen de activiteit in bepaalde hersenmodules en taakprestaties. Dit suggereert dat deze subgroepen inderdaad verschillende neurale systemen gebruikten om succesvolle taakprestaties tot stand te brengen. Ook werden er verschillen gevonden in de mate van integriteit van de witte stof tussen de subgroepen. Het gebruik van verschillende neurale systemen lijkt hiermee deels samen te hangen met de manier waarop hersenstructuren variëren tussen personen.

Interventies om het geheugen te verbeteren zijn veelvuldig onderzocht in de context van normale en pathologische veroudering. Het blijft echter lastig om vast te stellen in hoeverre geheugeninterventies daadwerkelijk bijdragen aan verbeteringen in cognitieve functies, vanwege de grote variatie in interventieprotocollen en inconsistente beschrijving van de methoden en resultaten van bijbehorende studies. Daarom hebben wij in **hoofdstuk 7** een hulpmiddel ontworpen, namelijk de Classification Of MeMory InTerventions (COMMIT) tool. Om COMMIT te ontwikkelen, werd er eerst een categoriesysteem gemaakt voor de verschillende componenten van geheugeninterventies. Dit werd gedaan met behulp van een kwalitatieve inhoudsanalyse van de methoden secties van een steekproef van gepubliceerde geheugeninterventies tussen april 1983 en juli 2020. Op deze manier werd het gehele spectrum van de componenten van geheugeninterventies in eerdere studies vastgelegd. Vervolgens werd met behulp van interne en externe experts dit categoriesysteem beoordeeld, aangepast en vertaald naar een interactieve PDF. De resulterende COMMIT-tool bestaat uit een gestandaardiseerd format

om geheugeninterventies te beschrijven, samen met uitgebreide instructies voor het gebruik. Op deze manier ondersteunt COMMIT een geharmoniseerde rapportage van geheugeninterventies, wat ook kan helpen bij het systematisch vergelijken van dergelijke studies.

Conclusie

Samenvattend laten de resultaten in dit proefschrift zien dat cognitieve veroudering een dynamisch proces is, beïnvloed door een complex samenspel van verscheidene factoren die sterk verschillen van persoon tot persoon, zoals hersengezondheid, sociaal-gedragsmatige factoren en leefstijlfactoren. Het erkennen en benutten van deze interindividuele variabiliteit is cruciaal om de mechanismen van cognitieve veroudering beter te begrijpen. Met de introductie van een open dataset, een innovatieve methode voor het bestuderen van interindividuele variabiliteit in hersenactiviteit, en een gestandaardiseerde tool voor het rapporteren van geheugeninterventies, biedt dit proefschrift ook een basis voor toekomstig onderzoek naar interindividuele variabiliteit in cognitieve veroudering.

9

Appendices

References
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Research data management

This research followed the applicable local procedures, laws, and ethical guidelines. Research Data Management adhered to the FAIR (findable, accessible, interoperable, and re-usable) principles whenever possible. The paragraphs below specify in detail how this was achieved.

Ethics

All human studies presented in this thesis were conducted in accordance with the principles of the Declaration of Helsinki.

Research in **chapter 2** was approved by the local ethics committee of the VU University, Amsterdam. The research presented in **chapter 3** and **chapter 7** did not require ethical review and approval in accordance with the local legislation and institutional requirements.

The studies in **chapter 4** were approved by the University of Oxford Central University Research Ethics Committee (Whitehall II Imaging sub-study, application reference: MS IDREC-C1- 2011– 71) and the University College London Medical School Committee on the Ethics of Human Research (Whitehall II study, reference: 85/0938). The Whitehall II Imaging Sub-study was supported by the UK Medical Research Council (MRC) grants "Predicting MRI abnormalities with longitudinal data of the Whitehall II Sub-study" (G1001354; ClinicalTrials.gov Identifier: NCT03335696), and the HDH Wills 1965 Charitable Trust (1117747). The Whitehall II study was supported by the British Heart Foundation (RG/16/11/32334), UK Medical Research Council (R024227, S011676) and US National Institute on Aging (RF1AG062553; R01AG056477).

The study described in **chapter 5** fell under the blanket approval "Image Human Cognition" (Commissie Mensgebonden Onderzoek Arnhem-Nijmegen, 2014-288) and was approved by the Social Sciences Ethical Committee of the Radboud University (ECSW 2017-3001-46). Funding was received from the European FP7 program, FP7-PEOPLE-2013-ITN, Marie-Curie Action, "Initial Training Networks", named "Advanced Brain Imaging with MRI" (608123).

Research in **chapter 6** was approved by the Cambridgeshire 2 Research Ethics Committee, now known as the East of England – Cambridge Central Research Ethics Committee. The study received funding from the UK Biotechnology and

Biological Sciences Research Council (BB/H008217/1), the UK Medical Research Council Cognition & Brain Sciences Unit (CBU), University of Cambridge, UK.

Findable, accessible

An overview of where the data and research documentation can be found for each chapter is provided in the table below. The Radboud Data Repository (www.data.ru.nl) has been used for data management and/or research documentation unless specified otherwise. All data archived in a Data Sharing Collection (DSC) remain available for at least 10 years after the termination of the studies.

Chapter	DAC	RDC	DSC	License
3	DAC_2024.00074_984	RDC_2024.00074_067		
4			https://portal.dementiasplatform.uk/	Study-specific DUA[1]
5	DAC_3015046.06_241 DAC_2017.00024_669	RDC_3015046.06_216	DSC_3015046.06_419	RU-HD-SU-1.0
6			https://camcan-archive.mrc-cbu.cam.ac.uk/dataaccess/	Study-specific DUA[1]
7	DAC_2024.00084_861	RDC_2024.00084_366	https://osf.io/bg9q8	CC-BY-4.0

DAC = Data Acquisition Collection; RDC = Research Documentation Collection; DSC = Data Sharing Collection; DUA = Data User Agreement. [1]The DUA is study-specific and is provided on the corresponding data sharing platform.

The anonymized datasets analyzed in **chapters 2-4,** as well as corresponding analysis scripts, are available upon reasonable request via the corresponding author of the article.

For **chapter 5,** the original documents from the behavioural examination are archived in the central archive of the Radboud University, Nijmegen. Informed consent was obtained on paper following the local procedures. The forms are separately archived at the Donders Institute, Nijmegen, for at least 15 years after termination of the studies. Asides from the minimal dataset to replicate the results presented in this chapter (DSC_3015046.06_419), the anonymized MRI and behavioural data are available in separate DSCs. The DSC for the MRI data has been released previously (DSC_3015046.06_991). The DSC for the behavioural data will be released in November 2028 (DSC_2017.00024_776).

Access is provided for registered users under the Data Use Agreement for identifiable human data – scientific use (RU-HD-SU- 1.0).

The study in **chapter 6** is currently under review. The scripts and analysis pipeline are made available via Github (https://github.com/michellegjansen/).

Interoperable, reusable

The raw data are stored in the DACs in their original form. For the RDC and DSC, long-lived file formats (e.g., .csv) are used to ensure that the data remains useable in the future. Neuroimaging data are stored following the BIDS format (https://bids.neuroimaging.io/). Results are reproducible using the provided methodological descriptions, raw data (DAC), study-specific datasets (RDC or DSC), and analysis scripts or pipelines (RDC or DSC). To further enhance reproducibility, readme files are included, the scripts are documented, and the used software including version numbers is provided.

Privacy

For **chapters 2-4**, and **6**, data were stored in a fully anonymous database. **Chapter 7** did not include human participant data. For **chapter 5**, privacy-sensitive participant information was separately stored in a password-protected database, accessible only to the main investigators. Participant data (i.e., scientific data) was anonymized and stored using random subject codes on a separate network drive. A separate password-protected pseudonymization key was kept by one researcher in strict confidence. All privacy sensitive information and the key file were destroyed one year after study completion, unless permission was granted by participants to be contacted in the future to be asked to participate in other studies. All MRI data were defaced to ensure pseudonymization. Additionally, the data are available for registered users under the RU-HD-SU-1.0 license, which includes additional statements for protecting the identity of participants.

Portfolio

Courses and workshops		Organizer
2023	The art of finishing up	Radboud University
2022	Donders Graduate School Day	Donders Graduate School
	Scientific Integrity course	Donders Graduate School
2021	Psychologische Interventies (8 ECTS)	Radboud University
	Medical Image Computing Summer School	University College London
	Education in a Nutshell (1 ECTS)	Radboud University
	Psychopathology (8 ECTS)	Radboud University
2020	Donders Graduate School	Donders Graduate School
	Graduate school introduction Day	Donders Graduate School

Teaching activities	
2020 - 2023	Support coordinator Brain & Cognition II, BSc Psychology, Radboud University
	Workgroup teacher Brain & Cognition II, BSc Psychology, Radboud University
	Thesis and internship supervision, MSc Clinical Psychology, Radboud University
2023	Workshop brain age prediction, FemiLab, Lausanne University Hospital [online]

Grants and awards	
Jun 2024	Recipient Organisation of Human Brain Mapping abstract merit award
Jan 2024	Radboud Internationalization travel grant for outgoing PhD
Mar 2023	Christine Mohrmann stipend for promising female PhD candidates
Oct 2023	Awarded travel scholarship for the 4th Reserve and Resilience workshop
Dec 2022	Financial contribution international internship from Alzheimer Nederland
Oct 2022	Radboud Internationalization travel grant for outgoing PhD
Sep 2021	Awarded travel scholarship for the 3rd Reserve and Resilience workshop [not accepted due to COVID-19]

Presentations at (international) conferences	
Jun 2024	Organisation of Human Brain Mapping Conference, Seoul [posters] "Stable degenerate brain systems that underlie visual short-term memory across the adult lifespan" and "The Advanced Brain Imaging on ageing and Memory (ABRIM) study"
Jun 2022	The International Neuropsychological Society Conference, Barcelona [poster] "Classification Of MeMory InTerventions: Development of the COMMIT tool"
Sep 2021	VasCog conference [e-poster] "Association of cerebral small vessel disease burden with brain structure and cognitive and vascular risk trajectories in mid-to-late life"
Nov 2020	Alzheimer's Association International Conference Neuroscience Next [e-poster] "Cognitive reserve and the clinical expression of neuropathology in subjective cognitive decline, mild cognitive impairment, and Alzheimer's disease dementia"
Nov 2020	European Stroke Organisation Conference [e-poster] "Differences in MRI markers of cerebral small vessel disease between lacunar stroke and non-lobar intracerebral haemorrhage"

Curriculum vitae

Michelle Jansen was born on February 12, 1996, in Arnhem. She completed her secondary education (VWO) at De Heemgaard in Apeldoorn in 2014. During this time, she worked in a residential care home for the elderly, where she became intrigued by the ageing brain. Motivated by this interest, she pursued a Bachelor's degree in Psychology at Radboud University in Nijmegen, including an additional semester at the University of Glasgow. She also participated in the interdisciplinary Honours Programme, where she was part of a think tank on the 2016 United States presidential election (Trump vs. Clinton). After obtaining her degree in 2018, she continued with the Research Master in Cognitive Neuroscience at the Donders Institute in Nijmegen, specializing in Memory and Plasticity. As part of her Master's, she completed an internship on cerebral small vessel disease and stroke at the Department of Neurology at Radboud University Medical Center in Nijmegen (Dr. Kim Wiegertjes, Prof. Dr. Frank-Erik de Leeuw). To further develop her expertise in MRI techniques and longitudinal modeling, she visited the Heart and Brain Group at the University of Oxford (Dr. Sana Suri).

In March 2020, Michelle started her PhD on *understanding cognitive aging*, coincidentally on the first day of the COVID-19 lockdown in the Netherlands. Under the supervision of Prof. Dr. Joukje Oosterman, Prof. Dr. Roy Kessels, Dr. Linda Geerligs, and Dr. Inti Brazil, she completed her thesis, focusing on unraveling heterogeneity in cognitive ageing and advancing research in the field. During her PhD, she also initiated a research visit to the FemiLab at Lausanne University Hospital (Dr. Ann-Marie de Lange), where she explored novel methods to study the aging brain. Now, as a postdoctoral fellow at Amsterdam University Medical Center, her research focuses on the role of MRI quality in the precision and reliability of neuroimaging biomarkers. Michelle's interest in the ageing brain, along with the research perspectives presented in this thesis, remains central to her work.

List of publications

This thesis

Jansen M.G., Geerligs L., Claassen J.A.H.R., Overdorp E.J., Brazil I.A., Kessels R.P.C. & Oosterman J.M. (2021) Positive Effects of Education on Cognitive Functioning Depend on Clinical Status and Neuropathological Severity. *Frontiers Human Neuroscience, 15*, 723728.

Jansen, M.G., Griffanti, L., Mackay, C.E., Anatürk, M., Melazzini, L., Lange, A.G., Filippini, N., Zsoldos, E., Wiegertjes, K., de Leeuw, F.E., Singh-Manoux, A., Kivimäki, M., Ebmeier, K.P., & Suri, S. (2022). Association of cerebral small vessel disease burden with brain structure and cognitive and vascular risk trajectories in mid-to-late life. *Journal of cerebral blood flow and metabolism, 42*(4), 600–612.

Jansen, M.G., Oosterman, J.M., Folkerts, A.K., Chakraverty, D., Kessels, R.P.C., Kalbe, E., & Roheger, M. (2024). Classification Of MeMory InTerventions: Rationale and developmental process of the COMMIT tool. *Neuropsychological Rehabilitation, 34*(5), 679–700.

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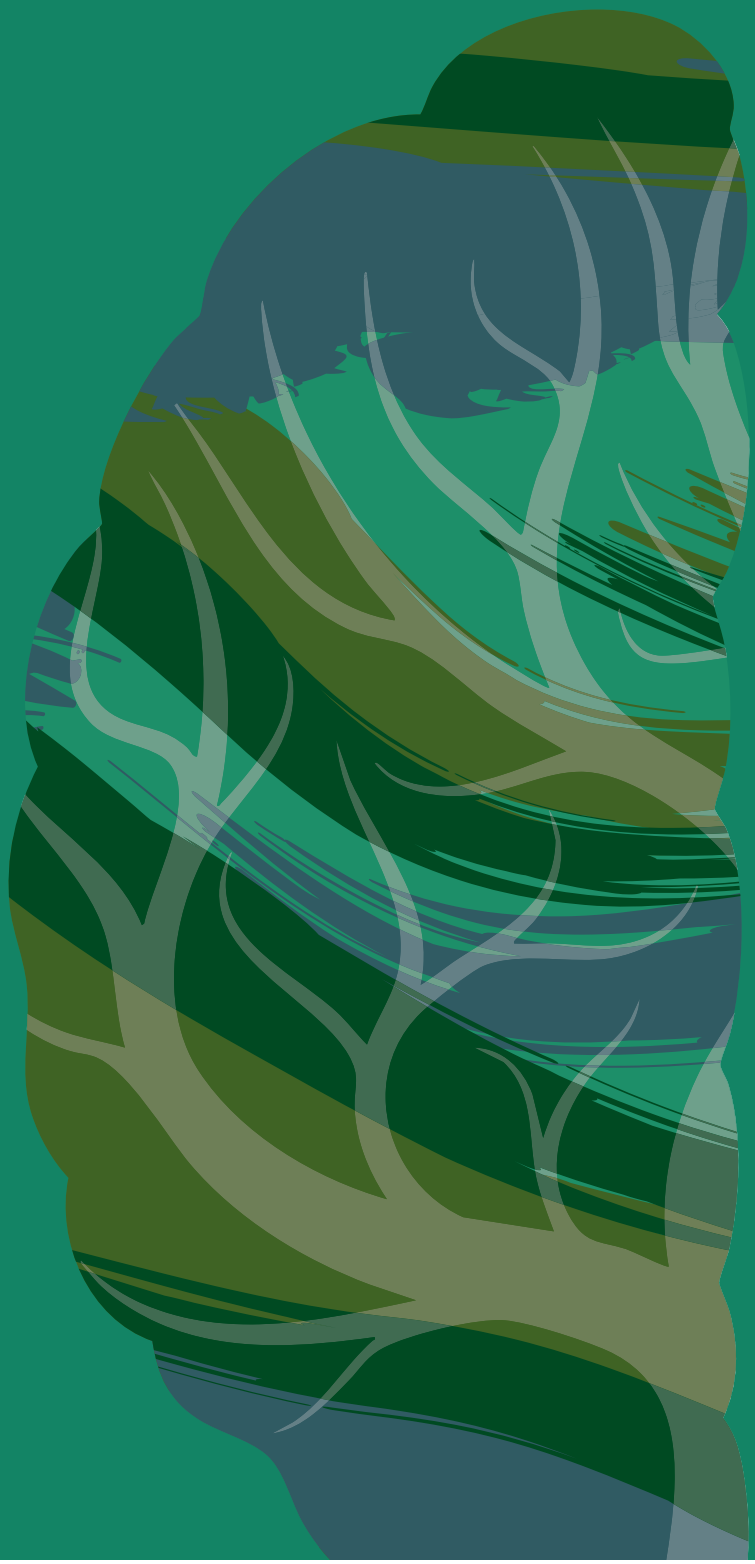

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