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Rīga Stradiņš University

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Relationship between Cognitive Reserve, Cognitive Functioning and Brain Volumetry in Non-Demented Older Adults

Doctoral Thesis for obtaining the scientific degree
"Doctor of Science (*PhD*)"

Sector Group – Social Sciences
Sector – Psychology
Sub-Sector – Cognitive Psychology

Riga, 2023

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Abstract

The aim of this study was to investigate the cognitive and neural correlates of cognitive reserve in healthy adults. The study tested four hypothesis: (1) higher levels of education, active employment and active daily lifestyle will be associated with better memory performance and higher scores of verbal fluency in healthy adults, (2) higher cognitive reserve will be associated with better cognitive performance in memory, information processing speed, visuo-spatial abilities, executive functions and language abilities in healthy older adults, (3) higher cognitive reserve will be associated with larger brain volume, especially in brain regions considered more vulnerable to ageing and dementia and (4) changes in cognitive performance over time will be associated with the baseline cognitive reserve score.

The first hypothesis was tested in a partially representative sample of 546 practically healthy Latvian speaking adults (M_{age} = 70.54, *SD* = 10.19, 37.2 % male). Secondary data on education, current employment and leisure were used as proxies for cognitive reserve, memory was assessed using a ten-word memory task and verbal fluency was assessed using semantic verbal fluency task. To better understand the relationship between variables, structural equation model was prepared and tested. Education, employment status, cognitive leisure activities and moderate physical activities were good predictors of the aforementioned cognitive functions, showing a good model fit ($\chi^2(7) = 30.837$, CFI = 0.970, RMSEA = 0.079, SRMR = 0.058).

The second hypothesis was tested in a sample of 61 Latvian speaking practically healthy older adults (M_{age} = 72.19, SD = 5.02). Cognitive reserve was measured using Cognitive Reserve Index questionnaire (Nucci et al., 2012), working memory, associative memory, processing speed and vocabulary was assessed with *Woodcock-Johnson III: Tests of Cognitive Abilities* (Paleja, 2006), short- and long-term memory measures were obtained with The Ten-word Memory test (Luria, 1976), reaction time was assessed using the *Handball goalie reaction test* and data on executive functions and visuo-spatial abilities were obtained using three subtests from Montreal Cognitive Assessment Scale (Nasreddine et al., 2005). Higher scores of cognitive reserve and its sub-indices – education and occupation – were associated with better short-term memory performance, larger vocabulary (CRI-Education) and higher verbal fluency scores and faster reaction times (CRI-Occupation). The results were partially compliant with the results from the larger sample.

The third hypothesis was tested in a sample of 58 Latvian speaking older adults (*M* = 72.19, *SD* = 5.02, 23.9 % male). Magnetic resonance imaging (MRI) data were obtained with Siemens 1.5 Tesla Avanto MRI scanner (Siemens, Erlangen, Germany) and analysed with Freesurfer 7.2. software. Results partially confirmed the hypothesis, showing that higher occupational achievement and higher cognitive reserve in general were associated with larger

cortical volume in left hemisphere middle temporal gyrus, bilateral inferior temporal gyrus, left hemisphere inferior parietal gyrus and right hemisphere *pars orbitalis*; however, there were no statistically significant associations between cognitive reserve and hippocampus and thalamus ($p > 0.05$).

The final hypothesis was that the changes in cognitive performance over time will be associated with the baseline cognitive reserve score. This hypothesis was tested in a sample of 23 women 68–83 ($M = 74.13$, $SD = 4.70$) drawn from the participant pool from the previous study. Same measures for cognitive reserve and cognitive function were used. The mean years between the testing were 3.391 ($SD = 0.656$). Statistically significant changes were found only in three measures – long-term memory, reaction time composite and clock drawing task. Out of these, only changes in the reaction time were associated with cognitive reserve, specifically – leisure activities, thus only partially confirming the hypothesis.

Overall, results indicate that higher cognitive reserve could be associated with better performance in short- and long-term memory, verbal abilities and reaction time even in healthy older adults. Similarly, higher occupational requirements and cognitive reserve as such could also be associated with larger cortical volume in temporal, parietal and frontal regions, thus providing protection against brain atrophy. Finally, changes in cognitive functioning over time, could be associated with active leisure; however, studies in a larger sample are needed.

Key words: ageing, healthy ageing, cognitive reserve, brain reserve, cognitive science, cognitive functions

Anotācija

Kognitīvo rezervju, kognitīvo funkciju un smadzeņu volumetrijas saistības gados vecākiem pieaugušajiem bez demences

Pētījuma mērķis bija izpētīt kognitīvo rezervju saistību ar kognitīvajām funkcijām un neirālajiem rādītājiem veseliem pieaugušajiem. Pētījuma ietvaros tika pārbaudītas četras hipotēzes: 1) augstāks sasniegtais izglītības līmenis, aktīva nodarbinātība un aktīvs dzīvesveids būs saistīts ar labākiem atmiņas rādītājiem un augstākiem verbālās veiklības rādītājiem praktiski veseliem pieaugušajiem; 2) augstākas kognitīvās rezerves būs saistītas ar labākiem tādu kognitīvo procesu rādītājiem kā atmiņa, informācijas apstrādes ātrums, vizuāli telpiskās spējas, vadības funkcijas un valodas spējas praktiski veseliem gados vecākiem pieaugušajiem; 3) augstākas kognitīvās rezerves būs saistītas ar lielāku smadzeņu tilpumu, jo īpaši reģionos, kas ir vairāk ievainojami novecojoties un saslimstot ar demenci; 4) izmaiņas kognitīvo funkciju rādītājos laika gaitā būs saistītas ar kognitīvo rezervju pirmreizējo mērījumu.

Pirmā hipotēze tika pārbaudīta daļēji reprezentatīvā izlasē, kurā piedalījās 546 praktiski veseli latviešu valodā runājoši pieaugušie (M = 70,54, SD = 10,19, 37,2 % vīriešu). Sekundārie dati par izglītību, pašreizējo nodarbinātību un brīvo laiku tika izmantoti kā kognitīvās rezerves starpniekmainīgie, atmiņa tika novērtēta, izmantojot desmit vārdu atmiņas uzdevumu, un verbālā veiklība tika novērtēta, izmantojot semantisko verbālās veiklības uzdevumu. Lai labāk izprastu attiecības starp mainīgajiem, tika sagatavots un pārbaudīts strukturālā vienādojuma modelis. Izglītība, nodarbinātības statuss, kognitīvās brīvā laika aktivitātes un mērenas fiziskās aktivitātes labi prognozēja iepriekšminētās kognitīvās funkcijas, uzrādot labu modeļa atbilstību ($\chi 2(7)$ = 30,837, CFI = 0,970, RMSEA = 0,079, SRMR = 0,058).

Otrā hipotēze tika pārbaudīta 61 praktiski veselu un latviski runājošu pieaugušo izlasē (M = 72,19, SD = 5,02). Kognitīvās rezerves tika mērītas, izmantojot Kognitīvo rezervju indeksa aptauju (Nucci et al., 2012), darba atmiņa, asociatīvā atmiņa, apstrādes ātrums un vārdu krājums tika novērtēts ar Vudkoka-Džonsones Kognitīvo spēju testiem (Paleja, 2006), īstermiņa un ilgtermiņa atmiņas mērījumi tika iegūti ar desmit vārdu atmiņas testu (Luria, 1976), reakcijas laiks tika novērtēts, izmantojot Rokasbumbas vārtsarga reakcijas testu, un dati par vadības funkcijām un vizuāli telpiskajām spējām tika iegūti, izmantojot trīs apakšskalas no Monreālas Kognitīvās novērtēšanas skalas (Nasreddine et al., 2005). Augstāki kognitīvo rezervju un to apakšindeksu – izglītības un nodarbošanās – rādītāji bija saistīti ar labāku īstermiņa atmiņas veiktspēju, lielāku vārdu krājumu (CRI-Izglītība) un augstākiem verbālās veiklības rādītājiem un ātrāku reakcijas laiku (CRI-Nodarbošanās). Rezultāti daļēji saskanēja ar rezultātiem no lielākās izlases.

Trešā hipotēze tika pārbaudīta 58 praktiski veselu latviski runājošo izlasē (M = 72,19, SD = 5,02, 23,9 % vīrieši). Magnētiskās rezonanses attēldiagnostikas (MRI) dati tika iegūti ar *Siemens 1.5 Tesla Avanto MRI* skeneri (Siemens, Erlangena, Vācija) un analizēti ar *Freesurfer 7.2.* programmatūru. Rezultāti daļēji apstiprināja hipotēzi, parādot, ka augstāki profesionālie sasniegumi un augstākas kognitīvās rezerves kopumā varētu būt saistītas ar lielāku garozas tilpumu kreisās puslodes vidējā deniņu krokā, bilaterāli apakšējā deniņu krokas daļā, kreisās puslodes apakšējā parietālajā krokā un labās puslodes *pars orbitalis*. Vienlaikus netika atklātas statistiski nozīmīgas saistības starp kognitīvajām rezervēm un hipokampu un talāmu (p > 0,05).

Noslēdzošā hipotēze tika pārbaudīta 23 sieviešu izlasē, vecumā no 68 līdz 83 gadiem (M = 74,13, SD = 4,70) veicot atkārtotus mērījumus dalībniecēm no iepriekšējā pētījuma. Vidējais laiks starp mērījumiem bija 3,391 (SD = 0,656). Statistiski nozīmīgas izmaiņas tika konstatētas vienīgi trīs mērījumos – ilgtermiņa atmiņa rādītājos, reakcijas laika kompozītā un pulksteņa zīmēšanas uzdevumā. No tiem tikai reakcijas laika izmaiņas bija saistītas ar kognitīvajām rezervēm, precīzāk – brīvā laika aktivitātēm, tādējādi tikai daļēji apstiprinot hipotēzi.

Kopumā rezultāti norāda uz to, ka augstāks iegūtās izglītības līmenis un profesionālās aktivitātes varētu būt saistītas ar labāku īstermiņa un ilgtermiņa atmiņas sniegumu, verbālajām spējām un reakcijas laiku pat praktiski veseliem gados vecākiem pieaugušajiem. Tāpat augstākas profesionālās prasības un kopējais kognitīvo rezervju mērījums varētu būt saistīti arī ar lielāku garozas tilpumu deniņu, parietālajos un frontālajos reģionos, tādējādi nodrošinot aizsardzību pret smadzeņu atrofiju. Visbeidzot, kognitīvo funkciju izmaiņas laika gaitā varētu būt saistītas ar aktīvu atpūtu (CRI-Leisure Activity), tomēr ir nepieciešami pētījumi lielākā izlasē.

Atslēgvārdi: novecošanās, veselīga novecošanās, kognitīvās rezerves, smadzeņu rezerves, kognitīvās zinātnes, kognitīvās funkcijas.

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Abbreviations used in the Thesis

AD	Alzheimer's disease
CRIq	Cognitive Reserve Index questionnaire
EE	electroencephalography
eTIV	estimated intracranial volume
fMRI	functional magnetic resonance imaging
MC	mild cognitive impairment
MR	magnetic resonance imaging
STAC	the Scaffolding Theory of Aging and Cognition
STAC-r	the Scaffolding Theory of Aging and Cognition – revised

Glossary

Associative memory – the ability to remember two initially unrelated items, e.g. an unknown proper noun and an unknown object (Suzuki, 2008)

Brain maintenance – the relative absence of changes in neural resources neuropathological change over time as a determinant of preserved cognition in older age (Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia Framework for Terms Used in the Research of Reserve and Resilience, 2022)

Brain reserve – a physical trait that each individual possesses and is characterized by neuronal resources such as neuronal and synaptic count (Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia Framework for Terms Used in the Research of Reserve and Resilience, 2022)

Cognitive functions – a variety of abilities aiming to ensure a successful daily life functioning (Palmese, 2011)

Cognitive reserve – 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 (Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia Framework for Terms Used in the Research of Reserve and Resilience, 2022)

Cortical volume – "the amount and size of neurons, dendritic processes and glial cells" (Schaer et al., 2006)

Cerebral cortex - part of the brain that is mainly composed of neuronal bodies (grey matter) and can be categorized either by the functional characteristics of the brain (sensory, motor, and association areas) or the division of sulcus and gyri (frontal, temporal, parietal and occipital lobes) (Javed et al., 2021)

Executive functions – a group of higher-level cognitive processes that are involved in performing a specific task or tasks and are generally divided into three main components: inhibition, working memory and cognitive flexibility (Diamond, 2013; Vaughan & Giovanello, 2010)

Hippocampus – a gray matter structure in the temporal lobe that is involved in episodic memory and spatial navigation (Lisman et al., 2017; Patel et al., 2022)

Long-term memory – a storage of knowledge and a record of prior events that can be kept for days, weeks or years (Cowan, 2008)

Memory – a cognitive function that can be structure according to its temporal dimension, content or mechanisms of acquisition (Brem et al., 2013)

Short-term memory – the ability to hold a limited amount of easily accessible information for a short period of time (Cowan, 2008). In this study, short-term memory is referred to in the context of storage.

Sociobehavioural proxies of cognitive reserve – approach to measure cognitive reserve using either individual sociobehavioural variables, such as, education, occupation and leisure activities, or a composite score of aforementioned variables.

Thalamus – a bilateral subcortical structure of the diencephalon that mostly functions as a relay between perceived stimulus and the respective cortical region (Sheridan & Tadi, 2022; Torrico & Munakomi, 2022)

Verbal fluency – a cognitive function that involves retrieval of information from memory and is characterized by the speed and ease of language production (Kemper & Altmann, 2009; Patterson, 2011)

Vocabulary – the full collection of words of a particular language, field or knowledge that is accumulated during the life-time (Steffani & Huang, 2011)

Working memory – the memory used to plan and carry out individual behavior (Cowan, 2008)

Introduction

Years 2021 to 2030 have been announced to be the United Nations Decade of Healthy Ageing that aims to bring together governments, civil society, international agencies, professionals, academia, the media and the private sector to endorse the activities needed for improving the lives of older and ageing adults, their families and the communities (World Health Organization, 2022). And, indeed, there is a rapid increase in the ageing population, predicting an increase in the median age by 4.5 years in 2050 in Europe (Eurostat, 2020). Increased age is still considered to be among the main risk factors for developing a neurodegenerative disease, such as dementia (Hou et al., 2019), therefore, the increase in the population aged over 65 years of age would also correlate with an increase in patients with neurodegenerative diseases. Currently, there are no pharmacological or non-pharmacological methods for the treatment of Alzheimer's Disease (AD) or dementia; however, the past two decades have highlighted the importance of life-style activities in preventing or delaying symptoms of cognitive decline. Among these activities, one of the most researched is cognitive reserve, a theory initially proposed by Robert Katzman in the late 1980s and later developed and expanded by Yaakov Stern.

The notion of the protective role of cognitive and social activities during life is not new. In late 1970s, Kaszniak and colleagues conducted a study, investigating the suspected changes in mentation in relation to education, age, cerebral atrophy, electroencephalography, and neuropsychological performance, and concluded that formal education should be taken into consideration when investigating the effects of age on cognitive functioning (Kaszniak et al., 1979); similar findings were also concluded in later studies in the next decade; however, the most significant studies regarding the relationship between cognitive activities and cognitive functioning and dementia can be found starting from the late 1980s, when Robert Katzman first mentioned the reserve theory, noting that there were differences between symptoms (or rather – lack of the symptoms) in patients with similar AD pathology (Katzman et al., 1988). This theory was further investigated during the 1990s, further developing the theories of cognitive and brain reserve and brain maintenance.

A couple of years later, in 1991, David Snowdon started a longitudinal study aiming to investigate ageing and AD. Participants were 678 Catholic sisters, born before 1917 who were also members of the School Sisters of Notre Dame congregation. Snowdon and colleagues obtained data from three different sources: early and midlife risk factors for AD, yearly health examinations, and post-mortem neuropathologic evaluation. The results of the study indicated that even though there was neuropathology present in some of the nuns, there were also protective factors that delayed the clinical symptoms of the disease. Initial findings showed that

those nuns who had shown lower density and lower grammatical complexity abilities in autobiographies written in early life, had worse cognitive function in later life (Snowdon et al., 2000; Snowdon, 2003).

There are several approaches that considers the cognitive decline associated with cognitive decline due to ageing. The Sensory System Decline proposes three explanatory models, suggesting that cognitive performance is impaired due to the weakening or degradation of perceptual signals (The Information Degradation Hypothesis), due to a concurrent peripheral and central decline (The Common-Cause Hypothesis) or due to lack of sufficient sensory stimulation that results in atrophy (The Sensory Deprivation Hypothesis) (Ebaid & Crewther, 2020). However, it should be noted that these approaches are focused on the unavoidable degradation of cognitive functions, rather than the potential compensatory mechanisms. As opposed to the aforementioned theories, both – the Cognitive Reserve Hypothesis and the Scaffolding Theory of Aging and Cognition (STAC) – can be defined as more compensatory-oriented and integrates life-style factors as potentially protective. This Thesis is based on main arguments found in both models, though more attention has been paid to the Cognitive Reserve Hypothesis as it encompasses mechanisms of cognitive reserve.

Cognitive reserve is characterised mainly by its flexibility and its compensatory and complementary nature. It is essentially the individual capacity of the brain that is either present in case of pathology, e.g. after brain trauma or delaying the onset of cognitive symptoms of neurodegenerative disease, or in case of being presented with a challenging task, thus allowing one to achieve better cognitive performance than expected. In turn, brain reserve refers to the actual physical measures of the brain, e.g. neuronal or synaptic count (Y. Stern et al., 2020, 2022). The relationship between cognitive and brain reserve has been established, and they are considered to be two sides of the same coin; however, the actual empirical associations are still being tested. The typical approach to measuring brain reserve is to use the estimated intracranial volume (eTIV); nevertheless, there have been several attempts to specify the regions using both – structural and functional methods (e.g. see Loenhoud et al., 2018 for the use of eTIV and Šneidere et al., 2020 for functional assessment with EEG).

While Cognitive Reserve theory has been extensively researched and tested, its focus has been mainly on pathological brain changes. The Scaffolding Theory of Aging and Cognition (STAC), in turn, proposes more wider and functional approach, noting that cognitive ageing as a process includes two main changes – neural and functional that can be mitigated (or – have scaffolding) through the life-course experience (Goh & Park, 2009; Reuter-Lorenz & Park, 2014). Therefore, this study proposes that also cognitive ageing includes changes in both – brain and cognition, especially in regions associated with memory functions (hippocampus, temporal

and parietal lobes, e.g. see Pettigrew et al., 2017) and information processing (thalamus). Investigating the relationship between separate brain regions and cognitive reserve, a single consensus has not been reached; however, some indications have been found for regions more sensitive to Alzheimer's disease (Liu et al., 2012; Pettigrew et al., 2017; van Loenhoud et al., 2017). Nevertheless, it should be noted that most studies have focused on specific regions, not considering the cortex as a whole.

In 2016 a systematic review with meta-analysis by Opdebeeck et al. was conducted, identifying the relationship between different socioeconomic proxies of cognitive reserve and global cognitive performance, executive function and memory. A more recent systematic review considering cognitive reserve and cognition in healthy adults was published, coming to a similar conclusion in a younger population, while still highlighting the importance of a unified approach to measuring reserve (Panico et al., 2022). However, in the aging population, research shows a greater tendency towards the positive impact of cognitive reserve on cognitive performance in both healthy and clinical older adult groups (Li et al., 2020).

While there have been extensive studies on cognitive reserve and its role in neural and psychological changes in cognitive ageing, here is still a need for an encompassing view of the relationship between the variables. In addition, the inconsistency in measuring cognitive reserve could yield different or even conflicting results. This study used a composite measure of sociobehavioural proxies of cognitive reserve, ensuring that not only education, but also other cognitively and socially challenging life-span activities are taken into consideration.

Aim of the Thesis

To investigate the cognitive and neural correlates of cognitive reserve in healthy adults.

Tasks of the Thesis

1. To prepare an integrative theoretical framework based on the Cognitive Reserve theory and the Scaffolding Theory of Cognition and Aging;
2. To empirically test the integrative theoretical integrative framework:
    1) To identify the relationship between cognitive reserve and cognitive functioning in a partially representative sample of Latvian adults;
    2) To investigate the relationship between cognitive reserve and cognitive functions in a sample of older Latvian adults;

3) To investigate the neural (cortical, hippocampal and thalamic volume) correlates of cognitive reserve in a sample of older Latvian adults;
4) To examine the association between the change in cognitive performance and baseline measures of cognitive reserve.

3. To analyse and describe the results of the study;
4. To draw conclusions based on the study results.

Hypothesis of the Thesis

1. Higher levels of education, active employment and active daily lifestyle will be associated with better memory performance and higher scores of verbal fluency in healthy adults;
2. Higher cognitive reserve will be associated with better cognitive performance in memory, information processing speed, visuo-spatial abilities, executive functions and language abilities in healthy older adults;
3. Higher cognitive reserve will be associated with larger brain volume, especially in brain regions considered more vulnerable to ageing and dementia;
4. Changes in cognitive performance over time will be associated with the baseline cognitive reserve score.

Novelty of the Thesis:

Cognitive ageing has been associated with changes in both levels – neural and cognitive. Initial models, such as The Scaffolding Theory of Aging and Cognition, has proposed that the decline is associated primary with changes in brain structure and function and the resulting changes in cognition is mediated by enrichment and scaffolding factors that are modifiable and can be integrated into lifestyle. These factors are also often present when considering the concept of cognitive reserve; however, both models consider reserve as more mediating factor and does not discuss the potential direct association with brain and with cognitive functioning. To investigate both – neural ageing (through brain structural measures) and cognitive ageing (through measuring cognitive function), an integrative theoretical framework, based on The Cognitive Reserve theory and The Scaffolding Theory of Aging and Cognition was created. The framework encompasses two main directions, namely, the relationship between cognitive reserve as measured by sociodemographic proxies and brain regions, including cortical regions, thalamus and hippocampus, and the relationship between cognitive reserve and cognitive functioning that includes memory, information processing speed, verbal abilities, executive functions and visuospatial abilities.

It should be noted that the initial studies of cognitive reserve used formal education as the proxy. Education in most cases, however, is an activity that is often finite, thus the effect provided by it, is fixed. More and more studies include more complex approach to measuring cognitive reserve, including verbal IQ, occupation and leisure activities as additional sociobehavioural proxies of the reserve. A sociobehavioural approach to measuring cognitive reserve offers a more extensive measures of the potential proxies of cognitive reserve; however, the significance of individual proxies are still understudied. Previous studies have considered the relationship between various proxies of cognitive reserve, often choosing one of the socio-behavioural proxies, such as education, verbal IQ measures, or individual differences in cognitive tests. Although all of these factors have been considered valid for measuring cognitive reserve, they create a discrepancy in the study results. This study used a combination of socio-behavioural proxies that include both – education and informal educational activities, and occupational and leisure activities that are a more dynamic proxies of cognitive reserve.

1 Literature review

1.1 The Reserve theory

Nearly 35 years ago, the late Robert Katzman, a neurologist and scientist at the University of California, San Diego, together with colleagues published an article on clinical, pathological, and neurochemical changes in dementia, where he discussed the results of *postmortem* examination on 137 residents of a skilled nursing facility. Together with different potential markers for Alzheimer's disease, he found that ten of his subjects with a diagnosed Alzheimer's disease (AD) had brain characteristics similar or even better when compared to the control group without AD. Thus Katzman and colleagues formed the conclusion that these patients might have had a greater reserve (Katzman et al., 1988). This notion was further investigated by other researchers, e.g. in the context of HIV-1 it was found that lower education, lower occupational attainment, and intelligence could be considered a risk factor for cognitive abnormalities and overall showed greater deficits in information processing speed, attention, verbal learning and memory, executive functioning, and visuospatial performance (Satz et al., 1993; R. A. Stern et al., 1996). Based on the aforementioned studies, a professor at the University of Columbia, Yaakov Stern, proposed a relationship between cognitive processes and education and occupation. While his first findings did not completely comply with the hypothesis derived from Katzman, Satz, and R. A. Stern, he found that those patients who had higher educational and occupational attainment would also have a more rapid memory decline in those patients who already presented with low initial memory scores. Thus, he developed a theoretical model to explain the observation (see more in sub-chapter 1.1.2) (Y. Stern et al., 1999).

Stern continued his work on cognitive reserve and three years later published a review, defining two models of reserve – a passive model or brain reserve and an active model or cognitive reserve. Furthermore, currently a *Collaboratory aiming to develop a framework of cognitive and brain reserve and brain maintenance* has been established. These concepts will be discussed in the following sub-chapters.

1.1.1 Brain reserve and brain maintenance

Brain reserve is defined as a physical trait that each individual possesses. It is characterised by lesser changes in such neural resources as neuronal and synaptic count or neuropathological change over time, i.e. it could also be named a neurobiological capital. This concept suggests that people with larger brain capacity or better 'hardware' will also be more resilient when faced with pathology as they will simply have "more to lose"; however, this also

means that there is a threshold after which cognitive and functional deficits could occur (Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia Framework for Terms Used in the Research of Reserve and Resilience, 2022; Y. Stern et al., 2020).

Studies by Katzman and the Nun Study have largely influenced the research on brain reserve and further investigations show that brain reserve might indeed be a factor in reducing the incidence of dementia. A systematic review by Valenzuela and colleagues indicated that high-reserve individuals had a 46 % lower risk of dementia, compared to low-reserve individuals (Valenzuela & Sachdev, 2006); however, to achieve better results, a confirmed measure of brain reserve is still necessary. As brain reserve encompasses the anatomical and structural aspects of the brain, it can be measured in different ways, using *in vivo, postmortem* techniques, or imaging methods (structural magnetic resonance imaging (MRI) measuring whole brain volume, cortical surface, cortical thickness, synaptic integrity, white matter microstructural properties, PET scans etc.). The different approaches are also a limitation to compare the existing proofs (Y. Stern et al., 2020). This can be illustrated by a study published in 2021, where there were no associations between intracranial volume as a proxy of brain reserve and clinical progression in Alzheimer's dementia, while composite value of fluorodeoxyglucose positron emission tomography as a proxy was a significant predictor of delaying AD dementia progression (Yoon et al., 2021). Nevertheless, intracranial volume is still considered the most often used proxy of brain reserve and its use has been thoroughly evaluated, noting that its use can still be justified in reserve research (van Loenhoud et al., 2018).

Although brain reserve reflects an invariable state of the brain, the concept of brain maintenance "refers to the relative absence of changes in neural resources neuropathologic change over time as a determinant of preserved cognition in older age" (Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia Framework for Terms Used in the Research of Reserve and Resilience, 2022). Thus, if brain reserve is measured at a point in time, brain maintenance refers to the reduction of potential decline in morphological structures, especially those associated with memory. Brain maintenance consequently displays the effect of modifiable risk factors, such as lifestyle, on the brain (Y. Stern et al., 2020).

Early on, Lars Nyberg noted that there are various genetic and lifestyle factors that could support brain maintenance. Different studies support the role of genetic factors, indicating that the individual differences are also closely linked to genetic variability. Meanwhile, lifestyle factors have been widely investigated, including education, cognitive, and social activities, as

well as physical activity, yielding different results (Nyberg et al., 2012). Longitudinal studies have supported the idea that a lifestyle contributes to brain maintenance. The results of a 5-year longitudinal study by Pani et al. showed that involvement in long-term physical exercise intervention had a protective effect against loss of structural complexity in temporal grey matter (Pani et al., 2022). Another study on brain maintenance investigating brain atrophy showed hippocampus-specific brain changes associated with changes in episodic memory performance in older age (Johansson et al., 2022).

1.1.2 Theoretical frameworks of cognitive reserve

As opposed to brain reserve, cognitive reserve is a flexible concept and is defined as "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" (Collaboratory on Research Definitions for Reserve and Resilience in Cognitive Aging and Dementia Framework for Terms Used in the Research of Reserve and Resilience, 2022). This is due to experience acquired during the lifetime that complements the competency of the brain to overcome pathological brain changes, e.g. as in case of Alzheimer's Disease or dementia, or brain injury (e.g. as a result of brain trauma or stroke) (Y. Stern et al., 2020). Two main mechanisms are proposed – neural compensation and neural reserve. Neural compensation refers to the use of different brain structures that would not be activated normally; however, the efficacy of the function would be lower. In turn, neural reserve refers to the individual properties of neural performance, namely, the efficacy or inefficacy of the neural network performance. As in neural compensation, also neural reserve is essential in case of pathology; however, EEG studies show that it is also present in healthy adults, when faced with highly complicated tasks. This could indicate that in different individuals the same task would require different levels of activation in order to produce the same results. It also implies that individuals with higher neural reserve would also show better cognitive flexibility (Gu et al., 2018; Y. Stern, 2017; Tucker & Stern, 2011).

There are several approaches to cognitive reserve frameworks. The initial findings by Stern enabled him to develop a theoretical model of the effects of cognitive reserve. Stern hypothesised that individuals with higher cognitive reserve will mediate the relationship between the Alzheimer's disease pathology and its clinical expression, thus delaying the onset of the symptoms of the disease (see Figure 1.1). The x-axis represents the development of the pathology over time, while y-axis represents the memory performance. Stern assumed that the changes in pathology are happening at the same rate in all individuals, independently from the levels of reserve and thus predicted that the point of infliction (the moment where memory

begins to be affected) will be delayed in case of higher cognitive reserve; however, after reaching the point of inflection, the clinical progression will be more rapid in individuals with high cognitive reserve in comparison with individuals with lower reserve (Y. Stern, 2009; Y. Stern et al., 1999).

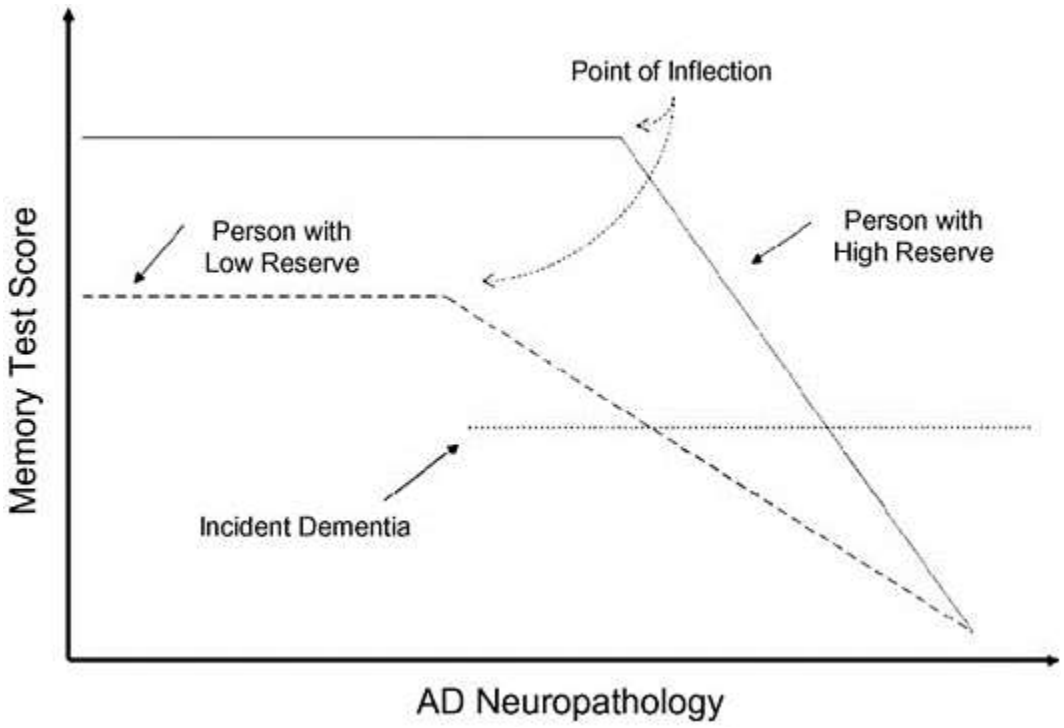

Figure 1.1 **Initial theoretical model explaining the effect of cognitive reserve**
(Stern, 2009; Stern, 1999)

A later study by Marioni and colleagues (Marioni et al., 2012) further complemented the model proposed by Stern, by assessing the relationship between cognitive lifestyle (reserve) and cognitive states over time in a population-based cohort of the elderly. The findings indicated that participants who had higher education, more complex occupation and who were also socially engaged had 8.5 more years spent with no cognitive impairment. There are two main implications that should be taken into consideration, namely, while cognitive reserve could potentially delay the onset of the symptoms, it can also delay the timely diagnosis of the disease thus overall worsening the outcome (Arenaza-Urquijo et al., 2015; Stern, 2009).

Another approach to cognitive reserve frameworks involve cognitive reserve as the moderator of the relationship between brain health and cognitive performance (see Figure 1.2).

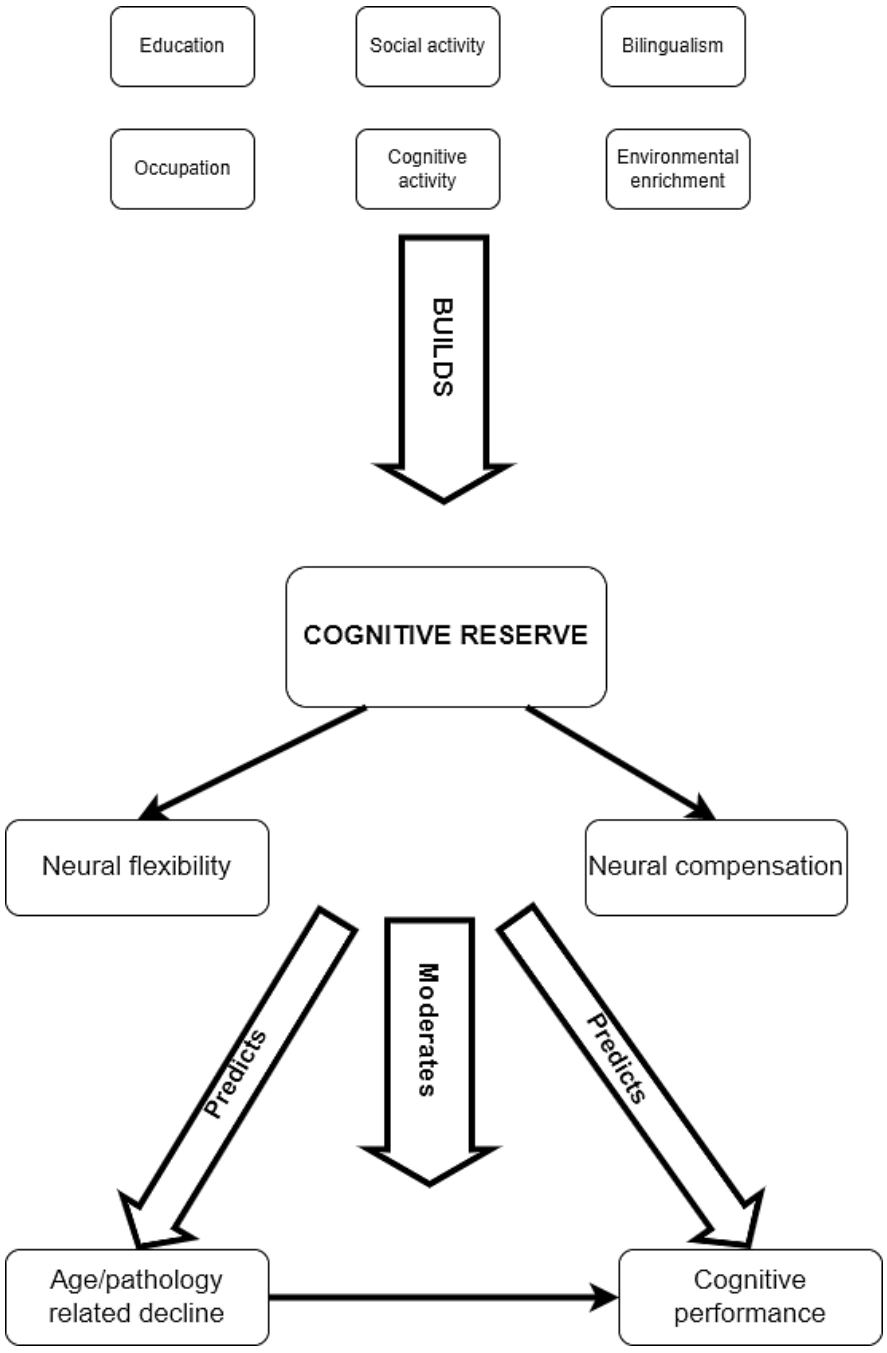

Figure 1.2 **Moderation / prediction model of cognitive reserve**

(Song et al., 2022, visualisation adapted and modified from Oosterhuis et al., 2022)

There are different factors that are considered significant in building CR. Initially, **education** was considered the main factor in CR and was also the most commonly used proxy for measuring it, often due to the relationship between lower education and a higher risk of dementia or Alzheimer's disease (Norton et al., 2014; Satz et al., 1993). Cross-sectional studies mostly support this claim (see, e.g. Sharp & Gatz, 2011; Takasugi et al., 2021), still longitudinal studies indicate that while education could affect cognitive performance before the onset of cognitive decline, it does not predict changes in cognitive performance or brain volume (Nyberg, Magnussen, Lundquist, Baaré, Bartrés-Faz, et al., 2021; Wilson et al., 2019).

Occupation is another factor considered in cognitive reserve. A now well-known study, but a pioneer at that time, was published in 2000 by Eleanor Maguire and colleagues, who investigated the differences in hippocampal volume in male taxi drivers and males, who did not work as drivers. The findings indicated a larger volume in a hippocampal region believed to be related to spatial navigation in taxi drivers, suggesting the relationship between occupational activity and brain volumetry (Maguire et al., 2000). Later studies showed that people who took part in more complex occupational activities are also able to better retain optimal cognitive performance even if they are already considered a risk group for AD or dementia (Boots et al., 2015). However, it should be noted that higher occupational complexity is often related to higher level of education and often involves additional training associated with work tasks (e.g. seminars, courses), thus education is still a significant covariate when considering occupation. This is also supported in the longitudinal study by Mondini and colleagues, noting that individuals with higher educational and occupational attainments showed lesser cognitive impairment (Mondini et al., 2022).

Cognitive and social **leisure activities** offer another approach to increasing cognitive reserve; however, this is also one of the hardest to measure due to different approaches to defining leisure activities. Some studies indicate that social, cultural and cognitive activity could be beneficial in decreasing the risk of developing a neurodegenerative disorder and showing better cognitive performance (e.g. see Wajman et al., 2018); however, the type, regularity and recency of the activity should be better defined.

Another factor associated with cognitive reserve is **verbal IQ** and **bilingualism**, though it is unclear whether verbal IQ is a part of increasing cognitive reserve or another proxy for measuring it. Initial role of language was identified through the Nun Study, identifying linguistic density as a strong predictor of Alzheimer's disease (Snowdon, 2003). Verbal IQ has been associated with cognitive performance in older adults (e.g. see Boyle et al., 2021), similarly as the effects of bilingualism. A study conducted by Macbeth and colleagues indicated that older participants who reported as bilingual had better structural indicators (volume, thickness) between regions necessary for executive control of memory in comparison with monolingual participants (Macbeth et al., 2021).

Environmental and global factors have also been implied to play a protective role in the case of cognitive decline. A review investigating the environment as a 'brain training' tool found that when comparing urban life with rural life, urban life offers more cognitive challenges and more accessible social activities, and, in addition, urban areas often have higher education thus there is an increased need to learn. However, the urban environment also includes a larger amount of visual and audial stimuli and has been associated with a worse visuospatial

perception. Rural life in turn shows lower access to and need for education, while it also offers lower risk of sedentary lifestyle and is easier for attention as contains less stimuli (Cassarino & Setti, 2015). Changes in the environment might also have a beneficial effect on CR, as found in a study by Mondini and colleagues, who compared the cognitive reserve of Italians living in Italy and Italians who emigrated to Montreal at around 20 years of age. The study results showed that emigration could act as an environmental factor in improving cognitive reserve (Mondini et al., 2014).

Although no longer serving as a protective factor rather than activities to maintain the well-being of AD patients, several studies have been conducted. The Botanical Garden of Oslo University in cooperation with the Norwegian Genetic Resource Centre and Oslo's Resource Centre for Dementia and Psychiatric Care for the Elderly opened the Great-granny's Garden, which was designed with two main goals - preserving the horticultural heritage of Norway, as well as function as a sensory garden for people with dementia and is considered to be a tool in the therapy of dementia (Borgen & Guldahl, 2011). The role of active cultural participation was also evaluated in a cross-cultural project coordinated between Sweden, Norway, Denmark, Hungary, and the UK that involved reminiscence sessions in open-air museums for people with dementia, in which they found an increase in subjective well-being (Hansen, 2017).

Even though the concept of cognitive reserve has been actively investigated for the past two decades, there is still a lot of unknown regarding this concept. Education, initially considered the most important factor in building CR, has recently shown to have a more passive role than other potential CR factors, such as occupation or leisure activities, still it is important to keep in mind that the aforementioned factors are intertwined and a combination of them could be the strongest predictor of cognitive performance in face of pathology and / or cognitive decline.

1.1.3 Measuring cognitive reserve

There are different approaches to measuring cognitive reserve. As cognitive reserve is not a directly observable concept, it is often measured using either a proxy approach (e.g. literacy, verbal IQ, education, occupation), functional (fMRI, EEG measures) or residual model approach.

Sociobehavioural proxy indicators

One of the oldest approaches to measure cognitive reserve, is the sociodemographic approach, beginning with measures of individual proxies, such as education. As discussed above, a single proxy, such as education, might not reflect the cognitive reserve completely,

considering the wide array of factors contributing to it, thus several questionnaires of combined proxies have been developed. While these proxies provide an overall understanding of cognitive reserve, are cost effective and beneficial for a screening in research or clinical settings, there has been a critique regarding the limitations of measurement properties, namely, lack of studies reflecting the psychometric properties of the questionnaires (Kartschmit et al., 2019), this approach has also been critiqued by Stern and colleagues, noting that these factors are global in nature and do not reflect cognitive reserve directly, but rather through the factors that contribute to building cognitive reserve (Stern et al., 2020).

Functional measures

There have been several attempts to measure cognitive reserve using objective measures. One of such approaches is the use of EEG aiming to identify a wave or waveform that would correspond to cognitive reserve. EEG studies indicate that higher cognitive reserve is also associated with better neural efficiency, possibly through optimising the brain to use different networks in the brain for more challenging tasks (as shown in Gu et al., 2018). Several studies highlight the waveform p300b as a potential marker of CR, based on the latency and amplitude of the waveform when reacting to a challenging task, still more in-depth studies are needed to understand the mechanism (for more detail see review by Šneidere et al., 2020).

Opposite to EEG studies, fMRI studies investigate the potential functional networks associated with cognitive reserve. Results of a systematic review comprised of 13 cross-sectional studies on older adults with normal cognition, mild cognitive impairment and / or Alzheimer's disease showed that there is a cortex-seeded default network that included medial temporal and anterior or posterior cingulate regions associated with neural reserve, and frontal regions and dorsal attentional network that was associated with neural compensation (Anthony & Lin, 2018), thus indicating the possibility to use fMRI as a measure. However, it is still vague whether it is possible to measure cognitive reserve with objective measures, without considering brain reserve.

Residual model approach

Another approach to measuring cognitive reserve was proposed by Reed and colleagues (Reed et al., 2010) , stating that it is possible to quantify cognitive reserve by decomposing episodic memory variance. That is, cognitive reserve is what is left after removing all other variables traditionally associated with CR – demographic factors, MRI variables. This is done using regression analysis and the CR score is the residual left. This method would comply with the original proposition of CR as a discrepancy between what is observed and what is expected,

and in longitudinal studies have proved to be a useful method in predicting brain changes (Zahodne et al., n.d.); however, the method has been widely criticized over the years, highlighting the fact that the residual approach comes with significant statistical considerations (e.g. the residual cannot be interpreted as an independent variable, but rather dependent of the original measure) (Elman et al., 2022).

Literature indicates different approaches to measuring cognitive reserve, with each presenting with different gains and limitations and different levels of validity and reliability. While sociobehavioural approach is based on assumption that certain factors could enhance cognitive functioning, it does not provide the possibility to actually measure the functionality of the brain. Residual approach does comply with the original proposition of reserve theory as such, but is limited by its statistical assumptions.

1.2 The Scaffolding Theory of Aging and Cognition (STAC)

In 2009 a conceptual model by Denise Park and Patricia Reuter-Lorenz was published, aiming to explain the differences in brain ageing. The Scaffolding Theory of Aging and Cognition (STAC) initially proposed that the brain, and consequentially, cognition, was affected by two types of factors – neural challenges (structural changes in the brain, e.g. decrement of the cortical volume and white matter, brain atrophy) and functional degradation (e.g. dedifferentiation of visual and motor areas, reduction in activity in temporal lobes, etc.). Although both of these categories could be present in ageing, the severity of decline could be moderated by compensatory scaffolding, namely, additional schemes that could support functions that do not work properly. In turn, these schemes (scaffolding enhancement) could be increased through learning, social engagement, physical activity (exercise) and cognitive training (Goh & Park, 2009; Park & Reuter-Lorenz, 2009) (see Figure 1.3).

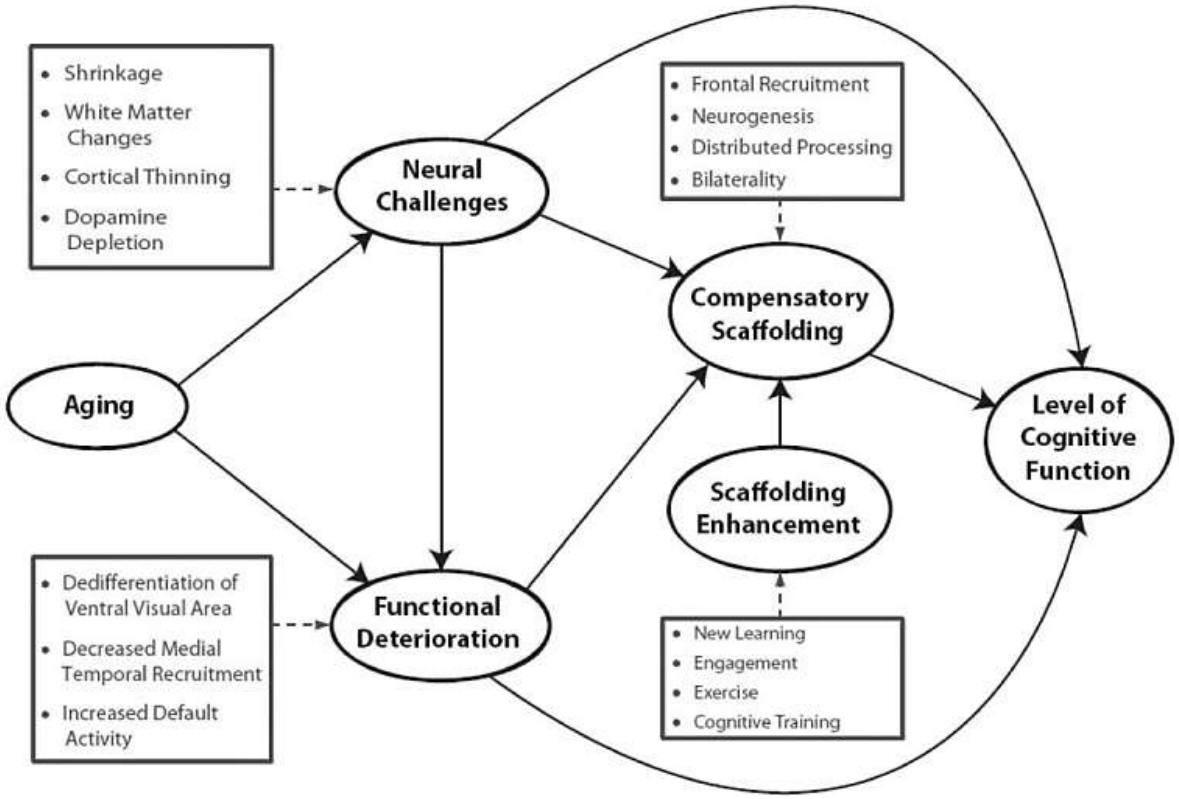

Figure 1.3 **Initial model of the Scaffolding Theory of Aging and Cognition**

(Park & Reuter-Lorenz, 2009)

After consideration, this model was revised (STAC-r), offering more complex and comprehensive description of both – ageing and compensatory processes (see Figure 1.4). Brain and cognitive function are still central to the model, proposing that biological aging impacts brain structures and function that in turn impacts cognitive functioning and the rate of cognitive change, still this impact is moderated by the compensatory scaffolding; however, the new model included the factors of life course experience. Life course experience would include modifiable and non-modifiable factors that might either enrich the neural resources (e.g. intellectual engagement, higher education, better fitness, multilingualism and overall better abilities), or deplete the neural resources (e.g. having APOε-4 gene, high stress, a vascular disease, lower SES, depression, neuroticism as a personality trait, head trauma or toxin exposure). The combination of these two factors together with biological ageing would impact the interaction between brain structure (cortical thickness, brain volume, white matter integrity, dopaminergic activity, Amyloid / Tau burden) and brain function (neural specificity, MTL activity, network connectivity, default network modulation). Furthermore, the neural resources could also impact the compensatory scaffolding more directly (Reuter-Lorenz & Park, 2014).

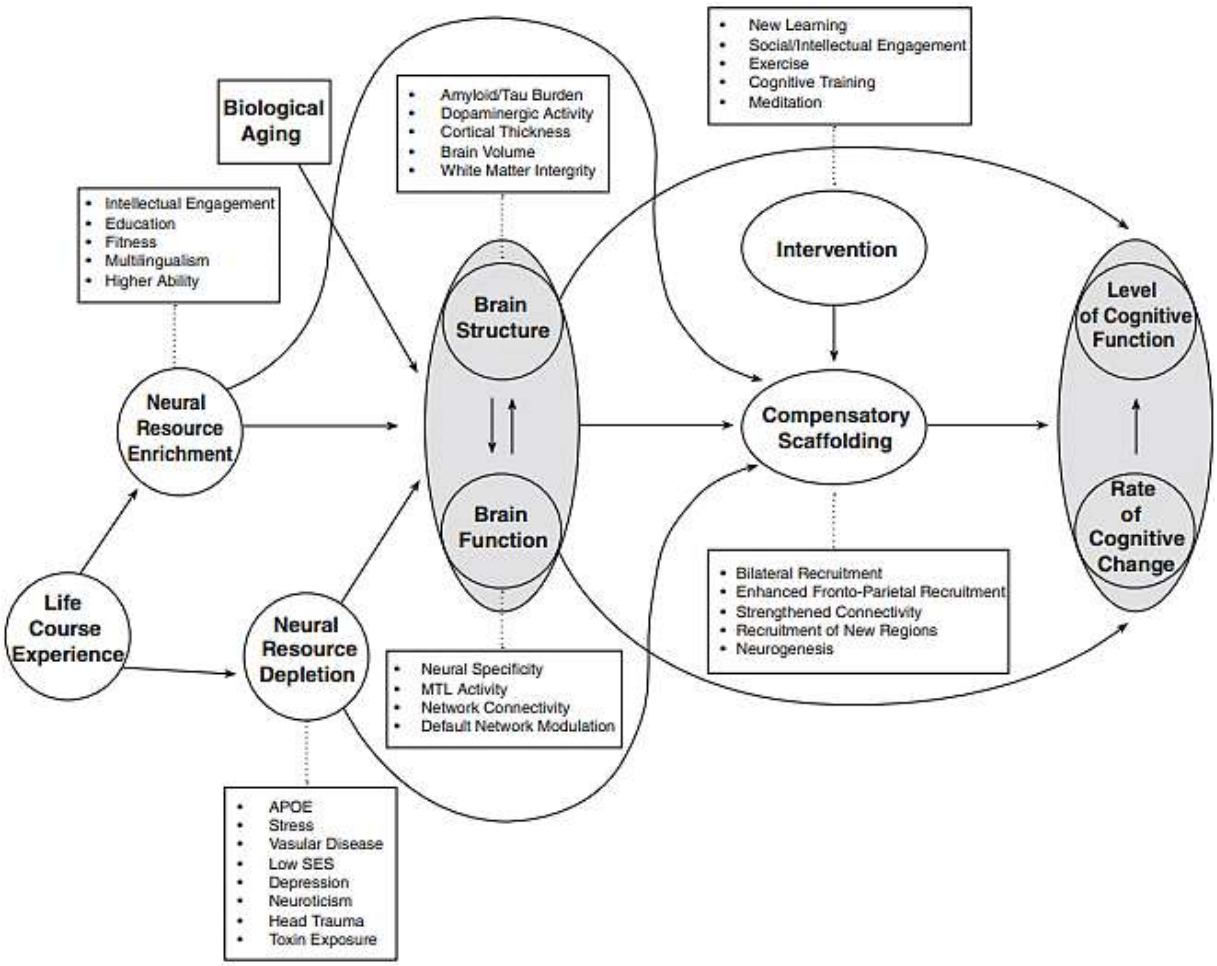

Figure 1.4 **The Scaffolding Theory of Aging and Cognition – Revised (STAC-R)**

(Reuter-Lorenz & Park, 2014)

The example of STAC shows the multidimensionality of the brain and the cognitive ageing process, and with it, the complexity of investigating the changes, as it is not a linear process. This is further supported by the results of a systematic review on the onset of cognitive decline in pathology, indicating the onset as early as three to seven years prior to diagnosis in the case of MCI and one to eleven years in case of dementia (Karr et al., 2018), thus highlighting the unpredictability of the disease, possibly, due to the wide variety of neural resources.

1.3 Comparison between the Cognitive Reserve theory and the STAC-r

While both theories suggest that the individual can compensate for age-related changes in the brain and can maintain cognitive functioning through the use of obtained and developed strategies, there are some differences (see Table 1.1).

Cognitive reserve theory is largely focused on the prior experiences, e.g. obtained education, occupational achievements etc., and the assumption is that the individual creates a reserve through life experiences that is later used for compensatory purposes. STAC-r opposes

this assumption and emphasises not only the role of prior experiences, but also the importance of current activities (interventions). Differences can also be found in the focus of each framework. While cognitive reserve considers the role of cognitive reserve in delaying cognitive decline, STAC-r encompasses effects of neural resource enrichment on both – brain structures and functions and cognitive performance (through compensatory scaffolding). Unlike STAC-r, the Cognitive Reserve theory does not directly consider life-style factors that might deplete the existing reserve or neural resources, though it should be noted that cognitive reserve initially was researched in the context of existing pathology. The Cognitive Reserve theory does not integrate a detailed explanation regarding the neural mechanisms contributing to cognitive ageing, though this is considered in the adjourning theories of brain reserve and brain maintenance. Finally, while both theories consider cognitive ageing from the same viewpoint, the Cognitive Reserve theory is more robust and structural and focused on the "building" blocks of the reserve, while the STAC-r approaches ageing from a more interactive and functional aspect, integrating the enrichment factors in an ongoing process.

Table 1.1

Conceptual differences between the Cognitive Reserve and the STAC-r theories

Factor	Cognitive Reserve theory (Stern et al., 2020)	STAC-r theory (Reuter-Lorenz & Park, 2014)
Level of detail	More robust, provides main steps of the compensation	More detailed, offers specific tasks for the compensation
Time	Focus on the prior experiences (previous life-style creates "a reserve")	Emphasises role of both - prior and current experience
Intervention	Focused on cognitive level	Encompasses both – cognitive and brain level
Cognitive and brain decline	Excludes life-style factors that could deplete the reserve and facilitate the decline	Takes into consideration the factors promoting brain and cognitive decline
Neural mechanisms	Original theory does not explain the neural changes (though it is done through brain reserve and brain maintenance theories)	Integrates neural changes in the model
Approach	More structural, explains what ageing includes	More functional, explains, how cognitive functioning is changed

Overall, both theories offer an explanation to differences in cognitive ageing. The cognitive reserve or scaffolding and enrichment factors are considered to have a moderator role between the variables and cognitive changes are presumed to be directly related only to the neural changes. Based on the aforementioned frameworks, an integrative theoretical framework was developed.

1.4 Cognitive functions

The term "cognitive functions" refer to a variety of abilities aiming to ensure a successful daily life functioning. Cognitive functions are, e.g. memory, attention, mental processing speed, executive functions, language, visuo-spatial abilities etc. (Palmese, 2011). Even in normal and healthy ageing, a decline in cognitive functioning is present and is often associated with structural and functional changes in the brain (Murman, 2015). In this subchapter, cognitive functions often associated with normal and pathological cognitive decline, are briefly discussed.

1.4.1 Language production (vocabulary and verbal fluency)

Language is a complex mainly communicative system that is used to rely individual thoughts and feelings through symbols – speech sounds or written words. Language includes distinctive vocabulary, grammar and phonological systems (APA Dictionary of Psychology, 2022). Production is one of the main characteristics of language and it involves the choice of appropriate syntax, morphology, and prosody, as well as, lexical selection and discourse planning, that further must be articulate to create meaningful message (Dell & Jacobs, 2016; Kemper & Altmann, 2009).

Verbal fluency is a cognitive function that involves retrieval of information from memory and is characterised by the speed and ease of language production. It is often also damaged in dementia (e.g. Parkinsonian or Alzheimer's dementia) (Kemper & Altmann, 2009; Patterson, 2011). Verbal fluency or fluency of speech is normally measured by the quantity of words produced in either of two ways – semantic (also – category) and phonemic (also – letter). Semantic fluency includes semantic category exemplars, e.g. names of animals, flowers, vegetables etc. (category guided), while phonemic fluency is usually assessed by asking to name as many words as possible starting with a specific letter (letter guided). The chosen letters are often limited to the specifics of the task (Patterson, 2011). In both cases, the tasks are often timed and strict rules regarding the type of words and repetitions are given beforehand (Lezak et al., 2012).

Verbal fluency is not possible without vocabulary (also – lexicon). Vocabulary is the full collection of words of a particular language, field or knowledge that is accumulated during the life-time. It can be divided into receptive vocabulary (understanding of words) and expressive vocabulary (use of words) and is often used in cognitive tests to reflect crystallized abilities – verbal abilities (Steffani & Huang, 2011). Vocabulary can also be considered from the aspect of breadth and depth. Breadth refers to the amount of words known to an individual,

while depth – to the understanding the meaning of the words (e.g. you may be aware of the word “onomatopoeia”; however, do not know that it is, according to the Cambridge Dictionary, “the act of creating or using words that include sounds that are similar to the noises the words refer to”). Several studies have found a relationship between vocabulary breadth and depth and reading comprehension and reading rate, showing that stronger depth of vocabulary could affect reading comprehension in adults with different levels of literacy skills (Binder et al., 2017; Tran et al., 2020).

1.4.2 Memory

Memory is a cognitive function that can be structured according to its temporal dimension (short and long-term memory), content (semantic or episodic memory) or mechanisms of acquisition (declarative and non-declarative memory). Memory also includes three main processes: encoding, consolidation, and retrieval (Brem et al., 2013). There are different approaches to memory storage processes, with the multistore memory model proposed by Atkinson and Shiffrin still being among the most popular (Atkinson & Shiffrin, 1968). For a composed visualization of the type and processes, see Figure 1.5.

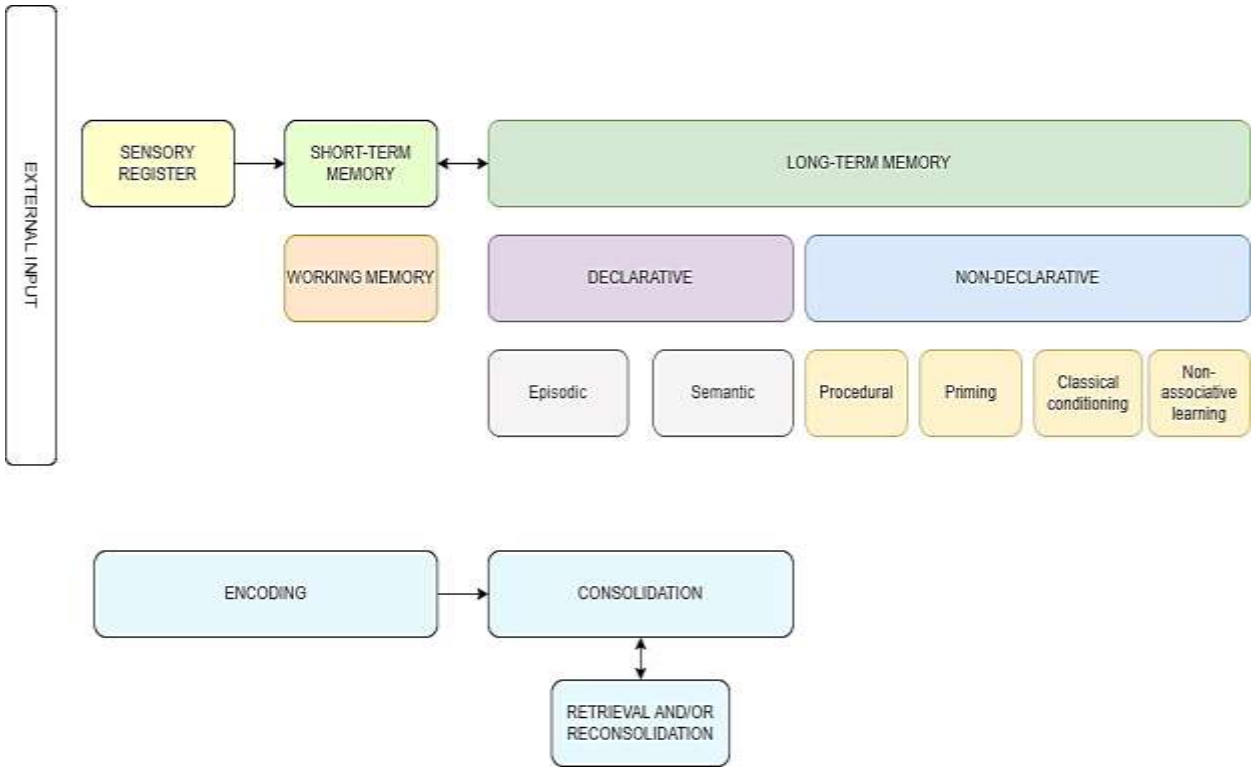

Figure 1.5 **Types of memory and memory processes**

Based on the temporal dimension, memory is traditionally divided into long-term and short-term memory. Long-term memory is "a vast store of knowledge and a record of prior events" (Cowan, 2008) that can be kept for days, weeks or years. Long-term memory is divided into two main systems – declarative memory (also – explicit memory) and non-declarative memory (also – implicit memory). Declarative memory is defined as "the capacity for conscious recollection about facts and events" (Squire, 2004). To differentiate memory from knowledge, Estonian-born cognitive neuroscientist Endel Tulving from the University of Toronto introduced the division of episodic and semantic memory. Episodic memory involves the autobiographical content of the memory, e.g. events and experiences that also include not only the fact, but context and emotions as well. In turn, semantic memory refers to actual facts, symbols, and concepts (Tulving, 1972).

Non-declarative memory or procedural memory, refers to several memory systems and is mainly focussed on skill-based information (skills - performance) and habit formation. As opposed to declarative memory, non-declarative memory is not formed as a storage of information but is rather retrieved through performance and reactivation of the systems through which they were learnt (e.g. the skill of riding a bike would be recollected through motor action when actually riding the bike, while episodic memory would recall the experience of the event of riding the bike for the first time) (Squire, 2004, 2009).

Another element of multi-store model is short-term memory. Short-term memory refers to the ability to hold a limited amount of easily accessible information for a short period of time (Cowan, 2008). There are rather opposite approaches to the origins of short-term memory, with some researchers concluding that it is a separate storage of information (e.g. see review by Norris, 2017), while others view it as an activation of long-term memory storage (e.g. Cowan, 2008). Similar debate has been present regarding the differences between short-term memory and working memory. In this study, we refer to short-term memory in the context of its storage, while working memory – in the context of manipulation of the information stored in the short-term memory. Working memory thus refers to the memory used to plan and carry out individual behaviour (Cowan, 2008) and is also often referred to as one of the executive functions (e.g. see review by Diamond, 2013).

1.4.3 Executive functions

Executive function (also – executive control, cognitive control) is a group of higher-level cognitive processes that are involved in performing a specific task or tasks and is generally divided into three main components: inhibition, working memory and cognitive flexibility (Diamond, 2013; Vaughan & Giovanello, 2010), though there are different approaches to

defining the processes involved, adding other processes, such as set-shifting. Many researchers refer to executive functions as to an umbrella term, that encompasses top-down control mechanisms that further support more complex processes, such as decision making and others (Putkinen & Saarikivi, 2018).

Inhibition refers to the ability to manage one's attention, behaviour, thoughts and emotions in order to override a dominant reaction, thus allowing one to focus on the task at hand. Cognitive flexibility refers to the ability to quickly adjust to a changing situation, change perspectives, think "outside the box", while the concept of working memory, as discussed before, refers to the manipulation and remembering of the goal-related information (Diamond, 2013; Ganesan & Steinbeis, 2022). Set-shifting, meanwhile, refers to switching between response strategies (Putkinen & Saarikivi, 2018)

Another approach to executive functions is the distinction of hot and cold domains of executive function. Cold executive functions involve purely cognitive processes and include working memory, set shifting, response inhibitions, attentional control, cognitive flexibility, verbal fluency and others, while hot executive functions refer to emotional reactions, such as emotion regulation, reward processing, social cognition and others. Cold executive functions are located in prefrontal regions (dorsolateral and lateral prefrontal cortex), inferior frontal cortex and anterior cingulate cortex, as well as, hippocampus and basal ganglia. Meanwhile, hot executive functions are associated with three other prefrontal cortex areas (medial and ventrolateral prefrontal cortex and orbitofrontal cortex), as well as, limbic system, insula and striatum (Salehinejad et al., 2021).

1.4.4 Information processing speed

Information processing speed (also – mental speed, cognitive speed) is defined as "a measure of the efficiency of cognitive function" and is assessed through timing tasks, measuring either the time spent in doing a specific test (e. g. reaction time tests) or the amount of correct answers within a time frame (e.g. Visual Matching Task in Woodcock-Johnson test of Cognitive Abilities) (Deary & Ritchie, 2016; Sweet, 2011). Often used proxy for processing speed is the reaction time (also – response time, response latency) that is the time spent from the moment a stimulus is received till action is performed (e.g. go / no-go tasks). It is often measured in seconds or milliseconds and can be distinguished depending from the complexity of the stimulus or action. Simple reaction time refers to an easy stimulus and easy action, e.g. catching a falling object. Recognition reaction time, another type of reaction, refers to individuals' ability to choose the right reaction to the action necessary, e.g. recognising the colour of the light in a traffic light and choosing to wait or walk. Choice reaction time includes

multiple stimuli and multiple actions to be performed (Baayen & Milin, 2010; Balakrishnan et al., 2014).

Processing speed has been associated with different cognitive functions. In 2016, Kievit and colleagues proposed that there is a hierarchical relationship between brain white matter, different types of information processing and fluid intelligence, thus contributing to the processing speed theory of ageing introduced by Timothy Salthouse in 1996 (Salthouse, 1996). Kievit and his team used three different processing speed reaction times (simple, choice response and audio-visual cued response time), including mean and SD scores in further analysis. For fluid intelligence, Cattell's Culture Fair Scale 2 Form A was used, that includes subtests on abstract reasoning – series completion, classification, matrices and conditions. White matter fractional anisotropy (FA) was measured in ten different tracts. The results confirmed the hierarchical structure hypothesis, showing that white matter integrity predicts processing speed and in turn - processing speed predicts fluid intelligence (Kievit et al., 2016). The role of processing speed and cognitive performance has also been widely investigated within the ageing framework.

Possibly the best-known theory on processing speed is aforementioned processing-speed theory proposed by Salthouse. He argued that the decrease in speed is associated with at least some of age-related differences in cognitive performance in aging adults, thus it is not the process *per se* that has a decline, but rather there is a decline in information processing speed that supports the aforementioned process (Salthouse, 1996). Further studies have partially supported Salthouses' claim, noting that while processing speed could be a significant factor in age-related cognitive decline, there are additional variables involved (Robitaille et al., 2013; Schubert et al., 2019). This indicate that in future ageing studies, processing speed could function as a mediator between objective and behavioural measures.

1.5 Brain anatomy and the associated functions

The history of assigning the functional marker to a specific brain region is long and initially focused on the lesion-deficit approach that observes the behaviour of people with brain damage. Typical examples here are stories of Tan (Broca's aphasia and frontal lobe damage) or the case of Phineas Gage (prefrontal cortex damage) or more recent cases of H. M. (bilateral hippocampus damage) or S. M. (Kluver-Bucy syndrome). However, the twentieth century marks the age of introducing noninvasive methods into brain studies, specifically CT, PET, MRI and functional MRI (Raichle, 2009). Today, there are two main approaches to brain mapping – segregation and integration. **The segregation approach** refers to an assumption that the cerebral cortex can be divided into regionally distinct modules that are based on its

functional and structural properties, while the **integration approach** argues that no brain region is self-sufficient enough for executing a specific cognitive, sensory, or motor function, and thus there should be a dynamic exchange of information between several regions (Genon et al., 2018). In this Thesis, only the segregation approach, more specifically, the structure-behaviour correlation – is used; however, it should be stressed that these approaches do not contradict, but rather complement each other.

The brain is a part of the central nervous system and is crucial in commanding and coordinating task-evoked responses, senses, movement, emotions, and higher cognitive functions (Maldonado & Alsayouri, 2021). A significant part of the brain is the cerebral cortex, which is mainly composed of neuronal bodies (grey matter) and can be categorised by considering the functional characteristics of the brain (sensory, motor, and association areas) or based on the division of sulcus and gyri (frontal, temporal, parietal and occipital lobes). To ensure that the large brain can fit into the skull, it is folded. The deep fissures in the brain are called sulcus, whereas the bulges are called gyrus. There are in general four main sulci: Sylvian fissure (divides the frontal lobe from the temporal lobe), the central sulcus (separates the frontal and parietal lobe), the parieto-occipital sulcus (divides the parietal and occipital lobes) and the calcarine sulcus (divides the cuneus from the lingual gyrus) (Javed et al., 2021). There are also 12 main gyrus: angular gyrus, inferior frontal gyrus, inferior temporal gyrus, middle frontal gyrus, middle occipital gyrus, middle temporal gyrus, postcentral gyrus, precentral gyrus, superior frontal gyrus, supramarginal gyrus, superior occipital gyrus, superior temporal gyrus (Ribas, 2010).

There are several approaches to mapping the brain – based on gyrus and sulcus (frontal, temporal, parietal, occipital), based on their functionality (premotor, sensomotor, associative) and Brodmann areas. In this study, the gyrus and sulcus approach was used, thus it is discussed in more detail below.

1.5.1 Anatomy and function of cortical structures

The gyrus and sulcus approach divides brain into four main parts: frontal, temporal, parietal and occipital lobes (see Figure 1.6). It should be noted that often insula is considered separately as the fifth; however, due to the methodology used for data acquisition, in this Thesis the four-part approach will be used.

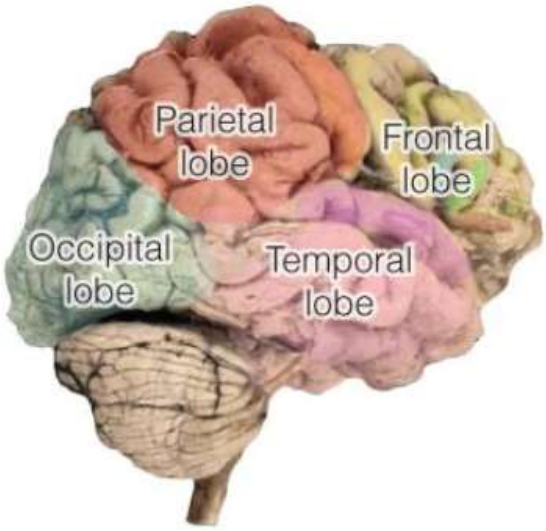

Figure 1.6 **Cortical division based on gyrus and sulcus: frontal, temporal, parietal and occipital lobes**

(Modified from Chauhan et al., 2021)

The frontal lobe is the largest lobe (more than a third of an entire hemisphere) of all four and is located anterior to the central sulcus and posterior to the lateral fissure and is further divided into five regions – the superior, middle, and inferior frontal gyrus, primary motor cortex, and orbital area and are mostly considered significant in ensuring voluntary motor control (movement), speech production (Broca's area in the left hemisphere), higher-order associations and complex cognitive behaviours (specifically – prefrontal cortex), impulse control, etc. (Bui & Das, 2022; El-Baba & Schury, 2022).

Regarding cognitive function, two regions should be specifically highlighted: the **prefrontal cortex** (PFC) and the **inferior frontal gyrus**, especially the pars orbitalis. Pars orbitalis is divided into two main parts, opercular and lateral which each has a separate function. Lateral inferior pars orbitalis is involved in semantics and emotional expression and has functional connectivity with limbic and language areas, while opercular area of pars orbitalis is associated with perceived expressions of emotion and has functional connectivity with the limbic system (Belyk et al., 2017). Meanwhile, the prefrontal cortex can be divided into medial, lateral, and orbital prefrontal cortex. The prefrontal cortex is normally associated with higher cognitive processes, such as executive functions and memory encoding (Hathaway & Newton, 2022; Siddiqui et al., 2008); however, it has also been implied to be involved in social brain, especially, self-awareness and self-knowledge, self-regulation (Heatherton, 2011), mentalization (Monticelli et al., 2021), etc.

The temporal lobe is located on both sides of the hemispheres and has conjunctions with the rest of the lobes – frontal, parietal, and occipital. It can be further divided into the superior, middle, and inferior temporal gyrus (lateral aspect) and entorhinal cortex,

parahippocampal cortex and fusiform gyrus (medial aspect). The temporal lobe also hosts the hippocampus and amygdala (subcortical structures) (Patel et al., 2022). Overall, the medial temporal lobe has traditionally been associated with long-term memory (medial temporal lobe memory system) and its involvement in spatial perception (Jeneson & Squire, 2012; Lech & Suchan, 2013; Ruiz et al., 2020).

As mentioned above, **the medial aspect of the temporal lobe** includes the entorhinal cortex, the parahippocampal cortex and the fusiform gyrus. The main function of the entorhinal cortex is to provide the primary cortical input to the hippocampus (Knierim et al., 2014) and it functions closely with the parahippocampal cortex in object-in-place memory (Yeung et al., 2019). The role of the entorhinal cortex has also been implied in information processing, executive functioning, and episodic memory (Tsapanou et al., 2019). The parahippocampal gyrus, meanwhile, has a central role in different visuospatial (scene perception, aforementioned object-in-place memory, spatial representation and navigation) and mnemonic processes (Baumann & Mattingley, 2016), as well as in episodic memory, emotion processing, distinguishing centre-periphery of the visual field and responding to visual stimuli (Aminoff et al., 2013). The parahippocampal region could also be present in olfactory decline (Iizuka et al., 2021) and thicker cortex in this region has been associated with better processing speed, executive functioning and episodic memory (Tsapanou et al., 2019). While the aforementioned structures have been more related to the execution of spatial aspects of memory, the fusiform gyrus has been associated with participation in face perception, object recognition, and reading (Weiner & Zilles, 2016).

If the medial aspect of the temporal lobe has been mostly associated with memory and visuo-spatial functions, the **lateral aspect of the temporal lobe** contains more functions associated with auditory stimuli, as well as is integrated in the social behaviour. The **superior temporal gyrus** (STG) includes the auditory cortex and stores the core audio-visual processing network together with the thalamus and amygdala (Gao et al., 2019). It has also been associated with a delayed auditory effect, i.e. asynchrony between speech production and its feedback to the auditory system that causes disruption of fluent speech (Hashimoto & Sakai, 2003) and is a part of a neural network involved in processing sounds coming from different locations (Brunetti et al., 2005). has been associated with social composition and is believed to play a significant role in the ventral visual pathway, which is especially involved in object, face, and scene perception (Conway, 2018; Yang & Bi, 2022). Left hemisphere **middle temporal gyrus** has shown a functional connectivity with hippocampus in rewiring and updating new information (Davey et al., 2016).

The parietal lobe has been associated with perception, sensation, and integration of sensory input with the visual system and includes the somatosensory cortex (Javed et al., 2021), although the role of the **posterior parietal cortex** particularly has been best known as the centre for computing motor commands based on sensory input (Rathelot et al., 2017). The parietal lobe together with the frontal lobe regions has also been implied to be involved in the writing process (Katanoda et al., 2001), and functional studies indicate the relationship between higher demanding working memory tasks and activation in the parietal and temporal regions (Van Snellenberg et al., 2015). It should also be noted that the **inferior parietal lobe** is a region proposed to be vulnerable to Alzheimer's disease (Jacobs et al., 2011).

The occipital lobe is the centre of visual information in humans and is located posterior to the temporal and parietal lobes. It is divided into three main gyri, superior, middle and inferior in is the main visual processing area for the brain, as it contains the primary and association visual cortex (Rehman & Khalili, 2022).

Overall, while it is relatively possible to distinguish between different anatomical structures based on gyrus and sulcus, current findings in neuroscience indicate that one structure cannot be responsible for just one cognitive function, rather, structure functional systems.

1.5.2 Anatomy and function of thalamus

The thalamus is a relatively large bilateral subcortical structure consisting mainly of grey matter and is a part of the diencephalon. Thalamus is not uniform, instead it consists of several nuclei. Overall, the nuclei can be categorized into three groups based either on the location or the function. The location is determined by internal and external medullary laminae (composed of white matter) and divides the thalamus into lateral, medial and anterior nuclear groups, while the categorization by function divides the thalamus into relay nuclei, reticular nucleus and intralaminar nuclei (Sheridan & Tadi, 2022; Torrico & Munakomi, 2022).

For a long time, the thalamus had been associated with a relatively passive role in ensuring cognitive functioning, namely, as the relay between perceived stimulus and the respective cortical region; however, the past decade of studies indicate the much more complex nature of this structure. While in the receiving and sending visual, auditory, etc. information is still an established function of the thalamus (Torrico & Munakomi, 2022), it has also been implied to be involved in several cognitive functions, mostly, in relation to its connectivity with other structures, thus thalamus have also been found to be a critical node in networks supporting verbal episodic memory, working memory, attention, and information processing speed (Fama & Sullivan, 2015). Later studies have indicated that thalamus nuclei are associated with cognitive flexibility (Hwang et al., 2019), as well as might function as a key mechanism in

maintaining and updating mental representations (Wolff & Vann, 2019). Even more, a significant role of thalamus in memory has been identified in a fMRI study by Geier and colleagues (Geier et al., 2020) finding a greater deactivation of the anterior part of the thalamus during a face-scene memory task encoding phase and a connectivity between the medial dorsal thalamus and the hippocampus, perirhinal, and parahippocampal cortex that are structures associated with memory function.

1.5.3 Anatomy and function of hippocampus

The hippocampus is a structure composed of grey matter tissue and is positioned within the parahippocampal area on the edge of the temporal lobe. It creates an S-shaped figure and can be largely separated into three main parts, head, body and tail, – and there are four hippocampal subfields – CA1, CA2, CA3 and CA4 (Anand & Dhikav, 2012; Fogwe et al., 2022) (see hippocampus position in axial, coronal, & sagittal planes in Figure 1.7).

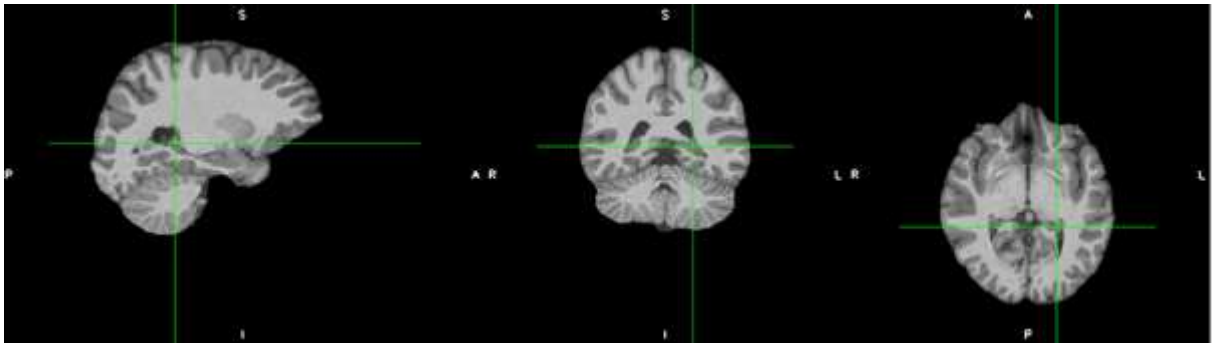

Figure 1.7 **Sagittal, coronal and axial view of hippocampus position**

Two best-known functions involving the hippocampus is episodic and spatial navigation, or, to be more precise, it provides "a spatial and temporal framework for relating experiences, creating a "cognitive map" of the organism's experienced world" (Lisman et al., 2017, pp 2). The role of the hippocampus has previously been investigated in terms of episodic memory and retrograde and anterograde amnesia. Possibly the best-known case that initiated extensive research was the case of H.M. and the case of K.C. that further facilitated the definition of episodic and semantic memories. K.C. was a middle-aged man who suffered widespread brain damage, including bilateral hippocampal lesions, due to a motorcycle accident. This caused a variety of cognitive symptoms, with the most prominent being the loss of memory regarding self (i.e. autobiographical memories), as well as partially intact visuo-spatial abilities (Rosenbaum et al., 2005). Nowadays, the interaction between memory as a cognitive function and hippocampus is seen as more complex, noting that in order to consolidate a coherent episodic memory representation, not only the encoding of the stimuli is

needed, but also their spatial, temporal, and conceptual representations (e.g. to remember the exam passed last year, there is need for perceived stimuli – visual, auditory, sensory, kinetic, etc., but also the when and where, as well as why and how is needed) (Voss et al., 2017). This closely correlates with another function associated with the hippocampus – the visuo-spatial abilities, especially, navigation. One of the earlier studies on effect of occupation on hippocampus was conducted by Eleanor Maguire and colleagues in the UK (Maguire et al., 2000), where they concluded that driving and navigating a taxi cab on a daily basis was associated with larger hippocampal volume that could be due to ensuring the visuo-spatial memory. Further studies have been conducted expanding Maguire's findings and currently the hippocampus together with the entorhinal cortex, parahippocampal and retrosplenial cortices and frontal lobe are identified as structural markers of so called "cognitive maps" (Epstein et al., 2017).

It should be stressed that this is a rather general description of hippocampal functions and current neuroimaging methods offer even more detailed insight into hippocampal functions and connectivity with other structures based on smaller hippocampal segments (e.g. see Sellami et al., 2017 for the relationship between temporal binding and CA1); however, since this is not the focus of the study, it will not be discussed here in more detail.

1.6 Integrative theoretical framework of the Thesis

While the Cognitive Reserve theory suggests that having higher cognitive reserve can be protective against age- or pathology related changes and maintain cognitive function, the Scaffolding Theory of Aging and Cognition proposes a more functional approach, namely – the use of developed strategies ("scaffolding") to compensate these changes. As discussed before, both frameworks are similar in nature; however, an integrative framework combining both theories would suggest that individuals with higher cognitive reserve might be able to utilize the developed scaffolding strategies more efficiently.

The changing brain and cognition due to ageing is often considered to be a part of the process. Cognitive ageing is often associated with decline in cognitive functioning that can be either objective, meaning that an actual impairment is present, or subjective, namely – cognitive testing shows no significant impairment; however, the individual perceives a persistent decline in one or several cognitive functions (Jessen et al., 2020). Nevertheless, there are some cognitive functions that seem to be more affected by the age than others, with some of the functions even remaining relatively unscathed (e.g. implicit memory). On the other hand, studies have shown a deterioration in executive functioning (Boucard et al., 2012), increased hardship in creating associations between an event and its context (Reuter-Lorenz & Park,

2010); however, a strong differentiation between subjective cognitive decline and cognitive impairment should be considered.

Similarly, even in normal brain ageing, volume loss, cortical thinning, white matter degradation, loss of gyrification, and ventricular enlargement are present (Blinkouskaya et al., 2021). A study aimed to identify the differences between pathological and physiological (normal) brain aging found that, while cortical thickness was depleted in both cases, the regions differed. Patients with MCI and AD showed decreased cortical thickness in the perisylvian regions, the *precuneus*, inferior temporal regions, and the medial temporal regions in those over 80 (Lee et al., 2019). The subcortical structures can also be affected. For example, the structure, function, and connectivity of the thalamus has shown decline due to the ageing process (Fama & Sullivan, 2015), though that could also be nuclei dependent. A recently published study by Choi and colleagues (2022), showed that thalamus atrophy can be as significant as 0.45 % per year; however, the significance of atrophy differs between nuclei, with the most notable being the lateral geniculate nucleus and the anteroventral nuclei (-0.77 % and 1.18 % per year), with the rate increasing around the age of 60. Similarly, while reductions in hippocampal volume have been identified in ageing, in this case the changes could also be structure-specific, namely, some studies have shown that the posterior hippocampus could be more sensitive to ageing than the anterior part of the hippocampus (Bettio et al., 2017).

As evidenced by the previous studies, the cognitive and neural (brain) changes are present in ageing. Cognitive reserve together with enhancement strategies has been found to be a factor compensating for the brain changes; therefore, an integrative theoretical framework encompassing the relationship between cognitive reserve and brain structural measures and cognitive functions was developed (see Figure 1.8).

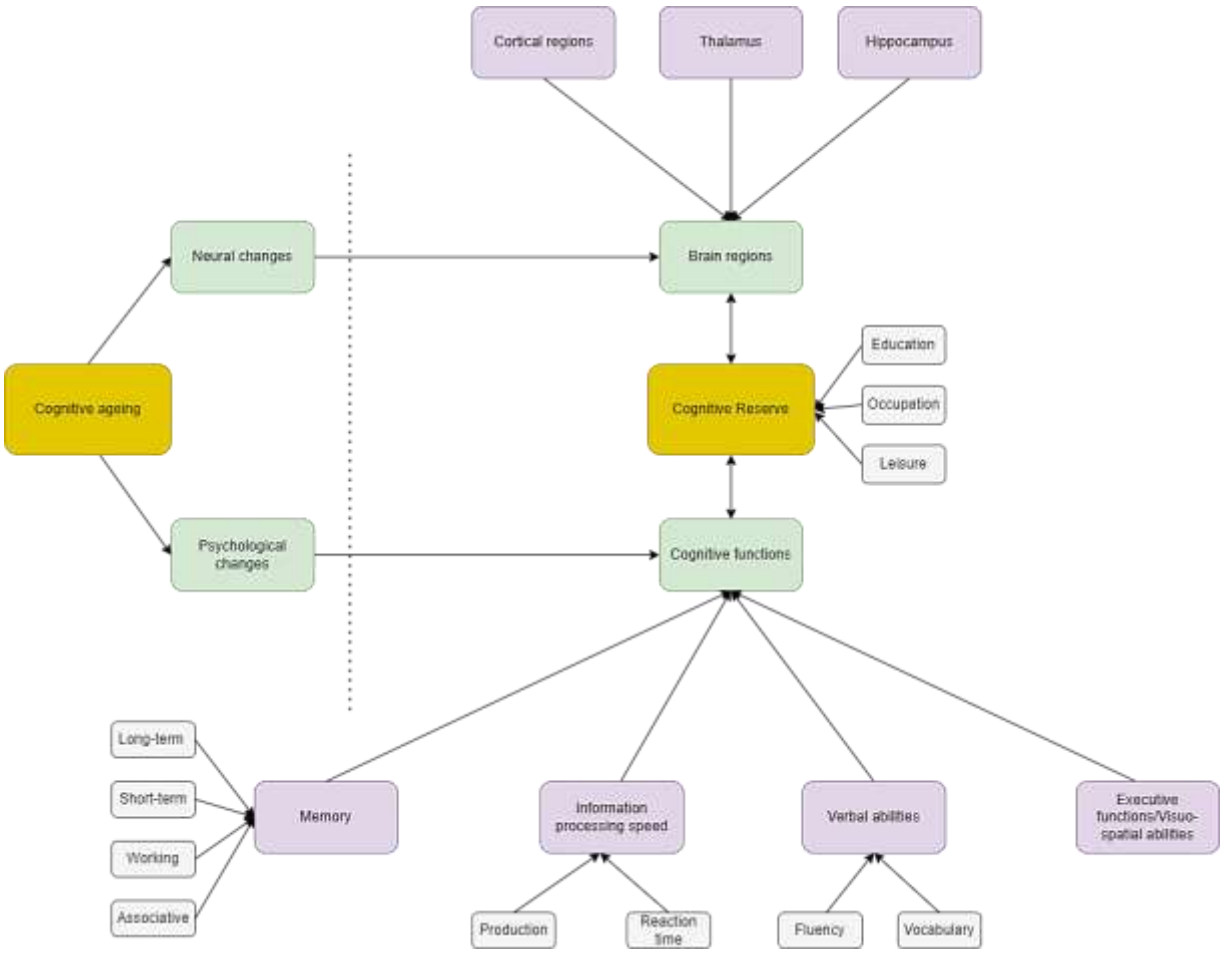

Figure 1.8 **Integrative theoretical framework of the study**

In 2013, Arenaza-Urquijo and colleagues published a study investigating the relationship between education and grey matter volume, brain metabolism, and resting-state functional connectivity. Results indicated that more years of education was also associated with larger volume in **right hemisphere superior temporal gyrus**, **left hemisphere insular cortex** and **bilateral anterior cingulate gyrus** (Arenaza-Urquijo et al., 2013). However, earlier studies indicate that the relationship may be more complex. The results of a study published in 2012 showed that higher educational attainment could be associated with a greater regional cortical thickness in the **transverse temporal cortex**, **the insula,** and the **isthmus** of the cingulate cortex in healthy older adults; however, the results were opposite in the AD sample, where higher education was associated with a smaller regional cortical thickness in the **temporal gyrus**, **inferior** and the **superior parietal gyri**, and **lateral occipital cortex** compared to the less educated participants. These findings support the findings of the longitudinal study by Nyberg et al., 2020, showing that education is beneficial for brain reserve until a fixed threshold is reached in a healthy brain. However, after the onset of pathology, cognitive reserve ensures the efficacy of cognitive performance (Liu et al., 2012).

Studies investigating **hippocampal** volume and its relationship to cognitive reserve have been sparse and show inconsistent results, e.g. depending on the type of cognitive reserve proxy used. A study by Serra and colleagues found that the relationship between cognitive reserve and hippocampal volume in groups of AD, MCI and healthy controls differed depending from whether a static measure of cognitive reserve (education) or a dynamic composite score based on MMSE results was used. Unsurprisingly, hippocampal volume was larger in AD and MCI patients with higher levels of education; however, the opposite was found in participants when cognitive reserve levels were based on the dynamic composite score, while no differences were found in healthy subjects (Serra et al., 2019). Similar conclusion was drawn, when investigating the microstructure of hippocampus in middle-aged adults – no relationship between composite score of cognitive reserve proxies (education, occupation and verbal IQ) and hippocampal grey matter mean diffusivity (MD) was found (Kalzendorf et al., 2020). Nevertheless, cognitive reserve has been found to be a mediator between hippocampal volume and episodic memory in cases of low reserve (Vuoksimaa et al., 2013).

The relationship between cognitive reserve and different brain structures is complex, and there are several factors that could impact this association. There is still no consensus on the cortical regions that might benefit from increased cognitive reserve; however, most studies indicate a relationship between cognitive reserve and the segments of the temporal regions and cingulate gyrus. Less consistent are the data on the hippocampus – studies highlight the need for a unified measure of cognitive reserve.

Most studies on the relationship between cognitive reserve and cognitive functioning have been focused on the role of cognitive reserve in pathology, e.g. in case of neurodegenerative disease or traumatic brain injury. A study by Krch and colleagues found that patients after brain injury, who had low cognitive reserve (as measured by vocabulary proxy), also had worse memory performance as compared with participants with high reserve, though this effect disappeared at the highest levels of neuropathology (Krch et al., 2019). These findings are consistent with other studies that have used education and composite scores as proxies and confirms the potentially positive effect of cognitive reserve and cognitive performance after brain injury (Leary et al., 2018; Sumowski et al., 2013). The role of cognitive reserve in delaying the onset of dementia has also been vastly investigated, providing similar findings to the ones of Katzman and Stern earlier.

A longitudinal study by Vonk and colleagues found that higher cognitive reserve as measured by two proxies – education and Dutch Adult Reading Task (DART) was associated with slower rate of memory decline, furthermore, memory decline in mid- and high-cognitive reserve groups was slower than the rate of brain atrophy (Vonk et al., 2022). These findings

partially support the results of Arenaza-Urquijo et al. (2013) showing that more years spent at school or higher education institution could be associated with better performance in semantic and phonological verbal fluency tasks, as well as in Stroop test. Similarly, a representative longitudinal study comprised of 10 different countries and using SHARE data found that education could have, albeit weak, protective effect on memory change; however, the association was the strongest at the baseline measure (Cadar et al., 2017). These findings complemented another study that investigated whether education as a proxy of cognitive reserve differentially associates with cognitive performance in healthy adults. The study found that education statistically significantly predicted not all, but several higher level cognitive functions, namely, attention, verbal fluency, visuo-spatial abilities and orientation in time and space, verbal memory (Lavrencic et al., 2017). Occupation has also been found to be a significant proxy for cognitive reserve. The results of a retrospective longitudinal study conducted by Mondini and colleagues highlighted the role of both – education and occupation – in protecting from cognitive decline (Mondini et al., 2022).

2 Materials and Methods

2.1 Relationship between cognitive reserve and cognitive functioning in a partially representative sample

To test the hypothesis that higher levels of education, active employment and active daily lifestyle will be associated with better memory performance and higher scores of verbal fluency in healthy adults, secondary data from Survey of Health, Ageing and Retirement in Europe (SHARE) project, Wave 8 were used (Bergmann & Börsch-Supan, 2022; Börsch-Supan, 2022; Börsch-Supan et al., 2013). SHARE is a research infrastructure that aims to investigate the effects of health, social, economic and environmental policies in 28 European countries and Israel since year 2004. Latvia has been a part of SHARE project since 2017 and have participated in the two last waves. SHARE data are freely available to the registered users and can be used for scientific purposes only.

2.1.1 Participants

546 Latvian-speaking participants with no diagnosis of dementia and aged 42–103 (M = 70.54, SD = 10.19, 37.2 % male) were included in the data analysis. All participants had at least primary school education (M_{years} = 11.56, SD = 2.83) and 26.9 % of them were still employed. 63.2 % of the participants were retired, 2.9 % were unemployed for other reasons, 5.5 % were reported as permanently sick or disabled, and 1.5 % noted that they are homemakers. The majority of participants noted that they are still married and live together while a spouse (57.3 %), with the rest reported either registered partnership, living separately, never being married, divorced, or widowed.

2.1.2 Measures and materials

Data on education, occupation, and leisure were used as proxies for cognitive reserve. For cognitive performance, short- and long-term memory measures, as well as verbal memory, were used (see Table 2.1 for more details).

Cognitive reserve proxies

Cognitive reserve was measured using three main domains – education, occupation, and leisure. Education scores were initially coded as level of highest educational degree obtained. For the purpose of this Thesis, the categories were quantified using computed mean years per category (e.g. acquired high-school degree would be 11 years, as that was the length of school).

Occupational activity was determined by identifying current job situation – retired, employed, or self-employed, permanently sick, disabled, and homemaker). For the purposes of SEM analysis, the responses were divided into two categories – currently employed and doing paid work or currently not employed.

The leisure activities were divided into two main parts - physical activity and general activities done. Physical activity was measured in two aspects, vigorous and moderate activities done in the past year and were ranged from more than once a week to hardly ever or never. Overall activities included voluntary or charity work, educational or training course, going to a social club or sports club, reading books, journals, newspapers, doing word or number puzzles, or playing chess or board games. The participants had to answer whether they are participating or not in the activity.

Cognitive function

Long- and short-term memory was measured using a ten-word task, in which the participant was presented with ten nonrelated words (e. g. a river, a king, a book, etc.) and asked to repeat the words in non-specific order. The participant was then asked to recall the words again approximately 10 minutes later, after finishing several other tasks.

Verbal fluency was measured using a semantic verbal fluency task in which participants were asked to name as many animals as possible in one minute.

Table 2.1

Variables, respective questions and scoring

Variable	Question	Scale / Score
Education	What higher or professional education levels have you obtained?	Computed mean years
Occupation	What is your current employment situation?	Nominal scale, where employment – 1, non-employment – 0
Leisure		
Activities done	Which of the activities listed on this card – if any – have you done in the last twelve months? 1) Done voluntary or charity work 2) Attended an educational or training course 3) Gone to a sport, social or other kind of club 4) Taken part in a political or community-related organization 5) Read books, magazines or newspapers 6) Did word or number games such as crossword puzzles or Sudoku 7) Played cards or games such as chess.	Nominal scale, where activity done – 1, activity not done – 0.

Table 2.1 continued

Variable	Question	Scale / Score
Leisure		
Vigorous physical activities	How often do you engage in vigorous physical activity, such as sports, heavy housework, or a job that involves physical labour?	Scale from 1–4, where 1 – hardly ever or never, 2 – one to three times a month, 3 – once a week, 4 – more than once per week
Moderate physical activities	How often do you engage in activities that require a moderate level of energy such as gardening, cleaning the car, or doing a walk?	Scale from 1–4, where 1 – hardly ever or never, 2 – one to three times a month, 3 – once a week, 4 – more than once per week
Memory		
Short-term memory	Please tell me all the words you can recall.	Sum of correct answers
Long-term memory	Please tell me all the words you can recall.	Sum of correct answers
Verbal fluency	I would like you to name as many different animals as you can think of. You have one minute to do this.	Sum of correct answers

2.1.3 Procedure

All data were obtained between November 2019 and March 20 using face-to-face interviews and the Computer Assisted Personal Interview (CAPI) method. Due to the onset of COVID-19, only approximately 70 % of the longitudinal interviews and 50 % of the refreshment interviews were obtained, thus the sample might not be fully representative. All data were obtained by trained specialists from the professional research agency Institute of Social Research. All interviews were conducted frontally with either the participant or their guardian present.

Ethical considerations

SHARE-project Wave 8 has been approved by the Ethical Committee of Max Planck Society. All participants signed informed consent prior to data acquisition and were informed about their rights to refuse further participation in the study. All data were anonymised. For the purposes of this Thesis, a confirmation from SHARE-project for the use of data was received (see Annex 1), as well as, research approval from Rīga Stradiņš University Ethics Committee (No. 2-PĒK-4/601/2022, see Annex 2).

2.1.4 Data analysis

Descriptive statistics included mean, standard deviation, minimum, and maximum scores, as well as percentage of frequency of the activity. To investigate the relationship between socio-behavioural proxies of cognitive reserve and memory and verbal fluency, the

Spearman's rank correlation coefficient was used. Finally, to understand the relationship between all variables, the structural equation model was created using R 4.2.1. software with the *lavaan* package (Rosseel, 2012).

2.2 Relationship between cognitive reserve and cognitive functions in a sample of older Latvian adults

To test the hypothesis that higher cognitive reserve will be associated with better cognitive performance in memory, information processing speed, visuo-spatial abilities, executive functions and language abilities in healthy older adults, primary data obtained through the National Research Program "BIOMEDICINE-LV" subproject "Establishing the Net Attainable Benefits of Long-term Exercise, ENABLE-LV" were used.

2.2.1 Participants

61 participants aged 65–85 (M = 71.87, 19.7 % male) were included in the study. All of the participants were living independently alone or with a partner, all had at least 11 years of education and had been employed at some point in their life. All participants were right-handed and had good or corrected vision.

Only participants with no self-reported neurological, cardiovascular, pulmonary, and respiratory disease that require inhalators, ongoing oncological disease, rheumatologic diseases that require pain medication, mental disease, and other factors, such as metallic implants, aged 65 and over and native Latvian speakers were included in the data analysis.

2.2.2 Measures and materials

In general, data on cognitive reserve, cognitive processes (memory, processing speed, verbal skills, visuo-spatial skills) and brain volume were obtained. Measures are described in more detail below (for a general overview, see Table 2.2).

Table 2.2

Measures of variables

Measure	Variable
Cognitive Reserve Index questionnaire	Cognitive reserve approximation based on sociobehavioural variables
Woodcock-Johnson III: Tests of Cognitive Abilities:	Neuropsychological test battery
Memory for Names	Associative and long-term memory
Numbers Reversed	Working memory
Visual Matching task	Visual attention, processing speed

Table 2.2 continued

Measure	Variable
Verbal Comprehension test	Verbal abilities
Handball goalie reaction test	Simple and choice reaction time
Memory Ten Word test	Short and long-term memory test
Trail-making task	Executive functions
Cube	Visuospatial task
The Clock Drawing Task	Visuospatial task, executive functions
Verbal fluency	Vocabulary production task

Cognitive reserve

Cognitive reserve was assessed using the Cognitive Reserve Index questionnaire (Nucci et al., 2012) which consists of three parts, information on education, occupation, and leisure activities starting from the age of 18. Data are obtained with a structured interview and three subscores (CRI-Education, CRI-Occupation and CRI-Leisure) and a main score (CRI-Total) are obtained (see more detail in Table 2.3). The permission to use CRIq was obtained prior to data acquisition (see Annex 3).

Table 2.3

Descriptions of subscales of CRIq

Subscale	Description
CRI-Education	Includes formal education (school, university, college etc.), as well as professional courses.
CRI-Occupation	Five levels of occupation, based on complexity and the level of responsibility. First level includes physical work that does not require additional education (e.g. maid, steward). Second level refers to physical jobs that require additional education (e.g. electrician, plumber). Third level is focused towards unskilled and low-responsibility intellectual work (e.g. office worker, receptionist). Fourth level regards qualified intellectual work (e.g. teacher, psychologist), and the fifth level refers to highly qualified work with high responsibility level (e.g. professor, surgeon, CEO etc.).
CRI-Leisure Activities	Activities in four blocks: Weekly activities (at least three times per week): reading journals and newspapers, doing home chores, driving a car etc. Monthly activities (at least three times per month): cinema or theatre, gardening, child care / parent care etc. Yearly activities (at least three times per year): reading books, travelling outside the country etc. Fixed activities: pet care, financial responsibilities etc.

CRI-Education includes two types of educational activity – formal education and vocational training. For formal education, years spent are registered, while for vocational education each three months spent in training equal .25 points.

CRI-Occupation registers five levels of activity, depending from the educational attainment needed, cognitive load of the tasks and the level of responsibility. All paid occupational activities that have been at least one year long are marked in years spent (e.g. working as a janitor for five years would equal five years in level one).

CRI-Leisure Activities include four blocks of activities – done at least three times per week, three times per month, three times per year and fixed activities. Years spent doing a specific activity are registered, but only if the activity has been done at least three times per week / month / year (e.g. reading journals and magazines is a weekly activity, therefore, reading a journal four days in a week for five years would count as an activity, while reading a journal only once per week would not be counted).

Cognitive function

Within the study long- and short-term memory, visuospatial perception, verbal abilities, vocabulary, executive functions and processing speed were assessed.

Subtests of Woodcock Johnson Tests of Cognitive Abilities (Woodcock et al., 2001, Paleja, 2006) were used for assessing associative long-term memory, working memory, processing speed and vocabulary (see Table 2.4). Results of each subtests were calculated according to the age and gender. The test is based on Cattel-Horn-Carroll theory of cognitive abilities and Caroll Three-stratum theory and the authors claim that intellect is a combination of several cognitive abilities. The test is standardised in Latvian population and all data were obtained under supervision of certified specialist (see rules of use in Annex 4).

"Memory of Names" aims to measure associative memory and the ability to retrieve information from the long-term memory storage. Participant is presented with 12 aliens one-by-one with unknown names, first showing the unique alien and naming him and then presenting a page with several aliens and asking to identify the one, whose name has been called.

"Numbers Reversed" test aims to measure the participants' ability to temporarily hold information for immediate use (working memory). Participant is verbally presented with a list of numbers (from two to seven numbers per list) that they immediately must recount in a reverse order. The difficulty level is gradually increased.

"Visual matching" test assesses information processing speed and the ability to focus attention, in order to do simple cognitive tasks. Participant is presented with a list of 60 rows with six random numbers per row. In each row, participant must circle two identic numbers. The difficulty level increases starting with just one-digit numbers up to three-digit numbers.

"Picture glossary" test investigates the participants' general knowledge of the culture. The participant is asked to name an object shown in a picture. The complexity of the pictures increases exponentially (e.g. a picture of a ball in the lower levels of the test and a picture of pagoda in the higher levels of the test).

Table 2.4

Woodcock – Johnson Tests of Cognitive Abilities subtests used in this study (Paleja, 2006)

Subtest Name	Cognitive Ability	Specific Cognitive Ability	Description	Task
Memory of Names	Long-term retrieval (Glr)	Associative memory	Ability to store information to later retrieve it	Participants are presented with 12 drawn aliens and asked to learn their names
Visual Matching Task	Processing speed (*Gs*)	Perception speed	Ability to quickly perform automatic cognitive tasks	To find and mark two identical numbers in a row of six
Numbers Reversed	Short-term memory (*Gsm*)	Working memory	Ability to temporarily hold information for immediate use	Recall a randomized list of numbers in reverse order
Picture Glossary	Comprehension – Knowledge	Verbal abilities	Individual's general knowledge of a culture	Participant is presented with a picture of an object that they must recognise

Additional measures of processing speed were obtained using a reaction time tasks from the **Handball goalie reaction test** (Molotanovs, 2009). Data were obtained in two digital tasks. In the first task, the participant was presented with a picture of goalie and a "Start" and "Stop" buttons on the screen. After pressing the "Start" button, a ball appeared by the goalies' right hand irregularly. The participant was asked to press "Stop" every time the ball appeared. The second task was slightly more complex and in this case the participant was presented with the same goalie, but different conditions – the ball could appear either by his hand or by his elbow. If the ball appeared by the hand, "E" key was to be pressed, if the ball appeared by the elbow, "U" key was to be pressed. Prior to starting the task, the participant had five practice tries for each test. Mean reaction times (*ms*) were recorded and used for data analysis. Permission to use the task was obtained prior to data acquisition (Annex 5).

Finally, a composite score for processing speed as measured by reaction time was created as an equal sum of standardized scores. The standardized scores were calculated using a formula adapted from Malek-Ahmadi et al. (2018), using two standard deviations for

identifying min and max scores (see the equation (1) below) and adding together the standardized scores.

$$Standardized\ score = \frac{(\text{raw score} - min\ \text{possible})}{(max\ \text{possible} - min\ \text{possible score})} \quad (1)$$

To assess short- and long-term memory, **Memory Ten-Word test** was used (Luria, 1976). In this task, the participant is verbally presented with a list of ten one- or two-syllable words. The list of words is read to the participants twice and they are asked to repeat the words each time. After the second time, participants must recall the words without cues three more times immediately and once after 60 minutes.

Three subtests from **Montreal Cognitive Assessment (MoCA)** were used to evaluate the executive functions and visuospatial abilities (Trailing task, Cube and The Clock Drawing Test) and the verbal fluency. Cube drawing test requires the participant to copy a picture of a cube as precisely as possible. The final figure should be three-dimensional, all lines should be connected and parallel to each other. If all criteria are met, participant receives one point. In the Clock Drawing Test, the participant is asked to draw a clock, write all dials and note the time – ten minutes past eleven. The final drawing should be a round clock with all dials and correct time, each correctly done criteria will get one point (three total). The verbal fluency task requires the participant to name as many words possible, starting with letter "L", excluding proper nouns and words stemming from a word already mentioned. 11 correct responses within a minute are required to pass the test (one point). Permission for the use of MoCA test for research purposes was also obtained (see Annex 6) and the author obtained MoCA test certification (certification no LVSNEKR176-01).

2.2.3 Procedure

All participants were interviewed through phone prior to data acquisition, specifying that they comply with the inclusion criteria. These interviews were not in any way stored or transcribed. Data acquisition for each participant was conducted in consecutive stages. After a general introduction to research and signing informed consent, cognitive and emotional measures were obtained by our team, including measures on memory, attention, and response time. Structural brain MRI was conducted at Pauls Stradiņš Clinical University hospital. Participants were recruited one per week and all data were obtained from them individually (see schematic representation in Figure 2.1).

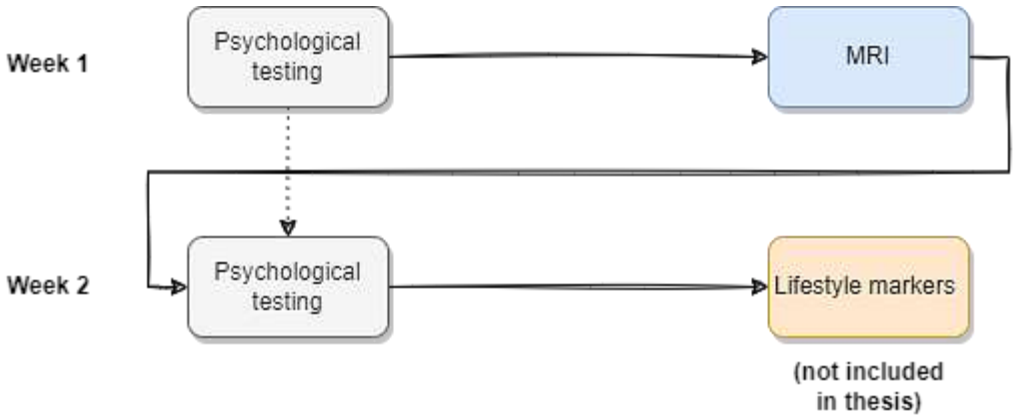

Figure 2.1 **Full procedural description of data acquisition for ENABLE-LV**

2.2.4 Data analysis

For descriptive statistics, median, standard deviation and min-max values were used. To investigate the relationship between cognitive reserve and its subindices and the rest of the variables, Spearman's rank correlation analysis was used due to small sample and non-normal distribution. Further, to better understand the association and to control for the age, hierarchal regression analysis was used. Missing values were calculated using two median approach.

2.3 The neural (cortical, hippocampal and thalamic volume) correlates of cognitive reserve

To test the third hypothesis, namely, that higher cognitive reserve will be associated with larger brain volume, especially, in regions considered more vulnerable to ageing and dementia, data from the National Research Program "BIOMEDICINE-LV" subproject "Establishing the Net Attainable Benefits of Long-term Exercise, ENABLE-LV" were used.

2.3.1 Participants

58 participants aged 65–85 (M = 71.83, SD = 5.016, 20.7 % male) were included in the analysis. All of the participants were living independently alone or with a partner, all had at least 11 years of education and had been employed at some point in their life. All participants were right-handed and had good or corrected vision.

Only participants with no self-reported neurological, cardiovascular, pulmonary, and respiratory disease that require inhalators, ongoing oncological disease, rheumatologic diseases that require pain medication, mental disease, and other factors, such as metallic implants, aged 65 and over and native Latvian speakers were included in the data analysis.

2.3.2 Measures

To obtain MRI data, a Siemens 1.5 Tesla Avanto MRI scanner (Siemens, Erlangen, Germany) was used in collaboration with University of Sussex, School of Psychology and Pauls Stradiņš Clinical University hospital. High-resolution anatomical images were acquired using a three-dimensional T1-weighted magnetisation prepared rapid acquisition gradient echo (MPRAGE) sequence [TR = 1160 ms; TE = 4.44 ms; inversion recovery time (TI) = 600ms; field of view (FOV), 230 × 230 mm2; matrix size, 256 × 256; flip angle = 1 degrees; voxel dimensions, 0.9 × 0.9 × 0.9 mm3; acquisition time, 5 min].

Volumetric analysis

Volumetric analysis was conducted using Freesurfer 7.2. software. Thalamus and hippocampal volumes were automatically segmented using regions of interest (ROI) maps. For cortical regions, Desikan-Killiany-Tourville (DKT) Atlas was applied (for regional mapping, see Figure 2.2, for more details regarding regional borders, see Alexander et al., 2019).

Lobe/wider region	Specific region
Temporal lobe (medial aspect)	
	entorhinal cortex
	parahippocampal gyrus
	fusiform gyrus
Temporal lobe (lateral aspect)	
	superior temporal gyrus
	middle temporal gyrus
	inferior temporal gyrus
	transverse temporal gyrus
Frontal lobe	
	superior frontal gyrus
	rostral middle frontal gyrus
	caudal middle frontal
	inferior frontal gyrus
	pars opercularis
	pars opercularis
	pars opercularis
	medial orbitofrontal gyrus
	lateral orbitofrontal gyrus
	paracentral lobule
	precentral gyrus
Parietal lobe	
	postcentral gyrus
	supramarginal gyrus
	superior parietal lobule
	inferior parietal lobule
	precuneus
Occipital lobe	
	lingual gyrus
	pericalcarine cortex
	cuneus cortex
	lateral occipital cortex
Cingulate cortex	
	caudal anterior cingulate
	rostral anterior cingulate
	posterior cingulate cortex
	isthmus of cingulate gyrus
	insula

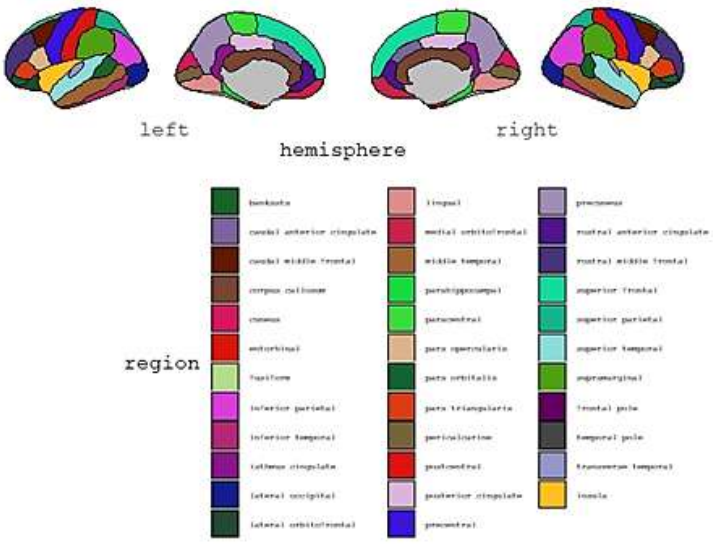

Figure 2.2 **Desikan-Killiany-Tourville (DKT) Atlas structures (Alexander et al., 2019) and visual representation of DKT regions**

(developed with ggseg package, Mowinckel & Vidal-Piñeiro, 2020).

2.3.3 Procedure

All participants were interviewed through phone prior to data acquisition, specifying that they comply with the inclusion criteria. These interviews were not in any way stored or transcribed. Data acquisition for each participant was conducted in consecutive stages. After a general introduction to research and signing informed consent, cognitive and emotional measures were obtained by our team, including measures on memory, attention, and response time. Structural brain MRI was conducted at Pauls Stradiņš Clinical University hospital. Participants were recruited one per week and all data were obtained from them individually (see schematic representation in Figure 2.1, subchapter 2.2.3).

Ethical considerations

All data were acquired adhering to the highest levels of research ethics. First, within the ENABLE-LV project, approval from Rīga Stradiņš University Ethics Committee was obtained (see Annex 7). Further, all research subjects were informed of the project's nature, theoretical approach, purpose and main objectives, intended outputs, and how the informants may access the research results. All participants were ensured of their anonymity and all signed an informed consent form prior to testing (see attached form in Latvian in Annex 8). The overall risk of physical harm was very low and involved mainly in relation to MRI acquisition. MRI diagnostics are non-invasive and can be dangerous only in the case of participants having implanted electronic devices (e.g. cardio stimulators) or having metallic objects (e.g. shrapnel fragments), the lack of which was discussed during the first interview and specified again before the MRI by a radiology technician.

2.3.4 Data analysis

For descriptive statistics, median, standard deviation and min-max values were used. To investigate the relationship between cognitive reserve and its subindices and the rest of the variables, Spearman's rank correlation analysis was used due to small sample and non-normal distribution. Further, to better understand the association and to control for the age and eTIV, hierarchal regression analysis was used.

2.4 Association between the change in cognitive performance and cognitive reserve

To test the fourth hypothesis, namely, that changes in cognitive performance over time will be associated with the baseline cognitive reserve score, longitudinal data from the follow-up study of ENABLE-LV, "The Role of Motor Reserve in Cognitive Dysfunction in Older Adults (MORE-COG)", were used.

2.4.1 Participants

24 women aged 68–83 (M = 74.25, SD = 4.64) at the second measure participated in this part of the study. All women were recruited from the ENABLE-LV recruitment pool and still had no diagnosis of dementia. After data screening, one participant was removed due to significant outliers, thus, 23 women aged 68–83 (M = 74.13, SD = 4.70) were included in data analysis. The mean years between the measures were 3.391 (SD = 0.656).

2.4.2 Measures

Measures for cognitive reserve and cognitive functioning remained the same as used in the baseline measure (see Table 2.5, for more detailed descriptions, see section 2.2.2.).

Table 2.5

Measures of cognitive reserve and cognitive functioning

Measure	Variable
Cognitive Reserve Index questionnaire	Cognitive reserve approximation based on sociobehavioural variables
Woodcock-Johnson III: Tests of Cognitive Abilities:	Neuropsychological test battery
Memory for Names	Associative and long-term memory
Numbers Reversed	Working memory
Visual Matching task	Visual attention, processing speed
Verbal Comprehension test	Verbal abilities
Handball goalie reaction test	Simple and choice reaction time
Memory Ten Word test	Short and long-term memory test
Trail-making task	Executive functions
Cube	Visuospatial task
The Clock Drawing Task	Visuospatial task, executive functions
Verbal fluency	Vocabulary production task

2.4.3 Procedure

All data were obtained using the same procedure adapted during the baseline measures (for more detail, see Figure 2.1, subchapter 2.2.3.).

Before starting the longitudinal part of the study, ethics approval within project *The Effect of Lifetime Physical Activity on the Burden Caused by Cognitive Disfunction and Depression in Elderly,* ELPA-COG was obtained from RSU Ethics Committee (see Annex 8). As part of the data were obtained after the onset of COVID-19, it should be noted that all epidemiological recommendations were taken into consideration.

2.4.4 Data analysis

To evaluate the differences between the first and second measure, median and standard deviation was calculated, as well as, Wilcoxon Signed Rank test was conducted. The changes in variables were calculated by retracting first measure from the second measure. Further, the relationship between cognitive reserve and its subindices and cognitive functions were analysed with partial correlation analysis, controlling for years between measures.

3 Results

3.1 Relationship between cognitive reserve and cognitive functioning in a partially representative sample

To test the first hypothesis, namely, that higher levels of education, active employment and active daily lifestyle will be associated with better memory performance and higher scores of verbal fluency in healthy middle aged and older adults, a structural equation model was prepared.

3.3.1 Descriptive statistics of the variables and correlation analysis

First, the mean, AD, minimal and maximal score values were calculated for education, short-term memory, long-term memory and verbal fluency (see Table 3.1).

Table 3.1

Descriptive statistics: education, memory and verbal fluency

Variable	Mean	SD	Min	Max
Education	11.56	2.83	4	26
Short-term memory	5.08	1.757	0	10
Long-term memory	3.59	2.152	0	10
Verbal fluency	20	7.321	2	47

Note. N = 546

Further, the frequency of the involvement in one of the leisure activities was calculated (see Table 3.2).

Table 3.2

Percentage of activities

Variable	Percentage involved in the activity (%)
Employment status	26.9
Voluntary or charity work	8.2
Educational or training course	6.4
Sport, social or other club	5.3
Political or community organization	0.9
Read books, magazines or newspapers	52.9
Word or number games	18.5
Played cards or games	2

Note. N = 546

In the sample only 26.9 % of the participants were still employed. Regarding leisure activities, 53.9 % of the participants noted reading books as a leisure activity, 18.5 % admitted doing word or number games, 8.2 % noted that they are involved in voluntary or charity work,

6.4 % obtained new knowledge through an educational or training course, and 5.3 % claimed that they have been involved in a sport, social or similar type of club. Less than 5 % played cards or games (2 %) and were involved in a political or community organization (0.9 %). 43.2 % reported doing vigorous physical activities at more than once a week, 21.8 % noted that they are doing vigorous activities once a week, 8.4 % noted that they are involved in vigorous activities one to three times a month, while 26.6 % noted that they hardly ever or never do vigorous physical activities. Most of the participants (74.2 %) noted that they are involved in moderate activities more than once a week, 14.8 % noted that they are doing moderate intensity activities at least once a week. Only 2.6 % indicated that they are doing vigorous activities one to three times a month and only 8.4 % noted that they are involved in moderate physical activities hardly ever or never.

In the next step, associations between education, employment, leisure activities, short- and long-term memory and verbal fluency were tested, using Spearman's rank correlation coefficient (Table 3.3).

Table 3.3

Associations between variables (Spearman's rank correlation)

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. Education	–											
2. Employment	**0.16****	–										
3. Voluntary work	0.02	**0.09***	–									
4. Course	0.10*	**0.20****	0.06	–								
5. Club	−0.00	0.02	0.02	**0.17****	–							
6. Organization	0.03	−0.02	**0.18*****	0.05	**0.15*****	–						
7. Reading	**0.15****	0.04	–0.04	**0.22****	0.09*	0.09	–					
8. Word games	**0.11****	−0.00	0.01	0.07	0.03	0.05	**0.33*****	–				
9. Card games	0.07	0.09*	−0.04	**0.12****	0.02	−0.01	0.08	0.07	–			
10.Short-term	**0.36*****	**0.25****	−0.06	**0.16*****	**0.13****	0.09*	**0.25*****	**0.18*****	0.05	–		
11.Long-term	**0.34*****	**0.23****	**−0.10***	**0.12****	0.09*	0.07	**0.25*****	**0.22*****	0.04	**0.80*****	–	
12. Verbal fluency	**0.29****	**0.31****	**0.15****	**0.19****	0.05	0.04	**0.19****	**0.16****	0.00	**0.45****	**0.43****	–

Note. $N = 546$, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

Spearman's rank correlation analysis indicated a statistically significant positive correlations between education and short- and long-term memory (r_s = 0.36 and r_s = 0.34, $p < 0.001$, accordingly), as well as, between verbal fluency score (r_s = 0.29, $p < 0.01$). Similarly, also current employment was positively associated with short- and long-term memory and verbal fluency scores, though the correlations were slightly lower for the short- and long-term memory than with education ($r_s = 0.25$, $r_s = 0.23$, and $r_s = 0.31$, $p < 0.01$, accordingly). Regarding the leisure activities, there were very weak correlations between short-term memory and taking educational courses and participating into social clubs ($r_s = 0.16$, $p < 0.001$ and $r_s = 0.13$, $p < 0.01$, accordingly), as well as weak positive correlations with reading and and playing word games ($r_s = 0.25$ and $r_s = 0.22$, $p < 0.001$, accordingly). Long-term memory showed very weak correlations with taking an educational course ($r_s = 0.12$, $p < 0.01$) and reading and playing word games ($r_s = 0.25$ and $r_s = 0.22$, $p < 0.001$, accordingly). Verbal fluency was also significantly and positively associated with participating in a social club, taking an educational course, reading and doing word games ($r_s = 0.15$, $r_s = 0.19$, $r_s = 0.19$ and $r_s = 0.16$, $p < 0.01$, accordingly).

When considering the relationship between socio-behavioural proxies of cognitive reserve, years spent in formal education were only very weakly associated with other proxies, including current employment status ($r_s = 0.16$, $p < 0.01$), reading activity ($r_s = 0.15$, $p < 0.01$) and playing word games ($r_s = 0.11$, $p < 0.01$). Employment status meanwhile was positively associated only with taking an educational course ($r_s = 0.20$, $p < 0.01$). Voluntary work showed a very weak association with participating in an organizing work ($r_s = 0.18$, $p < 0.001$), while taking an educational course was positively related to participating in a social club, reading, and playing card games ($r_s = 0.17$, $r_s = 0.22$, $r_s = 12$, $p < 0.01$, accordingly). In addition to taking educational course, participating in a social club was positively associated with participating in an organizational activity ($r_s = 0.15$, $p < 0.001$). Reading also showed a positive association with doing word games ($r_s = 0.33$, $p < 0.001$).

Finally, it should be noted that al the cognitive variables correlated with each other, with association between short- and long-term memory being very strong (rs = 0.80, p < 0.001) and the moderate association between verbal fluency and short- and long-term memory (rs = 0.45 and rs = 0.43, p < 0.001).

3.3.2 Creating Leisure Activity variable

First, for the purpose of SEM analysis, Leisure Activity composite variable was developed, using Confirmatory Factor Analysis (CFA). At first, a one scale Leisure Activity variable was proposed, composed of activities conducted in the last 12 months: participation in

voluntary or charity work, taking educational or training course, participating in a sport, social or other club, participating in a political or community organization, reading books, magazines or newspapers, playing word or number games and playing cards or games. However, the model fit indices (Model 0) did not confirm this as a good variable ($\chi^2(21) = 110.828$, CFI = 0.621, RMSEA = 0.067, SRMR = 0.053); therefore, two variable Leisure Activity measure was proposed, that included Cognitive activity and Social activity. In Model 1, Cognitive leisure activities included taking educational or training course, reading books, magazines or newspapers, playing word or number games as well as playing cards or board games, while Social leisure activities included participation in voluntary or charity work, participating in a sport, social or other club and participating in a political or community organization. Model 1, model fit indices were improving; however, still not achieving the optimal CFI score ($\chi^2(21) = 160.518$, CFI = 0.884, RMSEA = 0.048, SRMR = 0.044). Based on the regression analysis, the variable with the lowest value was removed (playing cards or board games), that also slightly improved the CFI score ($\chi^2(21) = 148.039$, CFI = 0.899, RMSEA = 0.055, SRMR = 0.045) (Model 2). Further. the best fit model was tested using ANOVA, showing Models 1 and 2 as best possible fit. Finally, based on CFI scores, Model 2 was chosen to be the best appropriate (see Table 3.4 and Figure 3.1 for a graphic representation).

Table 3.4

Fit indices for the Leisure Activity composite model

	Model	RMSEA	SRMR	CFI	AIC	BIC
1	Model 0 – baseline model	0.067	0.053	0.621	5893.7	5953.9
2	Model 1 – creating Cognitive and Social scales	0.048	0.044	0.884	–335.9	–271.3
3	**Model 2 – removing playing cards or board games**	**0.055**	**0.045**	**0.899**	**258.5**	**314.4**

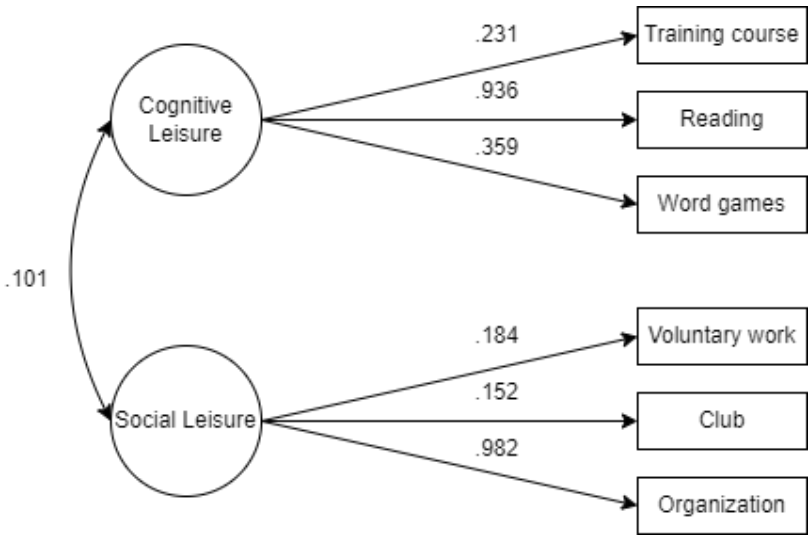

Figure 3.1 **Graphical representation of the Leisure Activity scale (Model 2)**

3.3.3 SEM analysis of the relationship between sociobehavioural proxies of cognitive reserve and memory

Prior to testing the first hypothesis, namely, that higher levels of education, active employment and active daily lifestyle that include cognitive, social and physical activities will be associated with better memory, a conceptual model of sociobehavioural factors was drawn (see Figure 3.2).

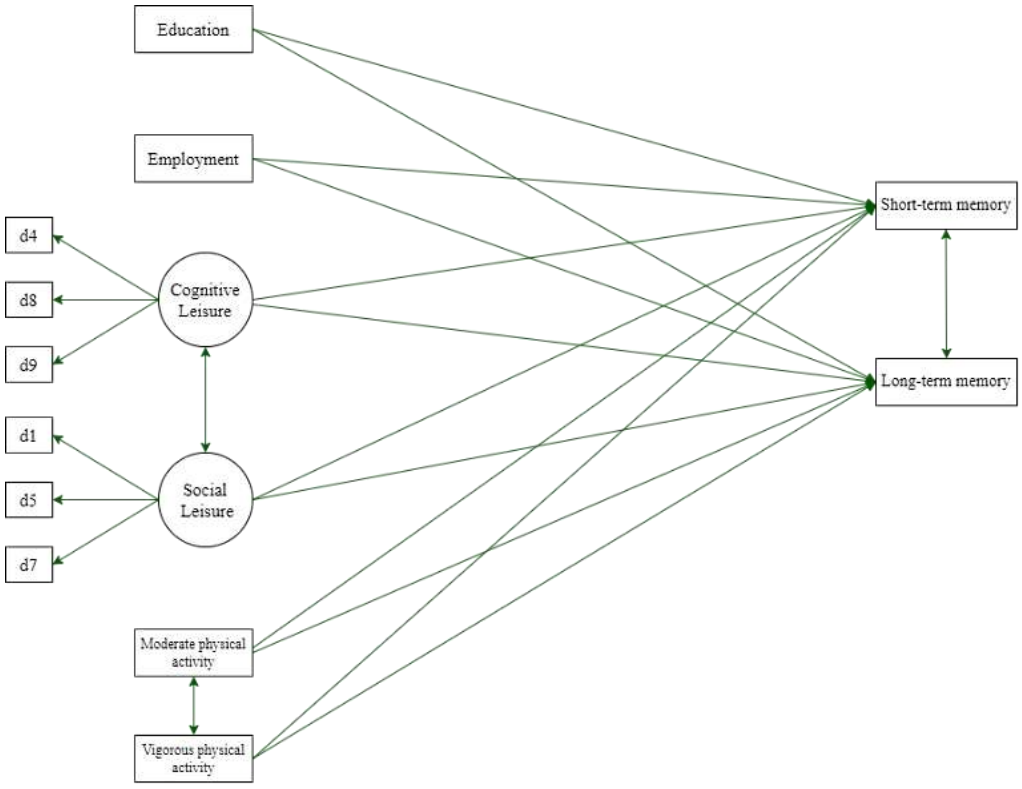

Figure 3.2 **Conceptual model of factors associated with memory in older adults**

Note. d1 – voluntary or charity work, d4 – educational or training course, d5 – sport, social or other club, d7 – political or community organization, d8 – reading books, magazines or newspapers, d9 – word or number games.

Testing the empirical model of factors associated with memory in older adults

The baseline model (Model 0) included all socio-behavioural proxies of cognitive reserve – education, employment status, cognitive and social factors and physical activity and short- and long-term memory measures. The initial model (Model 0) showed almost satisfactory model fit scores ($\chi^2(40) = 139.812$, CFI = 0.892, RMSEA = 0.068, SRMR = 0.066) and to improve the model, the variables that showed the lowest standardized estimate scores and were not statistically significant predictors were removed one by one. In the next step, the prediction "Social Leisure and Long-term memory" was removed, this did not significantly impact the model ($\chi^2(41) = 139.812$, CFI = 0.893, RMSEA = 0.066, SRMR = 0.066); therefore, in the next step, the prediction "Social Leisure and Short-term memory" was also removed. While the removal improved the CFI scores, it worsened the RMSEA score ($\chi^2(16) = 70.406$, CFI = 0.936, RMSEA = 0.079, SRMR = 0.067). Further, also the prediction "Vigorous physical activity and Long-term memory" was removed, this slightly changed the model fit indices ($\chi^2(17) = 73.430$, CFI = 0.933, RMSEA = 0.078, SRMR = 0.068), and afterwards the prediction "Vigorous physical activity and Short-term memory" was also removed ($\chi^2(13) = 61.801$, CFI = 0.941, RMSEA = 0.070, SRMR = 0.083) that significantly improved χ^2 and CFI scores; however, worsened the SRMR score. Therefore, the latent variable Cognitive Leisure was reconsidered and the activity "Educational and training courses" was removed from the analysis. The final model showed the best model fit indices, apart from RMSEA ($\chi^2(7) = 30.837$, CFI = 0.970, RMSEA = 0.079, SRMR = 0.058). One-Way ANOVA analysis also indicated the final model as the most appropriate (see Table 3.5).

The final model indicates that formal education was a good predictor for both – short- and long-term memories (standardized estimate = 0.34, $z = 8.967$ and standardized estimate = 0.311, $z = 8.053$, $p = 0.000$, accordingly). Second strongest predictors were Cognitive Leisure activities (standardized estimate = 0.27, $z = 3.878$, $p = 0.000$ for short-term memory and standardized estimate = 0.29, $z = 3.986$, $p = 0.000$ for long-term memory). Current employment status also was a significant predictor in both cases (standardized estimate = 0.16, $z = 4.283$ and standardized estimate = 0.16, $z = 4.063$, $p = 0.000$, short- and long-term memory respectively). Only moderate physical activities predicted short- and long-term memory performance (standardized estimate = −0.16, $z = -4.192$ and standardized estimate = −0.12, $z = -0.3025$, $p < 0.01$, accordingly) (see Figure 3.3).

Table 3.5

Model fit indices for the memory model

	Model	RMSEA	SRMR	CFI	AIC	BIC
1	Model 0 – baseline model	0.068	0.066	0.892	4120.9	4241.4
2	Model 1 – removing "Long-term memory ~ Social Leisure	0.066	0.066	0.893	4118.9	4235.1
3	Model 2 – removing "Short-term memory ~ Social Leisure"	0.067	0.079	0.936	5101.9	5183.6
4	Model 3 – removing "Long-term memory ~ Vigorous physical activity)	0.068	0.078	0.933	5102.9	5180.3
5	Model 4 – removing "Short-term memory ~ Vigorous physical activity)	0.07	0.083	0.941	5111.7	5184.9
6	**Model 5 – removing "Educational and training courses" from Cognitive Leisure**	**0.079**	**0.058**	**0.970**	**5117.7**	**5182.2**

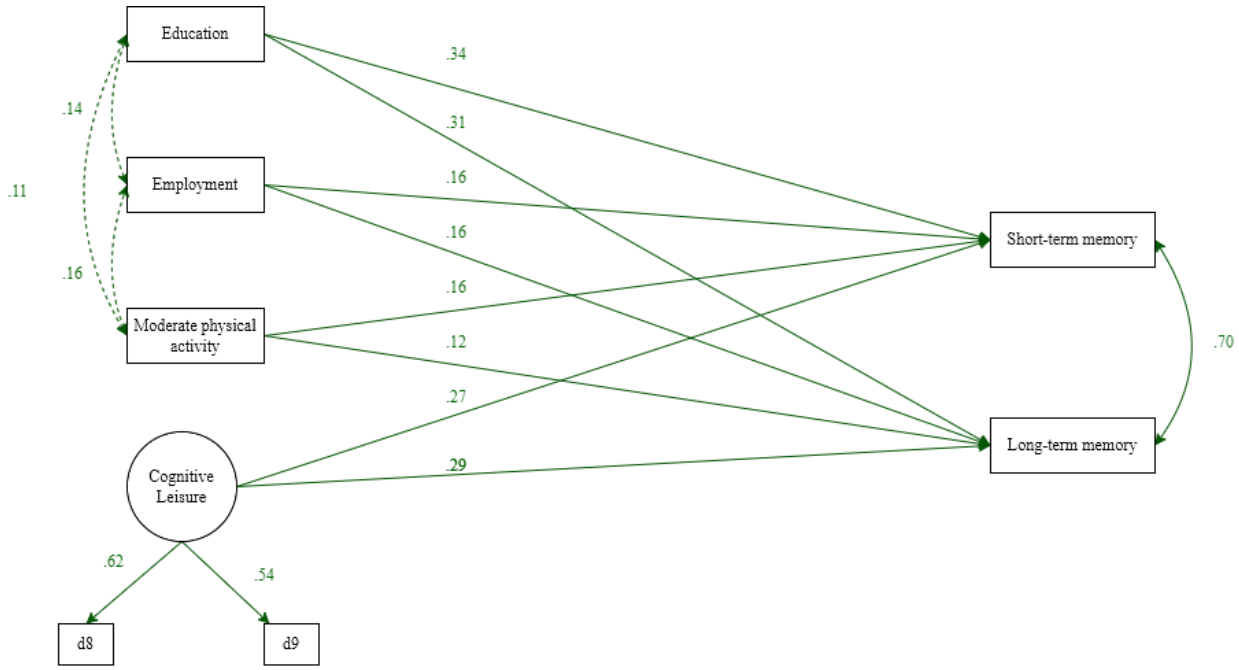

Figure 3.3 **The final model of the relationship between socio-behavioural proxies of cognitive reserve and memory**

Note. d8 – reading books, magazines or newspapers, d9 – word or number games

3.3.4 SEM analysis of the relationship between socio-behavioural proxies of cognitive reserve and verbal fluency

To better understand the relationship between socio-behavioural proxies of cognitive reserve and verbal fluency, a conceptual model was built (Figure 3.4).

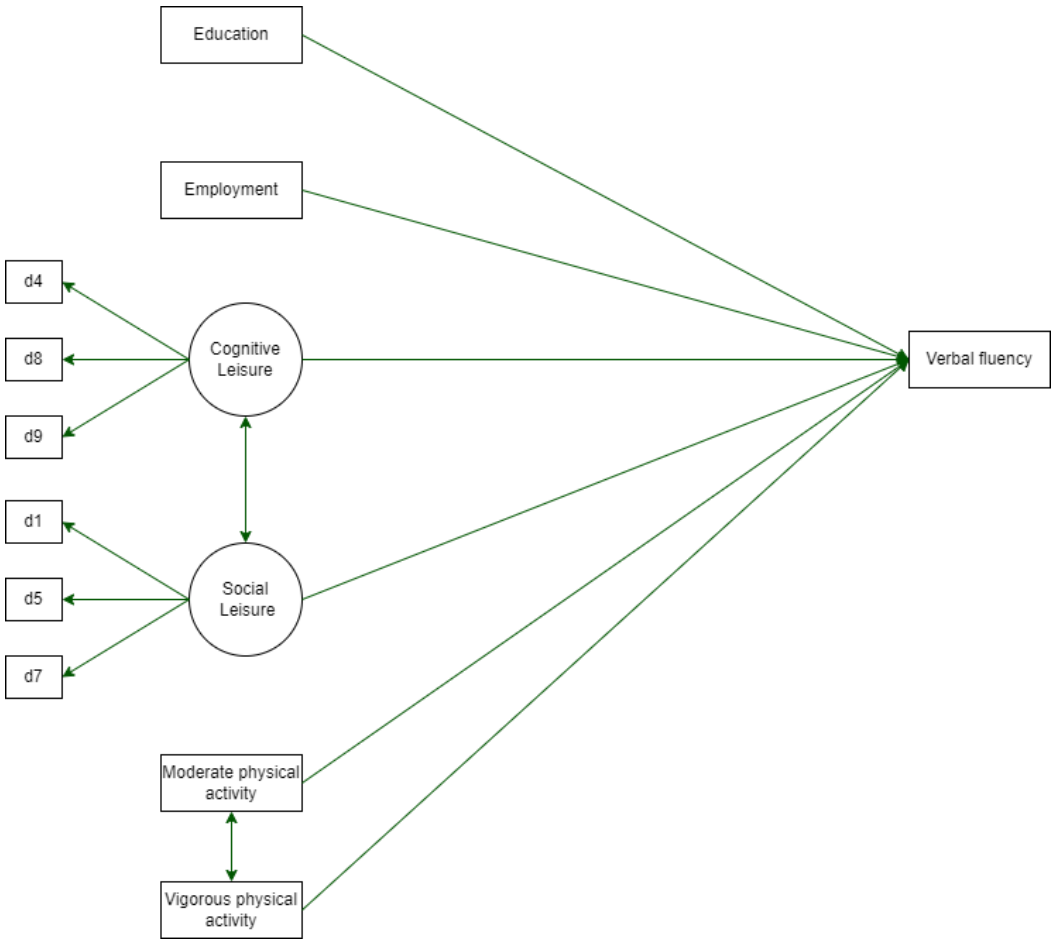

Figure 3.4 **Conceptual model of factors associated with verbal fluency in older adults**

Note. d1 – voluntary or charity work, d4 – educational or training course, d5 – sport, social or other club, d7 – political or community organization, d8 – reading books, magazines or newspapers, d9 – word or number games

Testing the empirical model of factors associated with verbal fluency in older adults

The baseline model (Model 0) included all socio-behavioural proxies of cognitive reserve – education, employment status, cognitive and social factors and physical activity. Baseline model indicated low model fit ($\chi^2(36) = 96.697$, CFI = 0.776, RMSEA = 0.056, SRMR = 0.061), thus further improvements were conducted, removing variables based on the standardized beta score (β). First, vigorous physical activity experience was removed from the model, slightly improving the baseline model fit ($\chi^2(11) = 47.381$, CFI = 0.829, RMSEA = 0.051, SRMR = 0.059), next Social leisure activities were removed, which significantly worsened the RMSEA and SRMR scores ($\chi^2(30) = 73.083$, CFI = 0.833, RMSEA = 0.078, SRMR = 0.070); therefore, the social leisure activities were re-evaluated and the activity of going to sport, social or any other kind of club, was removed due to having the lowest standardized estimate score. This slightly improved the model fit scores ($\chi^2(22) = 59.284$, CFI = 0.847, RMSEA = 0.056, SRMR = 0.061); however, they were still not

satisfactory, thus "Taking a training course" was removed from Cognitive leisure activities due to having the lowest standardized estimate score. This significantly improved the baseline model ($\chi^2(15) = 29.259$, CFI = 0.932, RMSEA = 0.042, SRMR = 0.048). Finally, as the latent variable of Social leisure activities did not statistically significantly predict verbal fluency scores, it was decided to remove it from the model again, this resulted in slightly worse RMSEA and SRMR scores ($\chi^2(6) = 17.716$, CFI = 0.935, RMSEA = 0.060, SRMR = 0.051). Afterwards, ANOVA analysis was conducted to identify the best fitting model, and based on AIC and BIC scores, the final model was deemed the best fit (see Table 3.6).

Table 3.6

Model fit scores for verbal fluency

	Model	RMSEA	SRMR	CFI	AIC	BIC
1	Model 0 – baseline model	0.056	0.061	0.776	9232.7	9318.8
2	Model 1 – removing vigorous physical activity	0.051	0.059	0.829	9233.0	9314.8
3	Model 2 – removing Social leisure variable	0.078	0.070	0.833	7240.4	7287.7
4	Model 3 – removing "Going to sport, social or any other kind of club" from Social leisure, adding Social leisure back	0.056	0.061	0.847	8267.4	8340.6
5	Model 4 – removing "Taking a training course" from Cognitive leisure	0.042	0.048	0.932	6990.9	7055.4
6	**Model 5 – removing all Social leisure activities**	**0.060**	**0.051**	**0.935**	**5964.2**	**6002.9**

The final model indicates that formal education (standardized estimate = 0.24, $z = 6.106$, $p = 0.000$) together with employment (standardized estimate = 0.23, $z = 5.845$, $p = 0.000$), and cognitive leisure activities (standardized estimate = 0.25, $z = 3.114$, $p = 0.002$), as well, as involvement in moderate physical activities (standardized estimate = −0.18, $z = -4.522$, $p = 0.000$), are the strongest predictors for verbal fluency scores (see Figure 3.5).

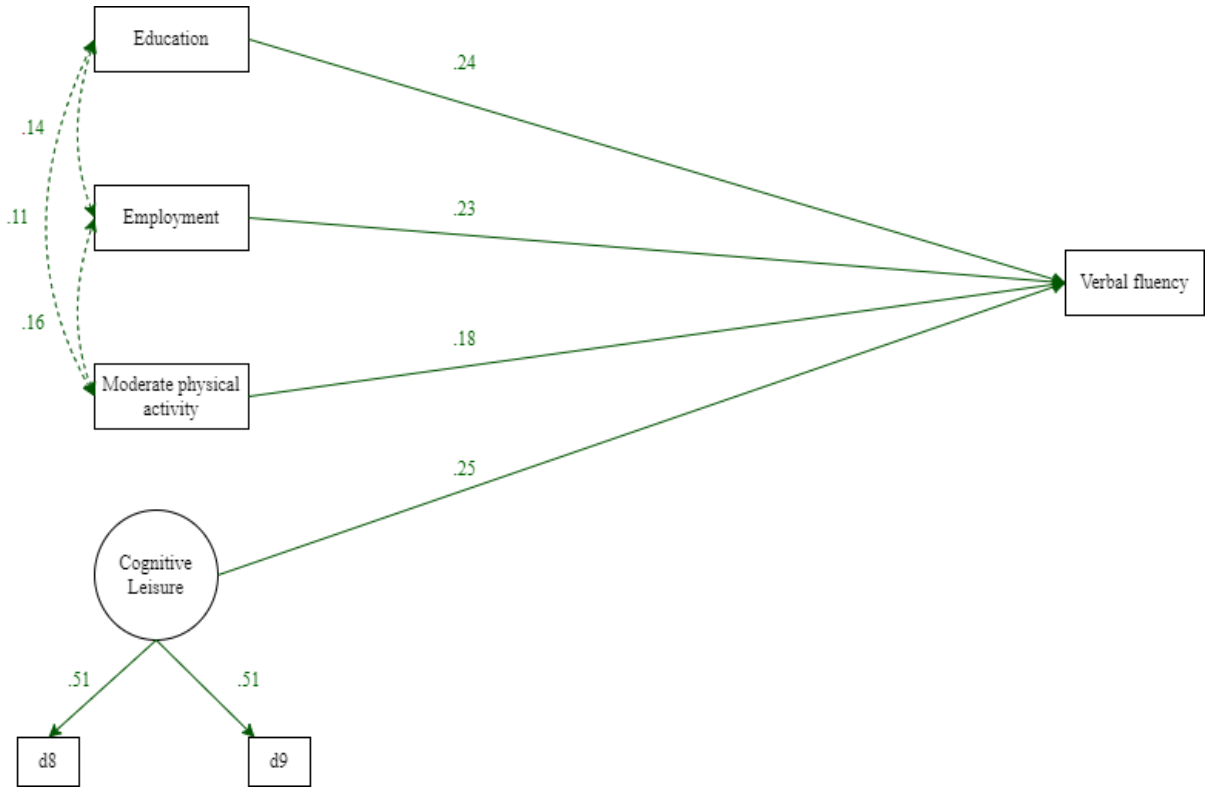

Figure 3.5 **The final model of the relationship between socio-behavioural proxies of cognitive reserve and verbal fluency**

Note. d8 – reading books, magazines or newspapers, d9 – word or number games

3.2 Relationship between cognitive reserve and cognitive functions in a sample of older Latvian adults

To test the hypothesis that higher cognitive reserve will be associated with better cognitive performance in memory, information processing speed, visuo-spatial abilities, executive functions and language abilities in healthy older adults, Spearman's rank correlation analysis, as well as, hierarchal regression analysis was conducted.

Descriptive statistics

For descriptive statistics, median, standard deviation, minimal and maximal values were obtained (see Table 3.7).

Table 3.7

Descriptive statistics of cognitive reserve and cognitive functions

Variable	Mdn	SD	Min	Max
CRI-Education	122	11.76	98	151
CRI-Occupation	116	22.63	88	187
CRI-Leisure Activity	132	16.15	90	172
CRI-Total	132	17.49	98	181
Associative memory	108	9.07	82	128

Table 3.7 continued

Variable	Mdn	SD	Min	Max
Working memory	101	10.81	74	128
Short-term memory	6	1.44	3	9
Long-term memory	7	2.04	2	10
Verbal fluency	12	3.91	3	22
Vocabulary	19	2.76	5	22
Reaction time composite	984	207.42	705	1934
Matching task	99	16.05	80	198
Trail-making task	1	0.47	0	1
Cube	1	0.473	0	0
Clock-drawing task	3	0.781	1	3

Note. N = 61, *Mdn* – median, *SD* – standard deviation. Reaction time composite is in milliseconds.

Further, to test the hypothesis, association between cognitive reserve and each cognitive function was first correlated and then hierarchal regression analysis was conducted, controlling for age.

First, the association between cognitive reserve and memory (associative memory, working memory, short- and long-term memory) were investigated, using the Spearman's rank correlation analysis (see Table 3.8).

Table 3.8

Association between cognitive reserve and memory (Spearman's ρ)

Variable	1	2	3	4	5	6	7	8
1. CRI-Education	–							
2. CRI-Occupation	0.435**	–						
3. CRI-Leisure Activity	0.335*	0.306*	–					
4. CRI-Total	0.705**	0.833**	0.653**	–				
5. Associative memory	0.170	0.137	−0.043	0.128	–			
6. Working memory	0.068	0.068	0.139	0.111	0.235	–		
7. Short-term memory	**0.360****	**0.293***	0.117	**0.304***	0.246	0.199	–	
8. Long-term memory	0.180	−0.029	0.029	0.041	0.192	−0.046	0.519**	–

Note. N = 61, **p < 0.01, *p < 0.05

Results indicated a statistically significant and positive correlations between short-term memory scores and CRI-Education (r_s = 0.360, p < 0.01) and CRI-Occupation and CRI-Total (r_s = 0.293 and r_s = 0.304, $p < 0.05$, accordingly). There were no other statistically significant correlations found. In the next step, three separate hierarchal regression analysis for the dependent variable "short-term memory", and independent variables CRI-Education, CRI-Occupation and CRI-Total were conducted. After controlling for age, CRI-Education explained 15.3 % of the short-term memory variation (R^2 = 0.154, adjusted R^2 = 0.124, ΔR^2 = 0.153, $F(1, 60)$ = 9.541, p = 0.008, DW = 1.664) (see Table 3.9). The total CRI-Occupation and CRI-Total did not statistically significantly predict short-term memory performance ($p > 0.05$).

Table 3.9

Hierarchal regression analysis for dependent variable "short-term memory" and independent variable CRI-Education, controlling for age

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	−0.021	0.035	−0.033
Step 2:			
Age	−0.021	0.035	−0.033
CRI-Education	0.048	0.015	0.393

Note. $N = 61$. Step 1. $R^2 = 0.001$, $p = 0.800$; Step 2. $R^2 = 0.154$, adjusted $R^2 = 0.124$, $\Delta R^2 = 0.153$, $p = 0.002$

Further, the relationship between cognitive reserve and linguistic factors (verbal fluency, speech production) was investigated, using Spearman's rank correlation (see Table 3.10).

Table 3.10

Association between cognitive reserve, verbal fluency and speech production (Spearman's rank correlation)

Variable	1	2	3	4	5	6
1. CRI-Education	–					
2. CRI-Occupation	0.435**	–				
3. CRI-Leisure Activity	0.335*	0.306*	–			
4. CRI-Total	0.705**	0.833**	0.653**	–		
5. Verbal fluency	0.202	**0.353****	0.193	**0.357****	–	
6. Vocabulary	**0.274***	0.126	0.046	0.195	0.417**	–

Note. $N = 61$, $^{**}p < 0.01$, $^{*}p < 0.05$

CRI-Education statistically significantly correlated with vocabulary ($r_s = 0.274$, $p < 0.05$). Verbal fluency scores were positively though weakly correlated with CRI-Occupation and the total CRI score ($r_s = 0.353$, $p < 0.01$ and $r_s = 0.357$, $p < 0.01$, accordingly). Hierarchal regression analysis was further conducted, controlling for age (see Tables 3.11, 3.12, and 3.13).

Table 3.11

Hierarchal regression analysis for dependent variable "vocabulary" and independent variable CRI-Education, controlling for age

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	0.029	0.071	0.053
Step 2:			
Age	0.008	0.067	0.015
CRI Education	0.090	0.029	0.383

Note. $N = 61$. Step 1. $R^2 = 0.053$, $p = 0.683$; Step 2. $R^2 = 0.148$, $\Delta R^2 = 0.145$, $p = 0.003$

After controlling for age, CRI-Education explained 14.5 % of the vocabulary variation (R^2 = 0.148, ΔR^2 = 0.145, F(2.60) = 5.039, p = 0.010, DW = 1.984).

Table 3.12

Hierarchal regression analysis for dependent variable "verbal fluency" and independent variable CRI-Occupation, controlling for age

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	−0.056	0.096	−0.076
Step 2:			
Age	−0.037	0.092	−0.049
CRI-Total	0.066	0.027	0.313

Note. N = 61. Step 1. R^2 = 0.006, p = 0.563; Step 2. R^2 = 0.091, ΔR^2 = 0.085, p = 0.023

While not significantly, CRI-Occupation did predict verbal fluency scores, explaining 8.5 % of the variation (R^2 = 0.091, ΔR^2 = 0.085, F(2, 60) = 2.896, p = 0.063, DW = 1.625) (see Table 3.12).

After controlling for age, the total CRI score explained 9.7 % of the verbal fluency variation (R^2 = 0.103, ΔR^2 = 0.097, F(2, 60) = 3.320, p = 0.043, DW = 1.518) (see Table 3.13).

Table 3.13

Hierarchal regression analysis for dependent variable "verbal fluency" and independent variable CRI-Total, controlling for age

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	−0.054	0.101	−0.071
Step 2:			
Age	−0.055	0.096	−0.072
CRI-Total	0079	0.030	0.332

Note. N = 61. Step 1. R^2 = 0.005, p = 0.598; Step 2. R^2 = 0.115, ΔR^2 = 0.110, p = 0.012

Two approaches to processing speed was used – based on reaction time (reaction time composite) and based on production (Matching task) and Spearman's rank correlation analysis was conducted to investigate the relationship between the variables (see Table 3.14).

Table 3.14

Association between cognitive reserve and processing speed variables (Spearman's rank correlation)

Variable	1	2	3	4	5	6
1. CRI-Education	–					
2. CRI-Occupation	0.435**	–				
3. CRI-Leisure Activity	0.335*	0.306*	–			

Table 3.14 continued

Variable	1	2	3	4	5	6
4. CRI-Total	0.705**	0.833**	0.653**	–		
5. Reaction time composite	−0.110	**−0.346****	−0.041	**−0.258***	–	
6. Matching task	−0.236	0.024	−0.078	−0.048	−0.052	–

Note. $N = 61$, $^{**}p < 0.01$, $^{*}p < 0.05$

The results indicated negative relationship between occupational cognitive reserve and the reaction time composite score ($r_s = -0.346$, $p < 0.01$), as well as, a weak negative correlation with the total CRI composite score ($r_s = -0.258$, $p < 0.05$). To control for the effects of age, hierarchal regression analysis was further conducted (see Table 3.15).

Table 3.15

Hierarchal regression analysis for dependent variable "reaction time composite" and independent variable CRI-Occupation, controlling for age

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	0.012	0.010	0.151
Step 2:			
Age	0.009	0.010	0.112
CRI-Occupation	−0.005	0.002	−0.278

Note. $N = 61$. Step 1. $R^2 = 0.023$, $p = 0.245$; Step 2. $R^2 = 0.099$, $\Delta R^2 = 0.076$, $p = 0.031$.

After controlling for age, CRI-Occupation explained 7.6 % of the composite reaction time score variation ($R^2 = 0.099$, $\Delta R^2 = 0.076$, $F(1, 59) = 3.178$, $p = 0.049$, $DW = 1.690$), while hierarchical regression analysis using Total CRI as a predictor was not statistically significant.

Finally, the association between cognitive reserve, executive functions and visuo-spatial perception were tested. Spearman's rank correlation analysis did not show a statistically significant relationship between any of the cognitive reserve proxies and executive functions and visuo-spatial perception (see Table 3.16).

Table 3.16

Association between cognitive reserve, executive functions and visuo-spatial perception (Spearman's ρ)

Variable	1	2	3		5.	6	7
1. CRI-Education	–						
2. CRI-Occupation	0.435**	–					
3. CRI-Leisure Activity	0.335*	0.306*	–				
4. CRI-Total	0.705**	0.833**	0.653**	–			
5. Trail-making task	−0.077	−061	−0.013	−0.013	–		
6. Cube	0.109	0.165	−0.051	0.136	0.405**	–	
7. Clock-drawing task	−0.025	0.197	−0.048	0.082	0.324*	0.219	–

Note. $N = 61$, $^{**}p < 0.01$, $^{*}p < 0.05$

3.3 Relationship between cortical regions and cognitive reserve

To test the hypothesis that higher cognitive reserve will be associated with larger volume in brain cortex, hippocampus and thalamus. Spearman's rank correlation analysis together with hierarchal regression analysis was conducted. All variables were controlled for estimated intracranial volume (eTIV) and age. For full tables of correlations between cognitive reserve and cortical regions, see Annex 10, Tables 10.1–10.6.

Descriptive statistics for cortical regions

Descriptive statistics of volumetric variables are available at Annex 9, Table 9.1. Due to several of the variables showing non-normal distribution, non-parametric correlation methods were used.

Association between cognitive reserve and temporal lobe (medial) regions

CRI-Occupation was statistically significantly, though weakly, correlated with the right hemisphere entorhinal cortex ($r_s = 0.336, p < 0.01$). There were no other significant correlations between cognitive reserve and temporal lobe (medial) regions (see Table 3.17).

Table 3.17

Spearman's rank correlation between cognitive reserve and temporal lobe (medial aspect) regions

Variable	1	2	3	4	5	6	7	8	9	10
1. CRI Education	–									
2. CRI Occupation	0.377**	–								
3. CRI Leisure	0.281*	0.258	–							
4. CRI Total	0.670**	0.817**	0.627**	–						
5. lh entorhinal	0.032	0.127	−0.163	−0.032	–					
6. rh entorhinal	0.203	0.336*	0.011	0.230	0.672**	–				
7. lh parahippocampal	0.079	0.071	−0.055	0.038	0.542**	0.410**	–			
8. rh parahippocampal	0.094	0.178	−0.007	0.105	0.474**	0.534**	0.568**	–		
9. lh fusiform	−0.031	0.114	−0.178	−0.033	0.328**	0.541**	0.265*	0.338**	–	
10. rh fusiform	−0.039	0.208	−0.105	0.043	0.343**	0.536**	0.333*	0.278*	0.587**	–

Note. $N = 58$, $*p \leq 0.05$, $**p < 0.01$

When controlling for age and eTIV, the hierarchical regression analysis did not indicated statistically significant relationship between the variables.

Association between cognitive reserve and temporal lobe (lateral) regions

CRI-Occupation also statistically significantly correlated with most of the lateral aspect regions of the temporal lobe, including bilaterally with the superior temporal gyrus ($r_s = 0.345$, $p = 0.008$ and $r_s = 0.316$, $p = 0.016$, left and right hemisphere, respectively) and inferior temporal gyrus ($r_s = 0.417$, $p = 0.001$ and $r_s = 0.45$, $p < 0.001$, left and right hemisphere, respectively). Only the middle temporal gyrus ($r_s = 0.384$, $p = 0.003$) and only the transverse temporal gyrus ($r_s = 0.285$, $p < 0.05$) were statistically significantly associated with CRI-Occupation. Furthermore, CRI-Total statistically significantly correlated with the middle temporal gyrus ($r_s = 0.259$, $p < 0.05$). There were no significant correlations between CRI-Education and the CRI-Leisure Activity and structures of the temporal lobe regions in lateral aspect see Table 3.18).

Table 3.18

Spearman's rank correlation between cognitive reserve and temporal lobe (lateral aspect) regions

Variable	1	2	3	4	5	6	7	8	9	1	11	12
1. CRI Education	–											
2. CRI Occu-pation	0.377**	–										
3. CRI Leisure	0.281*	0.258	–									
4. CRI Total	0.670**	0.817**	0.627**	–								
5. lh superior	0.066	0.345**	−0.162	0.131	–							
6. rh superior	0.115	0.316*	−0.039	0.187	0.826**	–						
7. lh middle	0.198	0.384**	0.033	0.259*	0.529**	0.543**	–					
8. rh middle	0.197	0.229	−0.026	0.147	0.544**	0.580**	0.684**	–				
9. lh inferior	0.207	0.417**	0.012	0.258	0.429**	0.544**	0.578**	0.523**	–			
10. rh inferior	0.171	0.450**	−0.016	0.255	0.525**	0.565**	0.646**	0.452**	0.607**	–		
11. lh transverse	−0.224	−0.050	−0.078	−0.073	0.277*	0.266*	0.138	−0.049	−0.035	0.237	–	
12. rh transverse	−0.011	0.285*	0.057	0.193	0.610**	0.623**	0.334*	0.396**	0.298*	0.345**	0.409**	–

Note. $N = 58$, *$p \leq 0.05$, **$p < 0.01$

When controlling for age and eTIV, hierarchical regression analysis partially confirmed correlation results. Occupational activity was significantly related to left hemisphere middle temporal gyrus ($R^2 = 0.396$, $\Delta R^2 = 0.063$, $F(1, 57) = 11.798$, $p < 0.001$), explaining 6.3 % of the variation in the regional volume (see Table 3.19).

Table 3.19

Hierarchal regression analysis for dependent variable "left hemisphere middle temporal gyrus" and independent variable CRI-Occupation, controlling for age and eTIV

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	−48.419	35.811	−0.160
eTIV	0.007	0.001	0.616
Step 2:			
Age	−41.510	34.517	−0.137
eTIV	0.007	0.001	0.593
CRI-Occupation	18.252	7.694	0.252

Note. $N = 58$. Step 1. $R^2 = 0.333$, $p < 0.001$; Step 2. $R^2 = 0.396$, $\Delta R^2 = 0.063$, $p = 0.021$.

CRI-Occupation was also significantly associated with the left inferior temporal gyrus explaining 9.6 % of the regional volume ($R^2 = 0.292$, $\Delta R^2 = 0.096$, $F(1,57) = 7.418$, $p < 0.001$) and the right inferior temporal gyrus explaining 8.5 % of the regional volume ($R^2 = 0.406$, $\Delta R^2 = 0.085$, $F(1,57) = 12.322$, $p < 0.001$) (see Table 3.20 and Table 3.21).

Table 3.20

Hierarchal regression analysis for dependent variable "left hemisphere inferior temporal gyrus" and independent variable CRI-Occupation, controlling for age and eTIV

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	−3.746	37.526	−0.013
eTIV	0.005	0.001	0.447
Step 2:			
Age	4.405	35.662	0.015
eTIV	0.004	0.001	0.418
CRI-Occupation	21.532	7.950	0.312

Note. $N = 58$. Step 1. $R^2 = 0.196$, $p = 0.003$; Step 2. $R^2 = 0.292$, $\Delta R^2 = 0.096$, $p = 0.009$.

Table 3.21

Hierarchal regression analysis for dependent variable "right hemisphere inferior temporal gyrus" and independent variable CRI-Occupation, controlling for age and eTIV

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	−49.392	31.473	−0.187
eTIV	0.006	0.001	0.608

Table 3.20 continued

Independent variables	B	SE B	β
Step 2:			
Age	−42.383	29.806	−0.161
eTIV	0.006	0.001	0.581
CRI-Occupation	18.514	6.644	0.294

Note. $N = 58$. Step 1. $R^2 = 0.321$, $p < 0.001$; Step 2. $R^2 = 0.406$, $\Delta R^2 = 0.085$, $p = 0.007$.

The CRI-Total score was related to the left hemisphere middle temporal gyrus, explaining 6.3 % of the regional volume ($R^2 = 0.396$, $\Delta R^2 = 0.063$, $F(1, 57) = 11.812$, $p < 0.001$) (see Table 3.22).

Table 3.22

Hierarchal regression analysis for dependent variable "left hemisphere middle temporal gyrus" and independent variable CRI-Total, controlling for age and eTIV

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	−48.419	35.811	−0.160
eTIV	0.007	0.001	0.605
Step 2:			
Age	−47.486	34.388	−0.157
eTIV	0.007	0.001	0.605
CRI-Occupation	23.752	9.988	0.252

Note. $N = 58$. Step 1. $R^2 = 0.333$, $p < 0.001$; Step 2. $R^2 = 0.396$, $\Delta R^2 = 0.063$, $p = 0.021$.

Association between cognitive reserve and frontal lobe regions

CRI-Education was statistically significantly negatively correlated only with right hemisphere paracentral lobule ($r_s = -0.293$, $p = 0.026$), however, there were a statistically significant relationships between CRI-Occupation and left hemisphere rostral middle frontal gyrus ($r_s = 0.306$, $p = 0.020$), left and right hemisphere pars orbitalis ($r_s = 0.296$, $p = 0.024$ and $r_s = 0.323$, $p = 0.013$, accordingly), both hemisphere lateral orbitofrontal gyrus ($r_s = 0.327$, $p = 0.012$ and $r_s = 0.247$, $p = 0.037$, accordingly), as well as, right hemisphere medial orbitofrontal cortex ($r_s = 0.285$, $p = 0.030$). Total CRI was associated with the right hemisphere pars orbitalis ($r_s = 0.411$, $p = 0.001$) (see Table 3.23 and Annex 10, Table 10.4 for full correlation table).

Table 3.23

Spearman's rank correlation between cognitive reserve and frontal lobe regions

Variable	CRI Education	CRI Occupation	CRI Leisure	CRI Total
lh superior frontal	0.066	0.162	−0.204	0.016
rh superior frontal	0.100	0.257	−0.122	0.139
lh rostral middle	−0.048	**0.306***	−0.101	0.084

Table 3.23 continued

Variable	CRI Education	CRI Occupation	CRI Leisure	CRI Total
rh rostral middle	0.024	0.164	−0.207	0.020
lh caudal middle	0.041	−0.060	−0.019	−0.046
rh caudal middle	0.221	0.142	−0.044	0.158
lh pars opercularis	−0.051	0.200	−0.062	0.045
rh pars opercularis	0.056	0.111	−0.171	0.009
lh pars triangularis	−0.130	0.031	−0.126	−0.066
rh pars triangularis	0.034	0.058	−0.098	0.008
lh pars orbitalis	0.063	**0.296***	−0.032	0.188
rh pars orbitalis	0.111	**0.323***	**0.339****	**0.411****
lh medial orbitofrontal	0.140	0.106	−0.028	0.045
rh medial orbitofrontal	0.242	**0.285***	−0.005	0.243
lh lateral orbitofrontal	0.216	**0.327***	−0.036	0.224
rh lateral orbitofrontal	0.186	**0.274***	0.101	0.241
lh paracentral lobule	−0.141	0.160	−0.139	−0.030
rh paracentral lobule	**−0.293***	−0.025	−0.171	−0.195
lh precentral gyrus	0.045	−0.093	0.047	0.001
rh precentral gyrus	0.024	−0.098	−0.068	−0.096

Note. $N = 58$, $^{*}p \leq 0.05$, $^{**}p < 0.01$

When controlling for age and eTIV, CRI-Education was no longer associated with paracentral lobule regions. Similarly, CRI-Occupation was no longer associated with bilateral pars orbitalis, lateral orbitofrontal cortex, rostral middle frontal gyrus, and right hemisphere medial orbitofrontal cortex. However, the CRI-Total explained 8.4 % of the right hemisphere pars orbitalis volume ($R^2 = 0.127$, $\Delta R^2 = 0.084$, $F(1, 57) = 2.613$, $p = 0.061$), though the model was not statistically significant (Table 3.24).

Table 3.24

Hierarchal regression analysis for dependent variable "right hemisphere pars orbitalis" and independent variable CRI-Total, controlling for age and eTIV

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	−4.179	7.122	−0.083
eTIV	0.000	0.000	0.221
Step 2:			
Age	−4.000	6.864	−0.080
eTIV	0.000	0.000	0.208
CRI-Occupation	4.556	1.994	0.291

Note. $N = 58$. Step 1. $R^2 = 0.042$, $p < 0.305$; Step 2. $R^2 = 0.127$, $\Delta R^2 = 0.084$, $p = 0.061$.

Association between cognitive reserve and parietal regions

CRI-Occupation statistically significantly correlated with the left hemisphere superior parietal lobule ($r_s = 0.262$, $p = 0.047$). Occupational activities were also significantly correlated with the left hemisphere inferior parietal lobule ($r_s = 0.471$, $p < 0.001$). Correlation with the left

hemisphere inferior parietal lobule was also found with CRI-Total ($r_s = 0.387$, $p = 0.003$) (see Table 3.25. and Annex 10, Table 10.5 for full correlation table).

Table 3.25

Spearman's rank correlation between cognitive reserve and parietal lobe regions

Variable	CRI Education	CRI Occupation	CRI Leisure	CRI Total
1. lh postcentral	0.096	0.095	−0.003	0.101
2. rh postcentral	0.041	−0.008	0.013	0.022
3. lh supramarginal	0.076	−0.007	0.159	0.066
4. rh supramarginal	0.117	0.250	0.085	0.179
5. lh superior parietal	0.105	0.262*	0.120	0.229
6. rh superior parietal	0.090	0.114	0.068	0.066
7. lh inferior parietal	0.233	0.471**	0.172	0.387*
8. rh inferior parietal	0.051	0.195	−0.054	0.071
9. lh precuneus	0.055	0.105	0.003	0.071
10.rh precuneus	0.096	0.033	−0.057	−0.010

Note. $N = 58$, $^*p \leq 0.05$, $^{**}p < 0.01$

After controlling for age and eTIV, CRI-Occupation no longer showed significant association with the volume of the left hemisphere superior parietal lobule; however, it was still associated with the left hemisphere inferior parietal lobule ($R^2 = 0.483$, $\Delta R^2 = 0.138$, $F(1, 54) = 14.404$, $p < 0.001$) explaining 13.8 % of the variation (see Table 3.26).

Table 3.26

Hierarchal regression analysis for dependent variable "left hemisphere inferior parietal lobule" and independent variable CRI-Occupation, controlling for age and eTIV

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	2.433	32.732	0.009
eTIV	0.006	0.001	0.584
Step 2:			
Age	11.857	24.455	0.043
eTIV	0.006	0.001	0.550
CRI-Occupation	24.920	6.566	0.373

Note. $N = 58$. Step 1. $R^2 = 0.345$, $p < 0.001$; Step 2. $R^2 = 0.483$, $\Delta R^2 = 0.138$, $p < 0.001$.

Also, the Total CRI was associated with the regional volume of the left hemisphere inferior parietal lobule, explaining 12 % of the variation ($R^2 = 0.465$, $\Delta R^2 = 0.120$, $F(1, 54) = 12.107$, $p = 0.001$) (see Table 3.27).

Table 3.27

Hierarchal regression analysis for dependent variable "left hemisphere inferior parietal lobule" and independent variable CRI-Total, controlling for age and eTIV

Independent variables	B	SE B	β
Step 1: covariate variable			
Age	2.433	32.731	0.009
eTIV	0.006	0.001	0.584
Step 2:			
Age	3.619	29.857	0.013
eTIV	0.006	0.001	0.568
CRI-Occupation	30.173	8.672	0.347

Note. $N = 58$. Step 1. $R^2 = 0.345$, $p < 0.001$; Step 2. $R^2 = 0.465$, $\Delta R^2 = 0.120$, $p = 0.001$.

Association between cognitive reserve and regions of the occipital lobe

Only Total CRI statistically significantly correlated with one of the occipital lobe regions – the right hemisphere pericalcarine ($r_s = 0.285$, $p < 0.030$) (see Table 3.28).

Table 3.28

Spearman's rank correlation between cognitive reserve and occipital lobe regions

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. CRI Education	–											
2. CRI Occupation	0.377**	–										
3. CRI Leisure	0.281*	0.258	–									
4. CRI Total	0.670**	0.817**	0.627**	–								
5. lh lingual	0.066	0.013	−0.176	−0.015	–							
6. rh lingual	0.163	0.094	0.050	0.137	0.523	–						
7. lh pericalcarine	0.014	−0.151	−0.071	−0.045	0.507	0.565	–					
8. rh pericalcarine	0.218	0.202	0.054	**0.285***	0.344	0.681	0.687	–				
9. lh cuneus	−0.043	−0.162	−0.211	−0.157	0.368	0.393	0.678	0.502	–			
10.rh cuneus	−0.008	−0.037	−0.219	−0.046	0.491	0.550	0.658	0.668	0.627	–		
11.lh lateral occipital	0.050	0.137	−0.114	0.025	0.255	0.240	0.139	0.169	0.202	0.312	–	
12.rh lateral occipital	−0.118	0.028	−0.257	−0.116	0.353	0.106	0.166	0.121	0.391	0.376	0.690	–

Note. $N = 58$, *$p \leq 0.05$, **$p < 0.01$

After controlling for age and eTIV, this relationship was not confirmed.

Association between cognitive reserve and regions of the cingulate gyrus

Spearman's rank correlation analysis indicated a relationship between CRI-Education and the right hemisphere rostral anterior cingulate ($r_s = 0.272$, $p = 0.039$), as well as, the left hemisphere posterior cingulate ($r_s = 0.266$, $p = 0.043$). CRI-Occupation score was statistically

significantly related to the left hemisphere caudal anterior cingulate gyrus ($r_s = 0.266$, $p = 0.044$), the left and right hemisphere rostral anterior cingulate gyrus ($r_s = 0.320$, $p = 0.014$ and $r_s = 0.301$, $p = 0.022$, respectively), and the left hemisphere insula ($r_s = 0.261$, $p = 0.048$). Total CRI was weakly associated with the right hemisphere rostral anterior cingulate ($r_s = 0.274$, $p = 0.038$) and the left and right hemisphere insula ($r_s = 0.294$, $p = 0.025$ and $r_s = 0.309$, $p = 0.018$) (see Table 3.29, for full correlation table see Annex 10, Table 10.6).

Table 3.29

Spearman's rank correlation between cognitive reserve and cingulate regions

Variable	CRI Education	CRI Occupation	CRI Leisure	CRI Total
1. lh caudal anterior	0.114	**0.266***	0.034	0.211
2. rh caudal anterior	−0.036	0.218	−0.099	0.081
3. lh rostral anterior	0.203	**0.320***	0.084	0.244
4. rh rostral anterior	**0.272***	**0.301***	0.032	**0.274***
5. lh posterior cingulate	**0.266***	0.155	0.074	0.229
6. rh posterior cingulate	−0.012	0.141	0.002	0.096
7. lh isthmus	0.251	0.062	0.180	0.237
8. rh isthmus	0.195	0.116	−0.145	0.115
9. lh insula	0.239	**0.261***	0.137	**0.294***
10. rh insula	0.238	0.247	0.188	**0.309***

Note. $N = 58$, $^*p \leq 0.05$, $^{**}p < 0.01$

When controlling for age and eTIV, the cognitive reserve proxies no longer indicated a statistically significant relationship with any of the aforementioned regions.

The visual representation of the cortical regions associated with cognitive reserve sociobehavioural proxies is depicted in Figure 3.6.

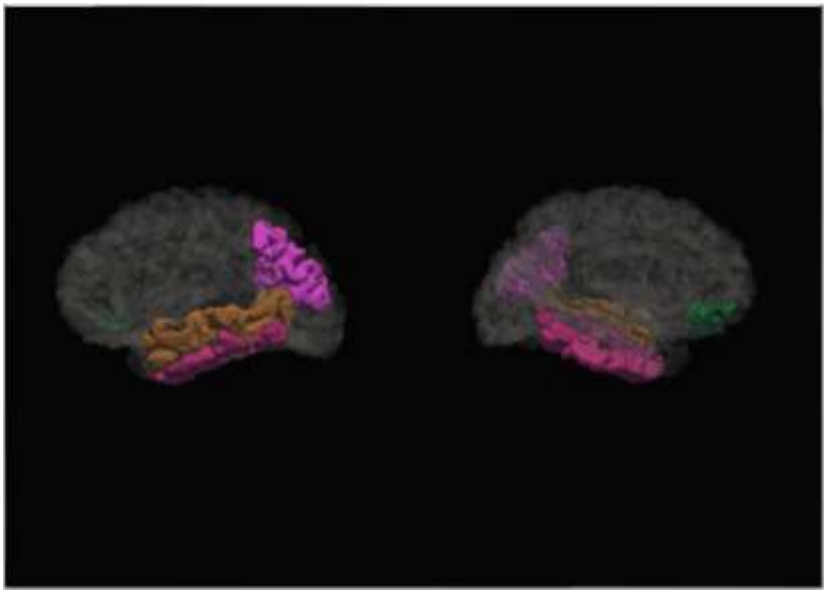

Figure 3.6 **Regions associated with cognitive reserve and its proxies**

Association between cognitive reserve and thalamus and hippocampus

To better understand the relationship between cognitive reserve and thalamus and hippocampus, Spearman's rank correlation analysis was conducted. There were no statistically significant relationships between cognitive reserve and its proxies and thalamus and hippocampus (see Table 3.30).

Table 3.30

Relationship between cognitive reserve and its proxies and thalamus and hippocampus (Spearman's ρ)

Variable	1	2	3	4	5	6	7	8	9	10
1. CRI Education	–									
2. CRI Occupation	0.377**	–								
3. CRI Leisure	0.281*	0.258	–							
4. CRI Total	0.670**	0.817**	0.627**	–						
5. lh thalamus	0.078	0.178	−0.034	0.128	–					
6. rh thalamus	0.101	0.158	0.038	0.147	0.909**	–				
7. Thalamus	0.099	0.177	0.011	0.146	0.973**	0.976**	–			
8. lh hippocampus	0.112	0.139	−0.012	0.107	0.704**	0.658**	0.700**	–		
9. rh hippocampus	0.050	−0.019	−0.043	0.000	0.656**	0.657**	0.683**	0.848**	–	
10.Hippo-campus	0.098	0.084	−0.021	0.076	0.709**	0.697**	0.726**	0.959**	0.956**	–

Note. $N = 61$, $^{**}p < 0.01$, $^{*}p < 0.05$

3.3.3 Association between the change in cognitive performance and cognitive reserve

To test the hypothesis that changes in cognitive performance over time will be associated with the baseline cognitive reserve score, first the differences between the first and second measure were identified using Wilcoxon test. Further, cognitive variables indicating significant changes over time, were included in partial correlation analysis, controlling for time between measures ($M = 3.38$ years). Only long-term memory, reaction time composite and cock-drawing task scores showed statistically significant changes, thus only these variables were included in further data analysis (see Table 3.31).

Table 3.31

Descriptive statistics and differences between measures

Variable	First measure		Second measure		z	p
	Mdn	SD	Mdn	SD		
Short-term memory	6	1.593	6	1.337	−0.510	0.610
Long-term memory	**8**	**1.880**	**6**	**2.313**	**−3.361**	**< 0.001**
Associative memory	107.00	9.160	109	15.117	−1.268	0.205
Working memory	99	11.766	102	10.920	−1.446	0.148
Verbal fluency	12	3.515	12	3.367	−0.935	0.350
Vocabulary	20	1.80	20	2.059	−0.805	0.421
Reaction time composite	**0.918**	**0.322**	**0.445**	**0.247**	**−4.197**	**< 0.001**
Visual Matching	102	9.395	105	21.013	0.000	0.000
Trail-making task	1	0.470	1	0.470	0.000	0.000
Cube	1	0.449	1	0.507	−1.155	0.248
Clock drawing task	**3**	**0.662**	**2**	**0.815**	**−2.352**	**0.019**

Note. Mdn – median, SD – standard deviation

For each cognitive function that showed statistically significant differences, a new variable was calculated depicting the changes over time (second measure minus the first measure). To investigate the association between the variables, partial correlation analysis was conducted, controlling for the time difference between measures (see Table 3.32).

Table 3.32

Partial correlation between cognitive reserve and its subindices and change in cognitive functions, controlling for time between measures

Variable	1	2	3	4	5	6	7
1. CRI-Education	–						
2. CRI-Occupation	0.292	–					
3. CRI-Leisure Activity	0.027	0.229	–				
4. CRI-Total	0.473*	0.876***	0.649***	–			
5. Long-term memory	−0.206	0.122	0.214	0.128	–		
6. Clock drawing task	−0.190	0.051	0.030	0.001	0.015	–	
7. Reaction time composite	−0.105	0.061	**−0.440***	−0.178	0.229	−0.002	–

Note. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

After controlling for the years between testing, a negative correlation was found between CRI-Leisure Activity and changes in the reaction time composite ($r_p = -0.440$, $p = 0.041$). Correlations between the rest of the cognitive variables and cognitive reserve were not statistically significant ($p > 0.05$).

4 Discussion

The aim of the Thesis was to investigate the cognitive and neural correlates of cognitive reserve in healthy adults. To achieve this goal, four main research objectives were submitted: first, to investigate the relationship between socio-behavioural proxies of cognitive reserve and memory and verbal fluency skills using secondary data from the SHARE project. Second, to identify the brain correlates of cognitive reserve in a sample of older Latvian adults, third, to examine the relationship between cognitive functions and cognitive reserve in a sample of older adults, and finally, to investigate the changes in cognitive functioning over time and examine the association between the change in cognitive functioning and baseline measures of cognitive reserve. In this chapter, first, the results of each individual objective are discussed, and then the results as a whole are considered. Furthermore, limitations are identified and future research steps are proposed.

The relationship between socio-behavioural proxies of cognitive reserve and memory and verbal fluency in a sample of Latvian adults

The structural equation models investigating the relationship between cognitive reserve and memory and verbal fluency indicated that education, current employment status, cognitive leisure activities such as reading and playing word games, and moderate physical activity are all significant predictors of short- and long-term memory and verbal fluency skills. Higher levels of education were closely associated with better memory and verbal fluency. These findings on verbal fluency are consistent in the literature, and several studies in various research samples have confirmed it (e. g. see Lubrini et al., 2022); however, attention should be paid to the type of verbal fluency task, namely, whether the task is phonological (name as many words as you can starting with the letter ‘P’) or semantic (name as many animals as you know).

Education was also a significant predictor of short- and long-term memory scores, showing that larger amount of years of education could be associated with better memory performance, a finding that has been consistent in the literature. Employment status was a weak predictor of short- and long-term memory performance. Although current employment status may not be fully reflective of cognitive reserve, several studies have shown the importance of occupation, highlighting the cognitive decline that often follows after retirement. However, it should be noted that to reach such conclusions in this study, a longitudinal approach would be needed, and thus this is a step for future research in this sample.

Leisure activities were initially planned to be looked at as a whole, in the accordance with the approach used in Cognitive Reserve Index questionnaire (CRIq); however, the confirmatory factor analysis (CFA) indicated the need to create two categories – Cognitive

leisure that involved attending educational or training course, reading, playing word or number games, and playing cards or games, and Social leisure that involved activities with a social component – doing voluntary or charity work, going to a sport, social or other kind of club, as well as taking part in a political or community-related organization. After CFA, playing cards or games were removed from the model due to poor fit. This could be related to the fact that playing cards or games can also be considered to be a social activity; however, in this case it might also be related to the small sample of participants who have done this activity (n = 11). After integrating the prepared Cognitive and Leisure activity scales, to further comply with the CRIq, physical activity experience was also integrated into the model; however, these variables were used separately due to differences in coding.

In the model, only Cognitive leisure was significant in predicting both – memory and verbal fluency. Even more, the model fit improved after removing educational or training course attendance. This was an unexpected find, as so far it has been suggested that informal education could be among the factors protective against cognitive decline and dementia (e.g. it has been included in several cognitive reserve questionnaires). However, these results could also be explained by the data, as it was not specified how long or what type of courses were taken. Language learning courses (even online) have been found to be beneficial for cognitive improvement in older adults (Wong et al., 2019), although taking university training courses as part of informal education have shown some mixed results (Matyas et al., 2019). To better understand the significance and involvement of the informal education as a part of cognitive reserve, more studies should be taken and clear criteria should be defined.

Word and number puzzles were indirectly associated with better short- and long-term memory and verbal fluency performance. So far there have been controversial results regarding the role of crossword and number puzzles, such as Sudoku, for improvement or maintenance of cognitive performance. Older studies have shown that adults, who overall showed better performance in doing Sudoku puzzles, also had better working memory performance, including when measured with semantic fluency tasks (Grabbe, 2011), other studies indicate that e.g. crossword puzzles should be tailored for a specific goal (Murphy et al., 2016). A study by Pillai and colleagues (Pillai et al., 2011) found that doing in crossword puzzles delayed onset of memory decline by 2.54 years in participants who later developed dementia; however, it also increased the rate of decline after the onset of memory decline. These findings comply with the overall assumptions regarding cognitive reserve, namely, higher cognitive reserve is protective only for a limited time after which the decline in memory performance is more rapid than in those with lower reserve (Stern et al., 1999).

In addition to solving crossword and number puzzles, reading books and newspapers were also indirectly associated with cognitive functions. While it has rarely been in the research focus, reading has also previously been associated with a lower risk of cognitive decline, even independent of the level of education (Chang et al., 2021). Some studies have indicated a positive relationship between reading and working memory, especially, when considering the developmental component – i.e. the time of reading acquisition and later reading performance (Peng et al., 2018); similarly, a relationship between higher reading ability and better episodic memory has been found in older adults (Sol et al., 2021). It should be noted that while Spearman's rank correlation analysis also indicated separate associations between reading, taking word and number puzzles, and cognitive functions, the combination of both into one variable increased the strength of the association. This might indicate that even though these activities might function separately, a combination of both could be more efficient.

Finally, in both models, aerobic physical activity was considered. Higher participation in moderate physical activities, such as taking a fast walk or gardening, predicted better short- and long-term memory performance scores, as well as verbal fluency scores. Vigorous physical activity was removed from the model, as it did not significantly predict the aforementioned cognitive functions. Aerobic physical activities include repetitive structured physical exercise that requires the body to use oxygen to produce more energy (Caspersen et al., 1985). The first studies identifying the effects of physical activity on cognitive function date back to the 1970s (Spirduso, 1975); however, research on the role of physical activity in reducing cognitive decline has been of interest only for the past 20 years. Although the relationship between physical activity and cognitive functions was expected, surprisingly vigorous physical activity did not statistically significantly predict neither memory nor verbal fluency. Nevertheless, it should be noted that in many experimental and cross-sectional studies, even moderately intensive activities, such as regular walks or lower intensity exercises, are found to be beneficial (Makizako et al., 2013; Sandroff et al., 2015; Varma et al., 2015).

Overall, the results of both models indicate that involvement in different long and short-term lifestyle activities could be beneficial for better cognitive functioning later in life, also highlighting the need for a combination of activities, rather than one individual. However, several limitations should be considered.

As secondary data were used, it was not possible to control the acquisition of socio-behavioural variables of cognitive reserve. The educational data had to be calculated based on the retrospective years of education during the respective time period. As it is not specified in which year the education was obtained, some of the cases can have an educational deviation by a year. Similarly, it was not possible to identify the specific amount of years and the exact

occupation for the participants, thus we could not fully represent the occupational factors of cognitive reserve. Finally, leisure activities were limited to the past year, thus again restricting the representation of cognitive reserve.

The relationship between cognitive functioning and cognitive reserve in a sample of older Latvian adults

Higher scores of cognitive reserve and its subindices – education, occupation and leisure – were associated with better short- term memory performance, larger vocabulary, higher verbal fluency scores and faster reaction times. The results were partially compliant with the results from the larger sample.

Higher level of education (CRI-Education) was associated with better short-term memory and larger vocabulary. A correlation with verbal fluency scores was expected (Nogueira et al., 2016); however, the correlation was very weak and not statistically significant, a result that could be explained by the limited sample size. More complex and responsible occupation activities (CRI-Occupation) were associated with better short-term memory scores; though, after controlling for age, this association was eliminated. However, occupation was also related to better verbal fluency performance and faster reaction time, even after controlling for age. In contrast to the findings of the first stage, leisure activities (CRI-Leisure) were not associated with any of the cognitive functions. This could be related to the fact that a composite score of all activities is used in the data analysis, rather than years of an individual activity. The total cognitive reserve index (CRI-Total) was associated with better short-term memory scores and better verbal fluency scores independent of the potential age effect.

Cortical, hippocampal and thalamic correlates of cognitive reserve in a sample of older Latvian adults

This objective of the study aimed to investigate the potential relationship between cognitive reserve and its proxies and cortical regions, thalamus, and hippocampus in older adults without a known diagnosis of dementia. After controlling for age and estimated intracranial volume (eTIV), higher occupational achievements (CRI-Occupation) were associated with larger cortical volume in the left-hemisphere middle temporal gyrus, the left and right hemisphere inferior temporal gyrus and the left hemisphere inferior parietal lobule, while the total cognitive reserve index (CRI-Total) was associated with larger cortical volume in the left hemisphere middle temporal gyrus and inferior parietal lobule and the right hemisphere *pars orbitalis*. Neither the thalamus nor the hippocampus was associated with cognitive reserve or its indices.

Cortical volume refers to a quantitative properties of the cerebral cortex and includes the amount of neurons, dendritic processes and glial cells (Schaer et al., 2006). Cortical volume loss has been associated with higher mortality and worsened cognitive functions (Mouton et al., 1998), thus the relationship between cognitive reserve and specific cortical regions could indicate a potentially protective effects of e.g. occupational activities or active lifestyle *per se*.

Previous studies have indicated a potential relationship between cognitive reserve and specific cortical regions, though these studies could be limited by the approach used to measure cognitive reserve, often focusing on education as a proxy or composite scores with verbal IQ and individual differences (e.g. see Arenaza-Urquijo et al., 2013; van Loenhoud et al., 2017). However, the results of the Thesis did not show a relationship between education as a proxy of cognitive reserve and any of the cortical regions. This could be explained considering that more recent studies have started to reinterpret the role of education in healthy ageing, highlighting it as a more passive variable, a threshold, thus not having a longitudinal impact (Cadar et al., 2017; Nyberg et al., 2021). Meanwhile, occupation, another proxy included in the Cognitive Reserve Index questionnaire, can be considered to be more active, often lasting long into late adulthood. Nevertheless, it should be stressed that the tasks of occupational complexity and level of responsibility often correlate with higher level of education, thus, while education may not be directly associated with cortical regions, the educational element could still be present and contribute to the effect of occupational activities. This has also been confirmed in a study by Mondini et al. (2022).

Higher occupational achievements and the total cognitive reserve index were associated with larger cortical volumes in the left hemisphere middle temporal gyrus and right hemisphere pars orbitalis – regions that are associated with linguistic abilities. Verbal intelligence has been associated with temporal regions in the left hemisphere (Heyer et al., 2021) and, considering that verbal IQ has often been used as a proxy of cognitive reserve, this might confirm the need for a more complex cognitive reserve proxy, combining vocabulary with socio-behavioural measures. Similarly, *pars orbitalis* in the left hemisphere, has long been associated with verbal abilities and speech production; however, the functional role of right hemisphere pars orbitalis is still debated. A study aiming to investigate verbal learning and fluency and its associated cortical regions in early stages of psychotic illness, found that greater right *pars orbitalis* volume was related to better verbal fluency scores in a group with recent-onset psychosis, though no such results were present in healthy controls (Kenney et al., 2017). Although studies on the *pars orbitalis* of the right hemisphere are sparse, several studies indicate that the inferior frontal gyrus, an area also vulnerable to different types of dementia (Schroeter et al., 2012) – can benefit from cognitive reserve. A recent FDG-PET study found that higher education in

participants with frontotemporal dementia also showed better MMSE scores, as well as detection of glucose metabolism alterations in patients with FTD and low education (Beyer et al., 2021).

There were no significant associations between cognitive reserve and thalamic and hippocampal volume. Earlier studies have implied the role of thalamus as a part of brain networks associated with cognitive reserve (Y. Stern et al., 2005), still, the literature on the effect of cognitive reserve on thalamus is sparse. Considering the general role of the thalamus, i.e. a relay between a stimulus and a cortical region, it is possible that the structural measures were not the most appropriate and further studies could gain from functional MRI or tractographies, focusing more on the network characteristics, rather than a structural measure.

Rather unexpectedly, hippocampal volume did not correlate with cognitive reserve, despite conclusions gained from previous studies (e.g. see Serra et al., 2019). However, this could be attributed to the compensation of other structures. A recent study investigated the type and regions of functional activation associated with reserve proxies, in addition evaluating how these activations moderate the detrimental effect of hippocampal atrophy on associative memory, finding that, while the hippocampus might not be directly affected by cognitive reserve, it can serve as a moderator between cognitive performance and reserve proxies (especially in low reserve), as well as collaborate with the temporal lobe (Belleville et al., 2021). This is overall consistent with other previous studies, highlighting the role of hippocampus as a mediator / moderator (Vuoksimaa et al., 2013).

These findings must be interpreted with caution due to several limitations. Magnetic resonance images were obtained using a 1.5 Tesla machine; thus, reduced image quality can be expected. This is also significant considering the blurred borders of cortical structures, i.e. one general region can house several functions depending on the segmentation. Due to the relatively low resolution of the scans, such detailed segmentation was not possible. Further studies should involve functional connectivity measures, potentially using the identified brain regions as ROI.

The association between the change in cognitive performance and baseline measures of cognitive reserve

In addition to cross-sectional data, longitudinal measures were obtained, with approximately 3.39 years between the measures. Wilcoxon Signed Ranks test indicated significant changes in only three cognitive functions – long-term memory, reaction time and visuo-spatial abilities, showing a decline in all cases. This is overall consistent with the literature, for example, a recent study by Korkki and colleagues (Korkki et al., 2020) confirmed age-related episodic memory changes in a sample of normally ageing individuals, and as early

as in 1996 Timothy Salthouse proposed his theory on age-related decrease in processing speed as a factor in cognitive decline (Salthouse, 1996). Although the processing speed was not used as a mediator in the Thesis, this could be the next step in future studies. The effects of ageing were also longitudinally investigated in a study by Cox and colleagues (Cox et al., 2021), finding that visuo-spatial abilities, memory, and processing speed are the cognitive functions most vulnerable to ageing – findings that are fully compliant with the current study.

To explore the role of cognitive reserve in changes in cognitive functioning, a partial correlation analysis was conducted and the years between testing were used as a controlled variable. Partial correlation analysis was chosen instead of hierarchal regression analysis due to the sample size. The results showed who participants that were more active in lifelong leisure activities (CRI-Leisure Activities) also showed less changes in reaction time. Surprisingly, such results were not found in education and occupation; however, this could indicate the role of staying active even after educational activities are concluded and retirement rather than cognitive reserve. These findings partially support the findings by Lars Nyberg (Nyberg et al., 2021), claiming that education can determine the baseline of cognitive functioning; however, it has a fixed effect. Therefore, the findings of this part of the Thesis are more consistent with the concept of cognitive maintenance.

However, caution should be taken when interpreting the data from this part of the study, as there are significant limitations. First, the sample size is insufficient to generalize any of the findings; thus, we can only discuss potential tendencies. Second, the sample consists only of women. This was a conscious choice due to gender inequality in the baseline sample, with the majority of participants being female. This, of course, highlights another limitation present in all samples, namely, traditionally more motivated adults take part in research studies, thus again the data cannot be generalized to the whole population.

General discussion

While all hypothesis were only partially confirmed, the results of the study indicate that higher level of education, higher occupational achievements and more active leisure could function as neural and cognitive enrichment in specific domains, thus potentially delaying the symptom onset of neuropathology, if it is already present. Due to the combination of cross-sectional and longitudinal designs, the results indicate that different types of cognitive reserve proxies and cognitive enrichment activities could have varied significance over the lifetime.

As discussed before, education has been largely used as a proxy measure of cognitive reserve since the first studies and is still often present in large scale studies using secondary data; however, as witnessed in the Thesis, education might actually have a limited effect that is

focused on the cognitive functioning at baseline and might not be directly a factor in brain health. This hypothesis, of course, is strongly limited by the sample size; nevertheless, it would explain the lack of significant relationship between education and e.g. frontal lobe cortical regions and hippocampus, despite predicting short and long-term memory measures. These findings, in turn, would more confirm the previously discussed role of cognitive reserve as a moderator between the brain and cognitive functioning (Song et al., 2022), rather than considered to be a direct predictor. Nevertheless, this was not present in all cognitive reserve proxies.

The STAC-r framework indicates the need for "interventions" and enrichment activities all through the life even after the onset of biological ageing. If formal education is traditionally obtained during the youth, occupation and leisure activities are present longer in life. Working activity often involves both – enriching and resource depleting factors. There are definite benefits present, when considering the enrichment aspect, e.g. work environment provides the opportunity to study and develop new skills, engage in social activities, establish a daily routine etc. (Vance et al., 2016), besides, employment is often present all through the life. EUROSTAT data indicate that employment rates among adults aged 55–64 and 65 and over increase significantly (*Ageing Europe – Statistics on Working and Moving into Retirement – Statistics Explained*, n.d.), this is a tendency that could mean that active employment would be a daily life factor even past the official retirement age.

The findings of this study showed a relationship between employment and occupational complexity in several cognitive domains, as well as, specific brain regions. The association between occupational activities and specific brain regions have been long established. Among the best known studies is the taxi driver study by Maguire et al. (2000), highlighting the effect of an occupational specificity; however, later studies have confirmed that specific occupational demands could be associated with better cognitive resistance to pathology (Spreng et al., 2011). While the current study did not differentiate between professions directly, the level of difficulty, education needed and the physical / mental load was considered through Cognitive Reserve Index questionnaire. Interestingly, occupational activity was associated with regions known to be involved in ensuring social communication, e.g. object and face recognition (inferior temporal gyrus) and mentalization (inferior parietal lobe) (Conway, 2018; Numssen et al., 2021; Yang & Bi, 2022), highlighting the potential role of occupation in building and maintaining social networks.

Higher occupational achievements were also associated with regions known for processing and updating new information, overriding the previous assumptions (left hemisphere middle temporal gyrus, in connectivity with hippocampus and medial temporal gyrus) and again

with inferior parietal lobe, that is a well-known hub from the "rich club"(Davey et al., 2016; Oldham & Fornito, 2019). Considering that occupational activity was associated with information processing, short-term memory and verbal fluency, it could indicate the significance of a continuing working activity in delaying the symptoms of dementia.

Consistent with both – Cognitive Reserve and STAC-r theories, leisure activities did show an association with better cognitive functioning; nevertheless, here the results are less clear and, considering the specificity of measures, points more towards an ongoing effect, rather than being only a part of reserve. As mentioned before, reading and doing word games were associated with better memory and verbal fluency performance; however, due to the specificity of secondary data, the obtained measures were relevant only for the past year. Thus, while not fully representative of cognitive reserve, it still does point to leisure activities as ongoing enrichment.

Furthermore, leisure activities were the only cognitive reserve sociobehavioural proxy that predicted changes in cognitive functioning, while cross-sectionally stronger predictors, such as education and occupation, did not. Here again it could be hypothesised that the cognitive reserve is a finite resource that can be depleted after finishing education and retiring, leaving leisure activities as more long-term and current activities for continuously supplementing the reserve. Previous studies have indicated that time away from work could predict cognitive decline later in life (Leist et al., 2013) and this is consistent with both compensatory models of cognitive ageing used in this study.

General strengths and limitations

Several important limitations should be considered. First, the findings from the first two stages are limited by the use of cross-sectional design and the results would benefit more from a longitudinal study. However, this was not possible within this study. While the SHARE project does offer longitudinal data, the data from Wave 7 did not include several of the variables used in the Wave 8, thus the datasets were not comparable. In case of MRI volumetric measures. Although the same protocol was activated when repeatedly obtaining imaging data, a General Electric 3T machine was used, thus rendering the data incomparable.

Second, the use of socio-behavioural proxies of cognitive reserve should be carefully considered. The Cognitive Reserve Index questionnaire was used in the second stage of the study and has shown a fairly good evidence for the validity of the content and the construct and, in general, it does account for the mismatch between cognitive performance and pathology (Kartschmit et al., 2019); however, there is still a high risk of memory bias, especially with

respect to leisure activities. Similar concerns can be expressed regarding the proxies used in the first stage.

Third, while the intended sample size for the first stage was nationally representative, it was somewhat limited by the onset of COVID-19; therefore, it was only partially representative. The results from the second and third stage could also be affected by the small sample size and lack of heterogeneity regarding the gender, as well as education and occupation that were notably towards higher levels.

An arguable weakness is that participants were not additional assessed for current neurodegenerative status, but the authors of the study relayed on the self-reported information regarding the potential diagnosis. While on the one hand it could be considered a limitation of the study, on the other hand, this allowed for a more heterogeneous sample in the second and third stage of the study, as symptoms of cognitive decline could have been masked by the effects of cognitive reserve, therefore, participants could be self-reliant daily and not express symptoms of mild cognitive impairment even after the onset of the disease. However, participants whose results on cognitive assessment and brain volume were less than two standard deviations from the mean were excluded from data analysis.

A key strength of the present study is the exploratory and multidisciplinary approach to the research objectives. The relationship between cognitive reserve, cognitive functioning and brain volumetry has been examined from three different angles – in a partially representative sample and replicating the results in a smaller sample, but using more detailed assessment, from the point of brain volumetry, and through the longitudinal prism of the study, thus obtaining a thorough overview of the relationship between the variables. It should also be stressed that this is a first study in Latvia investigating healthy ageing in a multidisciplinary setting, combining health and cognitive psychology with neuroscience.

To eliminate the limitations identified in this study, future studies should include analysis of functional brain networks in addition to the structural measures, thus transforming from the currently used segregation approach to integrative approach. This could be achieved through fMRI or EEG measures. Furthermore, the longitudinal perspective should be maintained and developed as the only means of investigating the fluent nature of cognitive reserve.

Conclusions

The aim of this study was to investigate the cognitive and neural correlates of cognitive reserve in healthy adults. Four main hypothesis were proposed: (1) higher levels of education, active employment and active daily lifestyle will be associated with better memory performance and higher scores of verbal fluency in healthy adults, (2) higher cognitive reserve will be associated with better cognitive performance in memory, information processing speed, visuo-spatial abilities, executive functions and language abilities in healthy older adults, (3) higher cognitive reserve will be associated with larger brain volume, especially in brain regions considered more vulnerable to ageing and dementia, and (4) Changes in cognitive performance over time will be associated with the baseline cognitive reserve score.

All four hypothesis were partially confirmed, and it was concluded that:

1. Such cognitive reserve proxies as education, current employment and cognitive and moderate leisure activities) is associated with better short- and long-term memory performance and better verbal fluency.
2. Higher educational achievements is associated with better short-term memory scores and larger vocabulary, while higher occupational complexity and responsibility was associated with shorter information processing speed and better verbal fluency; however, none of the cognitive reserve sub-indices were associated with long-term memory, working memory, and executive functions and visuo-spatial abilities.
3. More complex occupational activities are associated with larger cortical volume, especially in regions that are known to be more vulnerable to Alzheimer's disease, including temporal regions; however, hippocampal and thalamic regions were not associated with none of the cognitive reserve sub-indices.
4. There are recognisable changes in such cognitive functions as memory, processing speed and executive functions over time, though only lesser changes in the processing speed could be associated with cognitive reserve, more specifically, leisure activities.

The findings of the study provide an overview on the relationship between cognitive reserve, cognitive functioning and the brain in older Latvian adults. The results could contribute towards developing a new, evidence based, strategy on promoting healthy cognitive ageing and lessening the burden of cognitive dysfunction, as well as, can be directly applied in daily practice of psychological help providers. In collaboration with non-governmental associations, informative materials could be developed, educating on the main principle of healthy cognitive ageing. Further studies would gain from further expanding the longitudinal aspects of the study,

as well as integrating functional brain measures for better understanding of the interaction between brain and cognitive reserve.

List of Published Articles and Abstracts

List of Articles

1. Zdanovskis, N., Platkājis, A., Kostiks, A., Šneidere, K., Stepens, A., Naglis, R., & Karelis, G. 2022. Combined Score of Perivascular Space Dilatation and White Matter Hyperintensities in Patients with Normal Cognition, Mild Cognitive Impairment, and Dementia. *Medicina, 58*(7), 887.
2. Šneidere-Šustiņa, A., Šneidere, K., Dowell, N., & Stepens, A. 2021. Relationship between cognitive reserve, motor reserve and thalamus volumetry in older adults. *Society. Integration. Education. Proceedings of the International Scientific Conference. Vol. 4*, 480-490.
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4. Šneidere, K., Ozoliņa, Z., & Stepens, A. 2020. Work-related cognitive reserve predicts depression and cognitive functioning in non-demented older adult sample. Society. Integration. Education. *Proceedings of the International Scientific Conference, Vol.7*., 168 - 176.
5. Ulmane, Z., Upesleja, G., Šneidere, K., & Stepens, A. 2020. Changes in the daily activities of the Latvian population over the last 30 years. *Society. Integration. Education. Proceedings of the International Scientific Conference, Vol.6.*, 411 - 420.

List of Abstracts

1. Bērenfelde, L., Šneidere, K., & Stepens, A. 23.08.2022. Cognitive reserve predicts false memory paradigm effect in Latvian adults. *36th Annual Conference of the European Health Psychology Society: Charting New Territories in Health Psychology. Abstracts.*, 432.
2. Šneidere, K., & Stepens, A. 24.08.2022. Relationship between cognitive reserve and memory in nondemented older adults. *36th Annual Conference of the European Health Psychology Society: Charting New Territories in Health Psychology. Abstracts.*, 709.
3. Šneidere, K., Šneidere-Šustiņa, A., & Stepens, A. 21.05.2021. Relationship between cognitive reserve, physical activity, hippocampal volume and working memory in older adults. *EGREPA Conference 2021 "Active aging – new challenges and new opportunities", Book of Abstracts.*, 80.
4. Šneidere, K., & Stepens, A. 25.03.2021. Relationship between cognitive reserve and overall cognitive functioning in older women: longitudinal study. «*8th International Multidisciplinary Research Conference "Society. Health. Welfare», Abstracts.*, 139.
5. Šneidere, K., Šneidere-Šustiņa, A., & Stepens, A. 25.03.2021. Relationship between motor reserve, thalamus volume, working memory and information processing speed in older adults. *International Research Conference on Medical and Health Care Sciences. Knowledge for Use in Practice», Abstracts.*, 220.

List of conference presentations

1. Šneidere, K., Stepens, A., un Mondini, S. 21.04.2022. Kortikālo reģionu saistība ar kognitīvajiem procesiem un kognitīvajām rezervēm. Mutiskais referāts prezentēts 8. zinātniski praktiskajā konferencē "Veselība un personības attīstība: starpdisciplinārā pieeja", Rīga, tiešsaiste.
2. Bērenfelde, L., Šneidere, K., & Stepens, A. 23.08.2022. Cognitive reserve predicts false memory paradigm effect in Latvian adults. Poster presented at the *36th Annual Conference of the European Health Psychology Society: Charting New Territories in Health Psychology,* Bratislava, Slovakia.
3. Šneidere, K., & Stepens, A. 24.08.2022. Relationship between cognitive reserve and memory in nondemented older adults. Poster presented at the *36th Annual Conference of the European Health Psychology Society: Charting New Territories in Health Psychology,* Bratislava, Slovakia.
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5. Šneidere, K., Šneidere-Šustiņa, A., & Stepens, A. 25.03.2021. Relationship between motor reserve, thalamus volume, working memory and information processing speed in older adults. Paper presented at the «*8th International Multidisciplinary Research Conference "Society. Health. Welfare»*, Rīga, online.
6. Šneidere, K., Šneidere-Šustiņa, A., & Stepens, A. 20.05.2021. Relationship between cognitive reserve, physical activity, hippocampal volume and working memory in older adults. Poster presented at the *EGREPA Conference 2021 "Active aging – new challenges and new opportunities"*, Krakow, online
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2. CAJAL "Ageing cognition", 20 September – 8 October, Bordeaux, France
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4. The IFA Copenhagen Summit on Cognitive Reserve, 24–25 October, Copenhagen, Denmark

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Annexes

Submission for the use of SHARE data

SHARE
SURVEY OF HEALTH, AGEING AND RETIREMENT IN EUROPE

STATEMENT CONCERNING THE USE OF SHARE DATA

To apply for access to the SHARE data, applicants must complete the following form.

Personal and professional details *(if handwritten: please use capital letters)*

Last name, first name/s: Sneidere Kristine

Email address: kristine.sneidere@rsu.lv

Position and job title: researcher, teaching assistant

Institution/organisation name: Riga Stradins University

Type of institution/organisation: *(please tick appropriate option)*

- ☒ University
- ☐ Scientific research institution
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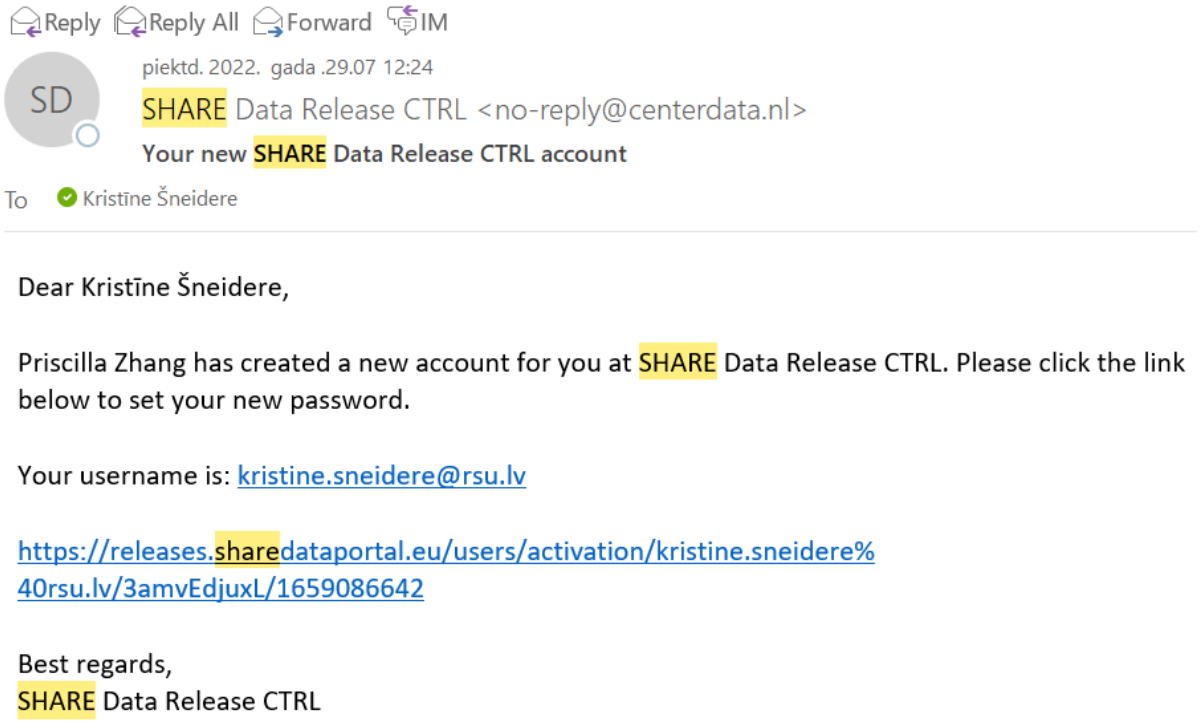

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Research approval from Rīga Stradiņš University Research Ethics Committee for the use of SHARE project data

Veidlapa Nr. E-9(3)
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7	Marina Siņkovska		Datu drošības un pārvaldības nodaļas vadītāja

Pieteikuma iesniedzējs/i: **Kristīne Šneidere, Doktorantūras nodaļa**

Pētījuma / pētnieciskā darba nosaukums: Kognitīvo rezervju saistība ar kognitīvo funkcionēšanu gados vecākiem pieaugušajiem bez demences diagnozes

Pētījumu ētikas komitejas sēdes datums: 24.11.2022.

Pētījuma protokols: Izskatot augstāk minētā pētījuma pieteikuma materiālus, t.sk., protokolu, ir redzams, ka pētījuma mērķi –izpētīt saistību starp kognitīvo rezervju sociobiheviorālajiem mainīgajiem un kognitīvajiem procesiem, ir paredzēts sasniegt, veicot jau iepriekš anketētu un intervētu dalībnieku (2019-2020) sniegto atbilžu datu apstrādi un analīzi. Rezultātus statistiski apstrādās un iegūtos rezultātus publiskos. Dalībnieku informēta brīvprātīga piekrišana piedalīties saņemta jau iepriekš, intervijas veikšanas laikā, iegūto personu datu apstrāde un aizsardzība, to pielietošana, glabāšana, anonimitāte un konfidencialitāte ir nodrošināta. Līdz ar to pieteikums atbilst pētījuma ētikas prasībām.

Komitejas lēmums: Piekrist pētījuma īstenošanai.

Komitejas priekšsēdētājs Jānis Vētra Tituls: Dr.habil. med., profesors.

ŠIS DOKUMENTS IR ELEKTRONISKI PARAKSTĪTS AR DROŠU ELEKTRONISKO PARAKSTU UN SATUR LAIKA ZĪMOGU

K. Kauķe
Tālrunis: 26691306

Permission to adapt and use Cognitive Reserve Index questionnaire

MA massimo.nucci@unipd.it
pr 31.08.2015. 9:15

Kam: Jeļena Harlamova;

Jūs atbildējāt 03.09.2015. 13:45.

Dear Jelena Harlamova,

please accept my apologies for my delay: I was on holiday. From our side there is no difficulties: you can translating CRIq and use it; feel free to contact me for anything you need. The only limitations are modify it substantially and sell it. Please pay close attention at CRIq administration instructions you find here:

http://cri.psy.unipd.it

Finally, if you send me the Latvian and Russian translations of CRIq I can turn it in Latex for the "classical" CRIq layout and share it in our web site.

Thanks for being interested in our work.

With best regards,

Massimo Nucci

Permission to use Woodcock-Johnson Test of Cognitive Abilities

LĪGUMS Nr. 2006/03 - 2/32

Līgums

Par Vudkoka-Džonsona starptautiskā izdevuma kognitīvo spēju testu latviešu valodā (turpmāk tekstā – VDž SI KOG)

Vudkoka-Munozas Fonds, turpmāk saukts "FONDS" no vienas puses un **JEĻENA HARLAMOVA** (personas kods 020674-10733), turpmāk saukts "TESTA LIETOTĀJS" no otras puses, noslēdza šādu līgumu.

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Vieta: Rīga, Latvija

Datums: 08.03.2006.

Paraksts: Ječena Harlamova _____

Vudkoka-Munozas Fonda Latvijas pārstāvju paraksti:

I. Paleja _____

I. Griškēviča _____

E. Strika _____

O. Vinogradova _____

Vudkoka-Munozas Fonda Latvijas pārstāvja organizācijas zīmogs

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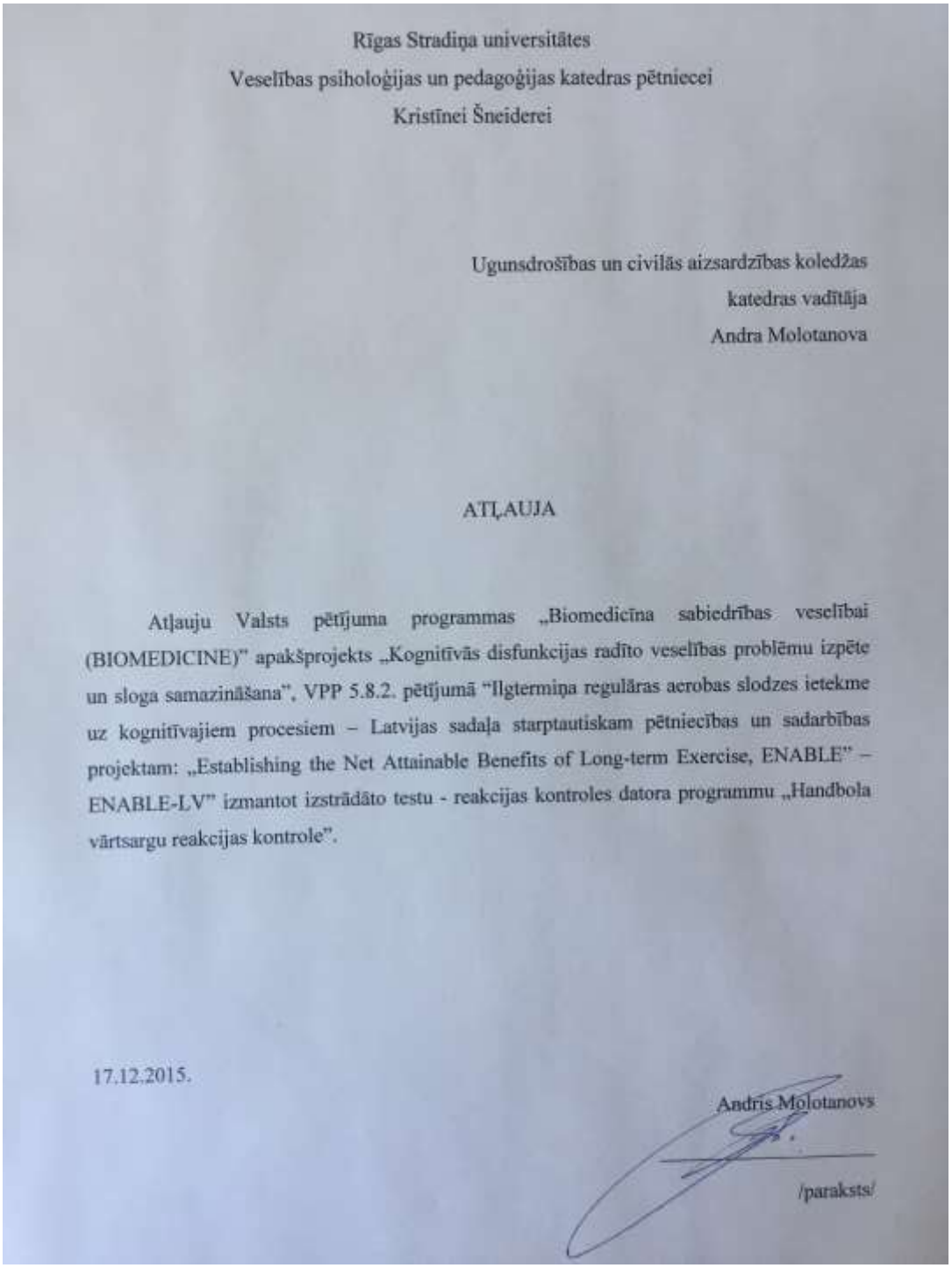
Permission to use Handball goalie reaction task test (in Latvian)



Rīgas Stradiņa universitātes
Veselības psiholoģijas un pedagoģijas katedras pētniecei
Kristīnei Šneiderei

Ugunsdrošības un civilās aizsardzības koledžas
katedras vadītāja
Andra Molotanova

ATĻAUJA

Atļauju Valsts pētījuma programmas „Biomedicīna sabiedrības veselībai (BIOMEDICINE)" apakšprojekts „Kognitīvās disfunkcijas radīto veselības problēmu izpēte un sloga samazināšana", VPP 5.8.2. pētījumā "Ilgtermiņa regulāras aerobas slodzes ietekme uz kognitīvajiem procesiem – Latvijas sadaļa starptautiskam pētniecības un sadarbības projektam: „Establishing the Net Attainable Benefits of Long-term Exercise, ENABLE" – ENABLE-LV" izmantot izstrādāto testu - reakcijas kontroles datora programmu „Handbola vārtsargu reakcijas kontrole".

17.12.2015.

Andris Molotanovs

/paraksts/

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Kathleen Gallant <kathleen.gallant@mocaclinic.ca>

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Occupational Therapist/ Psychometrician
On behalf of Dr Ziad Nasreddine, Neurologist, MoCA© Copyright Owner
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4896 Taschereau Blvd, suite 230
Greenfield Park, Quebec, Canada, J4V 2J2
kathleen.gallant@mocaclinic.ca
www.mocatest.org / www.alzheimer.TV

Ethics approval for study conduction (in Latvian)

Veidlapa Nr. E-9 (2)

RSU ĒTIKAS KOMITEJAS LĒMUMS NR. 51 / 25.02.2016.

Rīga, Dzirciema iela 16, LV-1007
Tel. 67061596

	Komitejas sastāvs	Kvalifikācija	Nodarbošanās
1.	Profesors Olafs Brūvers	Dr.theo.	teologs
2.	Profesore Vija Sīle	Dr.phil.	filozofs
3.	Asoc.prof. Santa Purviņa	Dr.med.	farmakologs
4.	Asoc.prof. Voldemārs Arnis	Dr.biol.	rehabilitologs
5.	Profesore Regīna Kleina	Dr.med.	patalogs
6.	Profesors Guntars Pupelis	Dr.med.	ķirurgs
7.	Asoc.prof. Viesturs Līguts	Dr.med.	toksikologs
8.	Docente Iveta Jankovska	Dr.med.	
9.	Docents Kristaps Circenis	Dr.med.	

Pieteikuma iesniedzējs: **Dr. med. Ainārs Stepens, VPP 5.8.2 vadītājs**
VPP 5.8.2

Pētījuma nosaukums: „ Ilgtermiņa regulāras aerobas slodzes ietekme uz kognitīvajiem procesiem"

Iesniegšanas datums: 25.02.2016.

Pētījuma protokols: Izskatot iesniegtos pētījuma dokumentus (protokolu) ir redzams, ka pētījums ir starptautiskas sadarbības projekts-pētījums kopīgi ar Saseksass (Sussex) universitāti Lielbritānijā. Pētījuma mērķis tiek sasniegts veicot, bez kāda apdraudējuma pacientu/dalībnieku veselībai, drošībai un dzīvībai, dažāda veida psiholoģisko testēšanu, dzīves paradumu dokumentēšanu un aerobo darbaspēju noteikšanu, iegūto datu apstrādi un analīzi, kā arī izsakot priekšlikumus. Personu (pacientu, dalībnieku) datu aizsardzība, brīvprātīga informēta piekrišana piedalīties pētījumā un konfidencialitāte tiek nodrošināta. Līdz ar to pieteikums atbilst biomedicīnas pētījuma ētikas prasībām.

Izskaidrošanas formulārs: ir

Piekrišana piedalīties pētījumā: ir

Komitejas lēmums: **piekrist** pētījumam

Komitejas priekšsēdētājs Olafs Brūvers Tituls: Dr. miss., prof.

Paraksts

RĪGAS STRADIŅA UNIVERSITĀTE ĒTIKAS KOMITEJA

Ētikas komitejas sēdes datums: 25.02.2016.

Informed consent (in Latvian)

Informācija par pētījumu

Cienījamo dalībniek!

Aicinām Jūs piedalīties Valsts nozīmes pētījumā par atmiņas un izziņas procesiem senioriem! Pirms piekrītat, Jums ir būtiski saprast iemeslus, kādēļ pētījums tiek veikts un kādus uzdevumus tas sevī ietver. Lūdzam Jūs rūpīgi un nesteidzīgi izlasīt sekojošo informāciju.

Droši jautājiet, ja kaut kas nav skaidrs vai arī vēlaties uzzināt ko vairāk. Nesteidzieties pieņemt lēmumu piedalīties. Pirms lēmuma pieņemšanas, Jūs drīkstat apspriest savu dalību pētījumā ar citiem.

1. Kāds ir pētījuma nosaukums?

Ilgtermiņa regulāras aerobas slodzes ietekme uz kognitīvajiem procesiem – Latvijas sadaļa starptautiskam pētniecības un sadarbības projektam: „*Establishing the Net Attainable Benefits for Long-term Exercise*, ENABLE"

2. Kāds ir pētījuma mērķis?

Rīgas Stradiņa universitātes pētnieki, sadarbībā ar kolēģiem Saseksas universitātē Lielbritānijā Valsts pētījumu programmas ietvaros pēta ilgtermiņa aerobas fiziskas slodzes ietekmi uz kognitīvajiem (izziņas un atmiņas) procesiem. Lai arī jau ir pierādīts, ka uzreiz pēc fiziskiem vingrojumiem uzlabojas atmiņas un izziņas procesi, šajā pētījumā mēs vēlamies izpētīt, vai regulāra aerobā slodze uzlabo kognitīvās funkcijas arī ilgtermiņā. Lai to noskaidrotu, mēs salīdzinām kognitīvās funkcijas dažādās senioru grupās. Tāpēc mēs aicinām pētījumā piedalīties gan profesionālus sportistus-seniorus, gan seniorus, kuri arī ir sociāli aktīvi, bet kuriem ir salīdzinoši neliela aerobā fiziskā slodze.

3. Kādēļ izvēlējāties mani?

Mēs Jūs izvēlējāmies, jo izrādījāt interesi par dalību mūsu pētījumā un atbilstat izvirzītajām prasībām.

4. Vai man noteikti ir jāpiedalās?

Nē, tā ir Jūsu brīva izvēle. Ja nolemsiet piedalīties, šo informatīvo materiālu varēsiet saglabāt un mēs lūgsim Jūs parakstīt piekrišanas veidlapu. Jūs jebkurā brīdī varat atteikties no dalības pētījumā, nepaskaidrojot iemeslus.

5. Kas ar mani notiks, ja piedalīšos?

Jums tiks veikta detalizēta psiholoģiskā testēšana, fizisko aktivitāšu un diētas paradumu dokumentēšana, tiks veikta ķermeņa kompozīcijas (muskuļu un tauku attiecība) analīze un noteiktas aerobās darbspējas, kā arī veikta galvas smadzeņu struktūras izmeklēšana ar magnētiskās rezonanses metodi.

Psiholoģiskā testēšana un aerobo darbspēju noteikšana norisināsies Rīgas Stradiņa universitātes (RSU) Medicīnas izglītības un tehnoloģiju centrā (MITC), kurš atrodas Rīgā, Anniņmuižas bulvārī 26a, savukārt galvas smadzeņu magnētiskās rezonanses (MR) izmeklējums tiks veikts P.Stradiņa Klīniskās universitātes slimnīcā Rīgā, Pilsoņu ielā 13. Transportu starp MITC un slimnīcu nodrošinās pētījuma organizatori.

Izpēte noritēs divu dienu laikā un par konkrētiem datumiem Jūs vienosieties ar pētnieku. Pirmajā izpētes dienā tiks veikta kognitīvo procesu izpēte, veloergometrijas un MR izmeklējumi. Otrajā izpētes dienā tiks ievākta informācija par dzīvesveida paradumiem un noteiktas aerobās darbspējas.

Ņemiet vērā, ka tiks ievērota strikta konfidencialitāte un neviens no izpētē iesaistītajiem cilvēkiem publiski neizpaudīs informāciju par Jūsu rezultātiem, bet, analizējot un publicējot rezultātus, Jūsu datus apzīmēs tikai ar identifikācijas kodu. Jūsu sniegtās informācijas un pētījuma datu apstrāde un uzglabāšana notiks saskaņā ar "Fizisko personu datu aizsardzības likumu".

6. Kādām prasībām man ir jāatbilst, lai varētu piedalīties?

Lai piedalītos pētījumā, jums ir jāatbilst sekojošajiem kritērijiem:

- esat vecāks par 65 gadiem;
- Jūsu dzimtā valoda – latviešu;
- Jūs ikdienā 1) nodarbojaties ar aerobās slodzes sporta veidiem (piem., skriešanu, riteņbraukšanu, peldēšanu) un piedalāties sacensībās; 2) brīvajā laikā izvēlaties nodarbības ar aerobas slodzes elementiem (piem., dejošanu, skriešanu, peldēšanu, braukšanu ar velosipēdu); 3) esat sociāli aktīvs, bet nenodarbojaties ar sportu;
- Jūs neslimojat ar kādu no sekojošajām slimībām:
  - nekompensēta arteriāla hipertensija [>140/>80 mmHg], stenokardija, sirds mazspēja;
  - cukura diabēts, aptaukošanās (ķermeņa masas indekss (ĶMI) pārsniedz 30);
  - plaušu un elpceļu slimības, kuru ārstēšanai nepieciešama inhalatoru lietošana;
  - kaulu un locītavu slimības, kuru ārstēšanai nepieciešama regulāra pretsāpju medikamentu lietošana;
  - noritoša onkoloģiska slimība;
  - psihisku slimību (depresija, demence, noritoša šizofrēnija, kuras ārstēšanai nepieciešama medikamentoza terapija);
  - citu hronisku slimību, kura ierobežo fizisko aktivitāti.
- Jums nav metālisku implantu.

7. Kas man būs jādara, ja izlemšu piedalīties?

Jūs veiksiet ikdienišķus uzdevumus, kādi bieži tiek lietoti, lai izmērītu prāta asumu, subjektīvo pieredzi un izmaiņas fizioloģiskajos procesos (piemēram, asinsspiedienu) sesiju laikā.

Ir būtiski, lai pirms katras izpētes Jūs:

- nelietotu kofeīnu saturošus dzērienus vismaz divas stundas pirms izpētes sākuma;
- nelietotu alkoholu vai citas psihoaktīvās vielas pētījuma dienā pirms nākšanas uz izpēti.

Lūdzu, ņemiet vērā, ka mēs neskatīsimies uz Jūsu individuālo sniegumu, bet gan visas brīvprātīgo dalībnieku grupas sniegumu. Visi dati būt anonīmi.

8. Kādi ir iespējamie riski un pētījuma trūkumi?

Dalība pētījumā nav saistīta ar būtiskiem riskiem Jūsu veselībai. Lai pārliecinātos par Jūsu piemērotību aerobo darbspēju noteikšanas testiem, drošības nolūkos pirms to veikšanas Jums veiks veloergometrijas testu sertificēta kardiologa uzraudzībā P.Stradiņa Klīniskās universitātes slimnīcā.

9. Kādi ir potenciālie ieguvumi?

Pētījums neparedz nekādu tiešu materiālo atlīdzību, taču Jūsu dalība pētījumā palīdzēs saprast, kā fiziski vingrojumi ietekmē prāta asumu un fizioloģiskos mērījumus cilvēkiem novecojot. Šie dati palīdzēs sekmīgi īstenot veselīgas novecošanās (*healthy aging*) stratēģijas.

Papildus, veicot magnētiskās rezonanses un veloergometrijas izmeklējumus, Jums bez maksas būs iespēja precizēt galvas smadzeņu un sirds funkcionālās veselības stāvokli.

10. Ko darīt, ja rodas problēmas?

Jebkuru sūdzību par Jūsu pieredzi pētījuma laikā vai pētījuma radītām sekām, vispirms būtu jāadresē pētniekiem, kontaktinformāciju skatīt zemāk. Ja vēlēsieties, Jums tiks sniegta informācija par to, kā šo jautājumu risināt tālāk.

11. Vai mana dalība pētījumā būs konfidenciāla?

Jā. Visa informācija par Jūsu dalību pētījumā būs anonīma un konfidenciāla. Mēs ievērosim striktu konfidencialitāti ar visiem iegūtajiem datiem.

12. Kādas personīgās mantas būs nepieciešamas izpētes laikā?

Lai nerastos grūtības izpildīt psiholoģiskos testus, lūdzam Jūs paņemt līdzi brilles. Lai arī aerobo darbspēju noteikšana nav saistīta ar pārmērīgu piepūli, iesakām līdzi paņemt arī ērtu apģērbu.

13. Pētnieku komandas kontaktinformācija

Atbildīgie par psiholoģisko testēšanu: Kristīne Šneidere, tel. 29911488, e-pasts: kristine.sneidere@gmail.com, Jeļena Harlamova, tel. 29129215, e-pasts: jelena.harlamova@rsu.lv

Atbildīgais par fizisko darbspēju noteikšanu: Voldemārs Arnis, tel. 29517305, e-pasts: voldemars.arnis@rsu.lv .

Atbildīgais pētnieks Latvijā: Ainārs Stepens, tel. 29227895, e-pasts: ainars.stepens@rsu.lv

Piekrišanas dalībai pētījumā forma

Apstiprinu, ka esmu izlasījis/-usi un sapratis/-usi informatīvo materiālu, kas datēts ar 2015. gada 23. septembri (1. versija) par pētījumu "Ilgtermiņa regulāras aerobas slodzes ietekme uz kognitīvajiem procesiem – Latvijas sadaļa starptautiskam pētniecības un sadarbības projektam: „*Establishing the Net Attainable Benefits for Long-term Exercise*, ENABLE"".

Man ir bijusi iespēja pārdomāt informāciju par pētījumu, uzdot man interesējošos jautājumus un esmu saņēmis/-usi uz tiem apmierinošas atbildes.

Es saprotu, ka mana dalība ir brīvprātīga un esmu tiesīgs/-a jebkurā brīdī izstāties, nesniedzot paskaidrojumus. Es saprotu, ka tad, ja izstājos no pētījuma, par mani iegūtie dati netiks izmantoti pētījumā.

Es saprotu, ka pētījuma laikā iegūtie dati tiks ievākti anonīmi, taču tos apskatīt varēs visi pētnieku komandas dalībnieki šobrīd un arī vēlāk nākotnē.

Parakstot šo piekrišanas formu, es piekrītu piedalīties iepriekšminētajā pētījumā.

_____	_____	_____
Dalībnieka vārds, uzvārds	Datums	Paraksts
_____	_____	_____
Pētnieka vārds, uzvārds	Datums	Paraksts

Forma aizpildīta divos eksemplāros.

Annex 9

Descriptive statistics of brain regions

Table 9.1

Descriptive statistics of brain regions

Measure	Mean	Median	D-value
eTIV	1415518.64 (±136466.87)	1397315	0.101
lh cortex	204038.68 (±15992.98)	203377	0.081
rh cortex	204899.17 (±16132.422)	204586	0.062
lh entorhinal	1670.44 (±335.07)	1679	0.123*
rh entorhinal	1661.03 (±438.74)	1607	0.111
lh fusiform	6999.56 (±940.67)	6965	0.072
rh fusiform	6699.75 (±1059.10)	6608	0.087
lh parahippocampal	1931.83 (±344.03)	1895	0.077
rh parahippocampal	1802.68 (±325.36)	1783	0.148**
lh superior	14322.45 (±1897.762)	14453	0.088
rh superior	13816.17 (±1575.08)	13783	0.065
lh middle	11124.32 (±1504.01)	10814	0.095
rh middle	11382.37 (±1368.04)	11269	0.127*
lh inferior	10599.56 (±1443.14)	10605	0.085
rh inferior	10401.8 (±1311.45)	10501	0.070
lh transverse	962.80 (±151.13)	946	0.081
rh transverse	743.71 (±121.62)	722	0.106
lh superior frontal	21649.85 (±2629.53)	21141	0.109
rh superior frontal	23848.46 (±23848.46)	23887	0.073
lh rostral middle	10292.69 (±2094.51)	9764	0.163***
rh rostral middle	10026.68 (±1695.57)	9850	0.091
lh caudal middle	5410.25 (±838.96)	5311	0.086
rh caudal middle	5198.25 (±1133.96)	5034	0.129*
lh pars opercularis	3782.17 (±834.79)	3639	0.100
rh pars opercularis	3853.71 (±655.21)	3724	0.115*
lh pars triangularis	3814.22 (±828.85)	3721	0.084
rh pars triangularis	3537 (±666.79)	3447	0.140**
lh pars orbitalis	1895.90 (±236.26)	1895	0.088
rh pars orbitalis	1905.81 (±258.29)	1897	0.081
lh medial orbitofrontal	4312.86 (±527.50)	4297	0.086
rh medial orbitofrontal	4118.98 (±523.81)	4104	0.075
lh lateral orbitofrontal	7601.42 (±639.62)	7581	0.089
rh lateral orbitofrontal	7502.97 (±621.35)	7573	0.102
lh paracentral lobule	3780.59 (±526.88)	3713	0.064
rh paracentral lobule	3593.85 (±812.82)	3573	0.076

Table 9.1 continued

Measure	Mean	Median	D-value
lh precentral gyrus	11531.36 (±1678.94)	11699	0.097
rh precentral gyrus	11297.73 (±1704.49)	11460	0.110
lh postcentral	9471.08 (±1556.50)	9663	0.064
rh postcentral	9004.69 (±1251.08)	9132	0.092
lh supramarginal	8158.88 (±1527.84)	8306	0.076
rh supramarginal	7785.71 (±1129.83)	7853	0.087
lh superior parietal	8522.78 (±1392.44)	8547	0.098
rh superior parietal	9001.80 (±1205.99)	9031	0.095
lh inferior parietal	9934.24 (±1386.83)	9655	0.141**
rh inferior parietal	11871.32 (±1628.87)	11713	0.120*
lh precuneus	7665.36 (±962.60)	7806	0.089
rh precuneus	8391.90 (±958.87)	8233	0.074
lh lingual	5964.88 (±757.63)	5911	0.068
rh lingual	6024.58 (±814.45)	5979	0.079
lh pericalcarine	1812.44 (±360.02)	1745	0.112
rh pericalcarine	2040.27 (±364.56)	2011	0.100
lh cuneus	3546.92 (±660.68)	3558	0.055
rh cuneus	3427.32 (±553.82)	3307	0.106
lh lateral occipital	10692.24 (±1325.94)	10444	0.083
rh lateral occipital	10915.37 (±1557.76)	10913	0.091
lh caudal anterior	2476.46 (±476.85)	2390	0.080
rh caudal anterior	1897.90 (±534.76)	1799	0.106
lh rostral anterior	3066.31 (±542.79)	3020	0.076
rh rostral anterior	2202.37 (±465.44)	2152	0.073
lh posterior cingulate	2809.95 (±431.85)	2813	0.102
rh posterior cingulate	2676.61 (±455.79)	2625	0.113
lh isthmus	2224.22 (±317.68)	2229	0.070
rh isthmus	2058.15 (±267.64)	2045	0.093
lh insula	5488.98 (±612.21)	5550	0.084
rh insula	5608.20 (±652.74)	5685	0.093
lh thalamus	6509.32 (±732.45)	6385.7	0.113*
rh thalamus	6492.63 (±764.21)	6488.25	0.05
Thalamus	13001.95 (±1465.72)	12897.85	0.0.08
lh hippocampus	3847.79 (±472.48)	3812.35	0.086
rh hippocampus	3911.02 (±410.93)	3890.35	0.075
Hippocampus	7758.80 (±856.58)	7674.05	0.083

Annex 10

Spearman's rank correlation tables

Table 10.1

Spearman's rank correlation between cognitive reserve and temporal lobe (medial aspect) regions

Variable	1	2	3	4	5	6	7	8	9	10
1. CRI Education	–									
2. CRI Occupation	0.377**	–								
3. CRI Leisure	0.281*	0.258	–							
4. CRI Total	0.670**	0.817**	0.627**	–						
5. lh entorhinal	−0.032	0.127	−0.163	−0.032	–					
6. rh entorhinal	0.203	**0.336***	0.011	0.230	0.672**	–				
7. lh parahippocampal	0.079	0.071	−0.055	0.038	0.542**	0.410**	–			
8. rh parahippocampal	0.094	0.178	−0.007	0.105	0.474**	0.534**	0.568**	–		
9. lh fusiform	−0.031	0.114	−0.178	−0.033	0.328**	0.541**	0.265*	0.338**	–	
10.rh fusiform	−0.039	0.208	−0.105	0.043	0.343**	0.536**	0.333*	0.278*	0.587**	–

Note. $N = 58$, *$p \leq 0.05$, **$p < 0.01$

Table 10.2

Spearman's rank correlation between cognitive reserve and temporal lobe (lateral aspect) regions

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. CRI Education	–											
2. CRI Occupation	0.377**	–										
3. CRI Leisure	0.281*	0.258	–									
4. CRI Total	0.670**	0.817**	0.627**	–								
5. lh superior	0.066	**0.345****	−0.162	0.131	–							
6. rh superior	0.115	**0.316***	−0.039	0.187	0.826**	–						
7. lh middle	0.198	**0.384****	0.033	**0.259***	0.529**	0.543**	–					
8. rh middle	0.197	0.229	−0.026	0.147	0.544**	0.580**	0.684**	–				
9. lh inferior	0.207	**0.417****	0.012	0.258	0.429**	0.544**	0.578**	0.523**	–			
10. rh inferior	0.171	**0.450****	−0.016	0.255	0.525**	0.565**	0.646**	0.452**	0.607**	–		
11. lh transverse	−0.224	−0.050	−0.078	−0.073	0.277*	0.266*	0.138	−0.049	−0.035	0.237	–	
12. rh transverse	−0.011	0.285*	0.057	0.193	0.610**	0.623**	0.334*	0.396**	0.298*	0.345**	0.409**	–

Note. $N = 58$, *$p \leq 0.05$, **$p < 0.01$

Table 10.3

Spearman's rank correlation between cognitive reserve and frontal lobe regions

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1. CRI Education	–																							
2. CRI Occupation	.377**	–																						
3. CRI Leisure	.281*	.258	–																					
4. CRI Total	.670**	.817**	.627**	–																				
5. lh superior frontal	.066	.162	−0.204	.016	–																			
6. rh superior frontal	.100	.257	−0.122	.139	.752	–																		
7. lh rostral middle	−0.048	**.306***	−0.101	.084	.714	.622	–																	
8. rh rostral middle	.024	.164	−0.207	.020	.568	.584	.689	–																
9. lh caudal middle	.041	−0.060	−0.019	−0.046	.246	.243	.076	.148	–															
10. rh caudal middle	.221	.142	−0.044	.158	.310	.292	.260	.257	.405	–														
11. lh pars opercularis	−0.051	.200	−0.062	.045	.494	.446	.634	.434	.243	.327	–													
12. rh pars opercularis	.056	.111	−0.171	.009	.316	.390	.319	.486	.110	.276	.503	–												
13. lh pars triangularis	−0.130	.031	−0.126	−0.066	.491	.388	.558	.341	−0.160	.212	.751	.336	–											
14. rh pars triangularis	.034	.058	−0.098	.008	.383	.316	.333	.380	−0.025	.002	.485	.581	.485	–										
15. lh pars orbitalis	.063	**.296***	−0.032	.188	.544	.445	.491	.321	−0.030	.149	.351	.235	.490	.453	–									
16. rh pars orbitalis	.111	**.323***	**.339****	**.411****	.188	.268	.143	.241	−0.038	−0.004	.023	.106	.090	.096	.452	–								

Annex 10 continued

Table 10.3 continued

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
17. lh medial orbitofrontal	.140	.106	−0.028	.045	.657	.537	.605	.404	.157	.166	.484	.349	.402	.354	.479	.093	–							
18. rh medial orbitofrontal	.242	**.285***	−0.005	.243	.485	.458	.438	.395	.060	.311	.229	.174	.292	.206	.446	.466	.441	–						
19. lh lateral orbitofrontal	.216	**.327***	−0.036	.224	.678	.592	.564	.353	.097	.337	.380	.303	.381	.353	.631	.318	.587	.619	–					
20. rh lateral orbitofrontal	.186	**.274***	.101	.241	.644	.494	.607	.360	.164	.291	.456	.130	.437	.232	.528	.356	.581	.664	.679	–				
21. lh paracentral lobule	−0.141	.160	−0.139	−0.030	.610	.425	.550	.335	.272	.363	.334	.174	.297	.155	.454	.136	.586	.532	.582	.473	–			
22. rh paracentral lobule	−**0.293***	−0.025	−0.171	−0.195	.465	.367	.388	.251	.310	.125	.227	.100	.107	.117	.368	.132	.529	.394	.414	.401	.571	–		
23. lh precentral gyrus	.045	−0.093	.047	.001	.096	.200	−0.121	.077	.377	.253	−0.159	.005	−0.186	−0.013	.142	.337	.176	.305	.150	.031	.427	.337	–	
24. rh precentral gyrus	.024	−0.098	−0.068	−0.096	.450	.341	.246	.065	.507	.473	.224	.014	.177	.056	.256	.030	.438	.391	.373	.367	.600	.535	.559	–

Note. $N = 58$, $^{*}p \leq 0.05$, $^{**}p < 0.01$

Table 10.4

Spearman's rank correlation between cognitive reserve and parietal lobe regions

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. CRI Education	–													
2. CRI Occupation	0.377**	–												
3. CRI Leisure	0.281*	0.258	–											
4. CRI Total	0.670**	0.817**	0.627**	–										
5. lh postcentral	0.096	0.095	−0.003	0.101	–									
6. rh postcentral	0.041	−0.008	0.013	0.022	0.689	–	–							
7. lh supramarginal	0.076	−0.007	0.159	0.066	0.732	0.498	–							
8. rh supramarginal	0.117	0.250	0.085	0.179	0.734	0.683	0.613	–						
9. lh superior parietal	0.105	**0.262***	0.120	0.229	0.390	0.250	0.442	0.291	–					
10. rh superior parietal	0.090	0.114	0.068	0.066	0.380	0.413	0.384	0.621	0.430	–				
11. lh inferior parietal	0.233	**0.471****	0.172	**0.387****	0.274	0.329	0.174	0.397	0.354	0.221	–			
12. rh inferior parietal	0.051	0.195	−0.054	0.071	0.274	0.343	0.150	0.318	0.074	0.340	0.502	–		
13. lh precuneus	0.055	0.105	0.003	0.071	0.489	0.432	0.454	0.305	0.653	0.198	0.234	0.137	–	
14. rh precuneus	0.096	0.033	−0.057	−0.010	0.600	0.615	0.506	0.511	0.451	0.482	0.234	0.444	0.660	–

Note. $N = 58$, $^{*}p \leq 0.05$, $^{**}p < 0.01$

Table 10.5

Spearman's rank correlation between cognitive reserve and occipital lobe regions

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1. CRI Education	–											
2. CRI Occupation	0.377**	–										
3. CRI Leisure	0.281*	0.258	–									
4. CRI Total	0.670**	0.817**	0.627**	–								
5. lh lingual	0.066	0.013	−0.176	−0.015	–							
6. rh lingual	0.163	0.094	0.050	0.137	0.523	–						
7. lh pericalcarine	0.014	−0.151	−0.071	−0.045	0.507	0.565	–					
8. rh pericalcarine	0.218	0.202	0.054	**0.285***	0.344	0.681	0.687	–				
9. lh cuneus	−0.043	−0.162	−0.211	−0.157	0.368	0.393	0.678	0.502	–			
10. rh cuneus	−0.008	−0.037	−0.219	−0.046	0.491	0.550	0.658	0.668	0.627	–		
11. lh lateral occipital	0.050	0.137	−0.114	0.025	0.255	0.240	0.139	0.169	0.202	0.312	–	
12. rh lateral occipital	−0.118	0.028	−0.257	−0.116	0.353	0.106	0.166	0.121	0.391	0.376	0.690	–

Note. $N = 58$, $^{*}p \leq 0.05$, $^{**}p < 0.01$

Table 10.6

Spearman's rank correlation between cognitive reserve and cingulate regions

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. CRI Education	–													
2. CRI Occupation	0.377**	–												
3. CRI Leisure	0.281*	0.258	–											
4. CRI Total	0.670**	0.817**	0.627**	–										
5. lh caudal anterior	0.114	**0.266***	0.034	0.211	–									
6. rh caudal anterior	−0.036	0.218	−0.099	0.081	0.621	–								
7. lh rostral anterior	0.203	**0.320***	0.084	0.244	0.628	0.256	–							
8. rh rostral anterior	**0.272***	**0.301***	0.032	**0.274***	0.495	0.623	0.388	–						
9. lh posterior cingulate	**0.266***	0.155	0.074	0.229	0.675	0.434	0.503	0.477	–					
10.rh posterior cingulate	−0.012	0.141	0.002	0.096	0.621	0.563	0.381	0.473	0.701	–				
11.lh isthmus	0.251	0.062	0.180	0.237	0.448	0.148	0.387	0.351	0.565	0.469	–			
12.rh isthmus	0.195	0.116	−0.145	0.115	0.483	0.263	0.493	0.336	0.494	0.450	0.607	–		
13.insula	0.239	**0.261***	0.137	**0.294***	0.481	0.254	0.595	0.512	0.520	0.476	0.425	0.415	–	
14.insula	0.238	0.247	0.188	**0.309***	0.437	0.157	0.572	0.438	0.486	0.476	0.441	0.477	0.906	–

Note. $N = 58$, $^{*}p \leq 0.05$, $^{**}p < 0.01$