doi:10.25143/prom-rsu_2023-07_dts

RĪGA STRADIŅŠ UNIVERSITY

Kristīne Šneidere

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

Summary of the 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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Kristīne Šneidere

ORCID 0000-0002-4392-9392

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The Doctoral Thesis was developed at Rīga Stradiņš University, Latvia

Supervisors of the Doctoral Thesis:

PhD, Associate Professor **Ainārs Stepens**,
Rīga Stradiņš University, Latvia

PhD, Associate Professor **Sara Mondini**,
University of Padua, Italy

Official Reviewers:

Dr. psych., Assistant Professor **Ingūna Griškēviča**,
Rīga Stradiņš University, Latvia

PhD, Professor **Jennifer Rusted**,
University of Sussex, United Kingdom

PhD, Professor **Jurģis Šķilters**,
University of Latvia

Defence of the Doctoral Thesis will take place at the public session of the Promotion Council of Psychology on 24 May 2023 at 9.00 in Hippocrates Lecture Theatre, 16 Dzirciema Street, Rīga Stradiņš University, and via Zoom online platform

The Doctoral Thesis is available in RSU Library and on RSU website:
https://www.rsu.lv/en/dissertations

European Social Fund and Latvian state budget within the project No. 8.2.2.0/20/I/004 “Support for involving doctoral students in scientific research and studies” at Rīga Stradiņš University

The Role of Motor Reserve in Cognitive Dysfunction in Older Adults (MORE-COG)”, 6-ZD-22/27/2022

Secretary of the Promotion Council:

Dr. psych., Lecturer **Ilona Krone**

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Abbreviations used in the Thesis

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

Introduction

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). Considering the age-related health risk factors and the rapid response needed to mitigate the potential burden on the health and well-being of the society, the years 2021–2030 have been announced to be the Decade of Healthy Ageing (WHO, 2020). Age is still considered to be one of the main non-modifiable risk factor for developing a neurodegenerative disease (Hou et al., 2019), thus an increase in the age of the population would correlate with an increase in patients with dementia or Alzheimer’s disease. While there is still a lack in pharmacological methods in treating Alzheimer’s disease, studies from the past two decades have marked the role of lifestyle in delaying or preventing the onset of dementia, specifically highlighting the role of cognitive reserve (Livingston et al., 2020).

The notion of the role of intellectual and social activities in healthy ageing is not new, and already in late 1970s first studies were conducted, identifying the role of formal education in lessening the cortical atrophy and maintaining optimal cognitive functioning (Kaszniak et al., 1979). The notion gained more popularity with the study by Robert Katzman (Katzman et al., 1988), Paul Satz (Satz et al., 1993) and Yaakov Stern (Stern et al., 1999), who identified the role of education and occupation in maintaining cognitive and brain health. These factors were later named cognitive reserve, namely, the capacity of the brain to maintain cognitive functioning despite age related changes, traumatic brain injury or a disease. This ability is developed through the lifestyle – education, work and leisure activities (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; Stern et al., 2020).

There are different frameworks clarifying the mechanisms of cognitive decline due to ageing; however, in this study only compensatory-oriented theories were included, namely, the Cognitive Reserve Hypothesis (Stern et al., 1999) and the Scaffolding Theory of Aging and Cognition-Revised (Reuter-Lorenz & Park, 2014) as they explain the individual differences in cognitive and brain functioning and are based on lifelong experiences as modifying factors in ageing. This Thesis is further based on main arguments found in both frameworks, though more attention has been paid to the Cognitive Reserve Hypothesis, as it encompasses mechanisms of 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. 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).

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.

Hypotheses 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 Hypothesis 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 socio-demographic 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 socio-behavioural proxies of the reserve. A socio-behavioural 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 Compensatory models of healthy cognitive ageing

There is a wide variety of healthy cognitive ageing models that aim to clarify the changes in cognitive functioning due to ageing. The Sensory System Decline approach proposes three explanatory models – (1) Information Degradation Model that claims that cognitive performance is impaired due degradation or weakening of perceptual signals, (2) the Common-Cause Hypothesis that suggests that the decline is present due to a concurrent peripheral and central decline, and (3) the Sensory Deprivation Hypothesis that proposes that the cause of cognitive decline is experienced due to lack of sufficient sensory stimulation (Ebaid & Crewther, 2020). Even though these models aim to clarify the inevitable changes in cognitive functioning, they do not fully explain the individual differences in ageing. This factor, in turn, can be found in so called compensatory theories, such as, the Cognitive Reserve Hypothesis and the Scaffolding Theory of Aging and Cognition. Both theories are considered in more detail in the following subchapters.

1.1 The Cognitive Reserve Hypothesis

Cognitive reserve refers to the individual differences in adapting or compensating cognitive functions when faced with a brain pathology (e.g. stroke or dementia) or a challenging task that would require additional cognitive resources (Stern et al., 2020). The history of the reserve research can be found at the end of the 20th century when in 1988 Robert Katzman, a neurologist and researcher at the University of California, USA, published a study, suggesting that there is a discrepancy between cognitive performance and brain clinical markers. Namely, when comparing the brains of patients with and without diagnosis of Alzheimer's Disease, it was concluded that in some cognitively healthy individuals the brain pathology was similar to those without pathology (Katzman et al., 1988).

The studies investigating the reserve concept were continued, though mostly in clinical research (e.g. see Satz et al., 1993). The concept of cognitive reserve as it is known now was first proposed by Yaakov Stern, professor at University of California, USA, suggesting that patients with higher cognitive reserve would also present clinical symptoms of dementia much later in comparison with patients with lower cognitive reserve, even if the onset of pathology has started simultaneously. Nevertheless, when the effect of the cognitive reserve is exhausted, the decline in cognitive functioning would be more rapid (see. Figure 1.1).

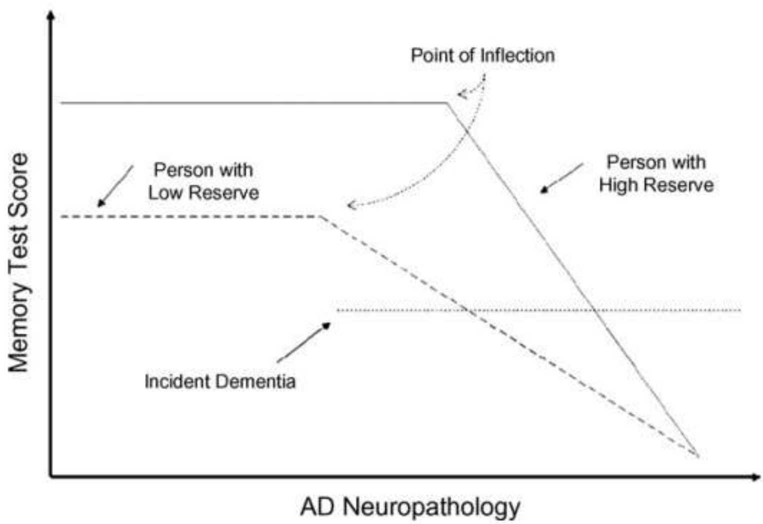

Figure 1.1 **Initial framework of cognitive reserve**

Stern further developed the concept of cognitive reserve, considering it as a mediator between the brain with or without pathology and cognitive functioning. The framework proposes that cognitive reserve is “built” based on different lifestyle factors combination of which is either moderating the impact of changes in cognitive functioning due to pathology or predicts the severity of the brain pathology and / or cognitive functioning (see Figure 1.2).

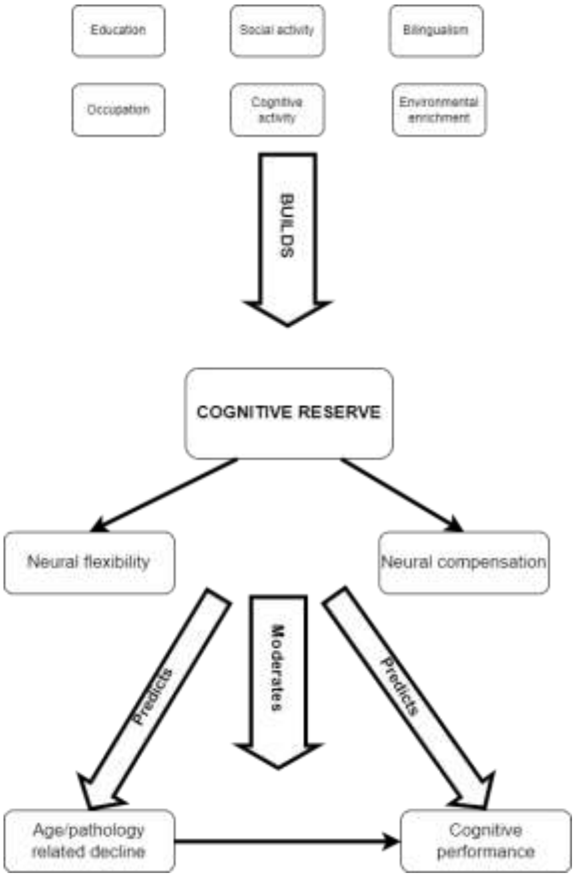

Figure 1.2 **Moderation / prediction model of cognitive reserve**

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

For a long time, **education** was considered to be one of the most significant factors in cognitive reserve. Previous cross-sectional studies have shown that lower levels of formal education could be associated with higher risk of Alzheimer's Disease (Norton et al., 2014; Satz et al., 1993); nevertheless, longitudinal research have yielded a different hypothesis, proposing that education as a socio-behavioural proxy of cognitive reserve functions only until the onset of the clinical symptoms and cannot predict the changes in brain or cognitive functioning in the long run (Nyberg et al., 2021; Wilson et al., 2019).

Occupation is another socio-behavioural proxy of cognitive reserve and an increasing amount of studies highlight the role of the complexity and level of responsibility at work in maintaining optimal cognitive functioning later in life (Boots et al., 2015; Mondini et al., 2022; Spreng et al., 2011). Engagement in **cognitive and social leisure activities** (Wajman et al., 2018), **bilingualism** (Macbeth et al., 2021), as well as different **environmental factors** (Cassarino & Setti, 2015) are also often highlighted as proxies of cognitive reserve; nevertheless, the evidence in this regard is sparse and ambiguous.

1.2 The Scaffolding Theory of Aging and Cognition (STAC)

The Scaffolding Theory of Aging and Cognition (STAC) was first published in 2009, proposing that brain and consequentially cognitive functions change due to two factors – neural challenges (structural changes in the brain) and functional deterioration (dedifferentiation in visual and motor areas, reduction in the activity in temporal lobes etc.). Even though these are inevitable changes in ageing, the rate of change together with its effect on the brain and cognitive function highly depend on other factors, namely, scaffolding. The scaffolding would include socio-behavioural factors, such as education and cognitive training, but it would also involve neural factors, e.g. neurogenesis (Park & Reuter-Lorenz, 2009). Park & Reuter-Lorenz further developed the theory and in 2014 a revised model (STAC-r) was published, that integrated more complex relationship, highlighting not only the moderating effect of the scaffolding, but also the reserve factors that could either enrich the neural resources, or deplete them (see Figure 1.3).

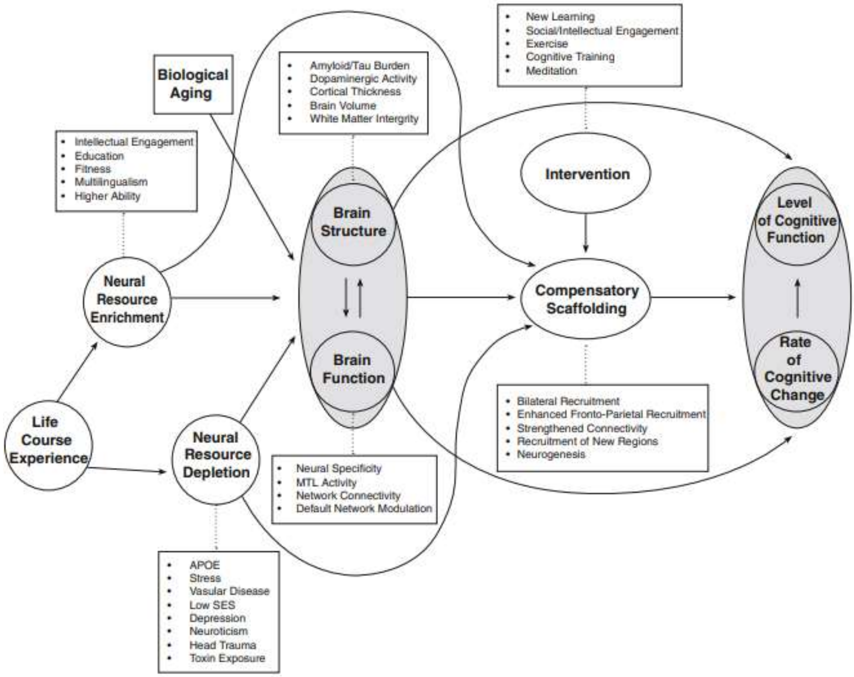

Figure 1.3 **The Scaffolding Theory of Aging and Cognition – Revised**

(Reuter-Lorenz & Park, 2014)

The revised model implemented the role of previous experiences in the scaffolding, proposing that biological ageing affects the structural and functional changes in the brain. These changes can be represented as Tau or Amyloid burden, depletion of brain volume and cortical thickness, lower activity in the medial temporal lobe etc. The severity of the implementation of these factors could depend from different factors accumulated during the lifetime. Structural and functional changes in the brain could be lessened through education, multilingualism, fitness, while they would be facilitated due to depression, low socio-economic status, traumatic brain injury, APOE-4 gene etc. These factors would further impact the building of the scaffolding. Additional activities implemented during the ageing or "interventions" would further strengthen the "scaffolding" (e.g. via cognitive training, physical activity, learning new things) and consequentially impact cognitive functioning (Reuter-Lorenz & Park, 2014).

1.3 Integrative framework of healthy cognitive ageing

While the Cognitive Reserve Hypothesis proposes that higher cognitive reserve could protect against or at least delay the changes associated with ageing, as well as help to maintain optimal cognitive functioning even after the onset of the symptoms, the STAC-r suggests that there are modifiable and non-modifiable factors that would help to develop strategies in overcoming the age-related challenges. These challenges are present even in normal ageing, where gradual structural and functional brain changes can be found – volume loss, cortical thinning, white matter degradation, loss of gyrification, as well as ventricular enlargement (Blinkouskaya et al., 2021).

As discussed before, several models propose that structural and functional brain changes would also predict changes in cognitive functioning. This can be especially seen in executive functions (Boucard et al., 2012), associative memory (Reuter-Lorenz & Park, 2010), processing speed (Salthouse, 1996) and others. Although aforementioned theories have mostly focussed on cognitive reserve and scaffolding factors as mediators, direct predictors of both – brain and cognitive functioning should be investigated to better understand the mechanisms of lifestyle associated with healthy aging. To achieve this goal, a new theoretical framework was proposed, encompassing cognitive reserve as both – experience accumulated during the lifetime and current experience (see Figure 1.4).

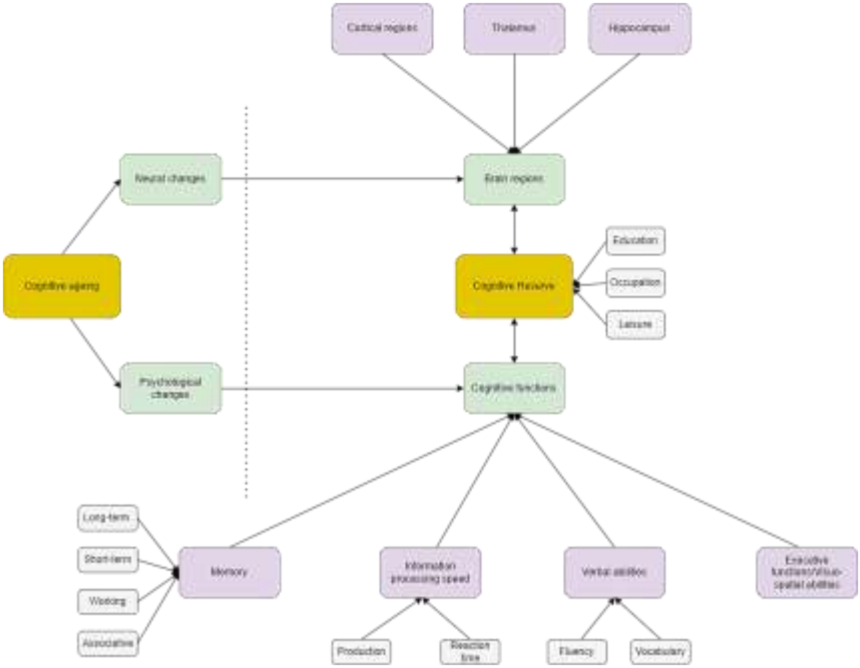

Figure 1.4 **Proposed theoretical framework of the study**

While association between individual factors has been considered before, the results are not definite, often due to variation in methodology, e.g. most studies have used education as the only proxy of cognitive reserve. Such research results have indicated a relationship between education and superior temporal gyrus and transverse gyrus, inferior and superior parietal gyrus, as well as with different regions of cingulate gyrus (e.g. see Arenaza-Urquijo et al., 2013; Liu et al., 2012). Wider studies have been conducted regarding the relationship between cognitive reserve and cognitive functioning, though studies in patient rather than healthy adult groups are more dominant. Cognitive reserve in healthy ageing has been associated with better memory performance (Krch et al., 2019; Vonk et al., 2022), semantic and phonetic verbal fluency, performance in Stroop task and others (Arenaza-Urquijo, Molinuevo, et al., 2013).

Overall, more studies are needed to encompass the relationship between cognitive reserve and its proxies and cortical and cognitive factors in ageing. There is still no consensus regarding the brain regions corresponding to the cognitive reserve, an issue potentially related to the differences in methodology used. The proposed theoretical model would encompass both – investigating the brain regions associated with cognitive decline and investigating cognitive reserve in more detail due to variety of socio-behavioural proxies used.

2 Methods and materials

2.1 The relationship between cognitive reserve and cognitive functioning in a partially representative sample

To test the first hypothesis, data from the Survey of Health, Ageing and Retirement in Europe (SHARE) Wave 8 were used (Bergmann & Börsch-Supan, 2022; A. Börsch-Supan, 2022; Axel Börsch-Supan et al., 2013). Permission for using the data was granted from the SHARE-project authors (Annex 1).

2.1.1 Participants

In the study, 546 Latvian speakers aged from 42 to 103 (M = 70.54, SD = 10.19, 37.2 % male) with no diagnosis of dementia, Parkinsons disease, ongoing oncological disease, stroke or cerebrovascular disease were included. Data from participants, whose data were obtained in Russian, were not included in the study.

2.1.2 Measures and materials

Cognitive reserve was measured using education, employment status and leisure activities done during the past year (see Table 2.1).

Table 2.1

Proxy measures of cognitive reserve

Proxy	Question	Scale
Education	What higher or professional education levels have you obtained?	Computed mean years of education
Occupation	What is your current employment situation?	Nominal scale, where employment – 1, non-employment – 0

Table 2.1 continued

<table>
<tr><th>Proxy</th><th>Question</th><th>Scale</th></tr>
<tr><td>Leisure Activity</td><td>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 on a political or community-related organization
5) Read books, magazines or newspapers
6) Did word or number games
7) Played cards or games</td><td>Nominal scale, where activity done – 1, activity omitted – 0</td></tr>
<tr><td>Vigorous physical activity</td><td>How often do you engage in vigorous physical activity, such as sports, heavy housework, or a job that involves physical labour?</td><td rowspan="2">Scale from 1 – 4, where 1 – hardly ever or never, 2 – one to three times a month, 3 – onve a week, 4 – more than once per week</td></tr>
<tr><td>Moderate physical activity</td><td>How often do you engage in activities that require a moderate level of energy, such as gardening, cleaning the car, or doing a walk?</td></tr>
</table>

Cognitive functions measured were short / long-term memory and semantic verbal fluency tasks. Memory was measured using a ten-word task, where participants were read a list of ten words and they had to recall it immediately and after 15 minutes. First measure was used for short-term memory, while the second measure – for long-term memory. Sum of correct answers was analysed.

Verbal fluency was assessed using a semantic task, where participants were asked to name as many animals as possible in 1 minute. Sum of correct answers were analysed.

2.1.3 Procedure

Data were obtained between November 2019 and March 2020 using face-to-face interviews with each participant individually or guardian present. Data were obtained using CAPI (Computer Assisted Personal Interview) method. All data were obtained by trained specialists from a research agency. 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 of their rights to refuse further participation in the study if they chose to. A research approval from Rīga Stradiņš University Ethics Committee (no. 2-PĒK-4/601/2022) was obtained as well (see Annex 2).

2.1.4 Data analysis

Descriptive statistics included mean, standard deviation, minimum and maximum scores, as well as, the frequency of the activity done. To investigate the relationship between the proxies of cognitive reserve and memory and verbal fluency, Spearman's Rank Correlation analysis and structural equation modelling using R 4.2.1. software with *lavaan* package (Rosseel, 2012) was conducted.

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

To test the second hypothesis, namely, 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 from the National Research Program "BIOMEDICINE-LV" subproject "Establishing the Net Attainable Benefits of Long-term Exercise, ENABLE-LV" were used.

2.2.1 Participants

There were 61 participants aged from 65 to 85 (M = 71.87, 19.7 % male) included in the study. All participants had at least 11 years of education (high school diploma) and they have been employed at some point in their lives. Only Latvian speaking older adults aged from 65, 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 were included in the study.

2.2.2 Measures and materials

Cognitive reserve was assessed using socio-behavioural approach and data were acquired with Cognitive Reserve Index questionnaire (Nucci et al., 2012; Šneidere et al., 2018). This questionnaire consists of three parts and includes information on education, occupation and leisure activities starting from the age of 18. Data are acquired using structured interview and participants reflect on how often have they taken part in a specific activity (if any). In data analysis, all years are rounded to five-year intervals and further calculated using a specific algorithm. As a result, one total index (CRI-Total) and three subindices (CRI-Education, CRI-Occupation and CRI-Leisure Activity) are obtained.

Cognitive functions were measured using a combination of cognitive tests that included measures of memory, processing speed, verbal abilities, executive functions and visuo-spatial abilities.

Memory measures

For **short- and long-term memory** measures, the Memory Ten-word Test was used (Luria, 1976). The aim of the test is to assess short- and long-term memory, as well as the process of learning. Participant is verbally presented with a list of ten words that they have to memorize and recall. Procedure is repeated five times and after an hour the participant is asked to recall the words again without any cues or prompts. Short-term memory is measured using the first recall, while long-term memory is measured using the last recall.

Working memory was assessed using The Numbers Reversed Task from the Woodcock-Johnson Tests of Cognitive Abilities (Paleja, 2006; Woodcock et al., 2001). In this task, the participant is presented with a list of numbers (from two to seven numbers) that they have to repeat in a reversed order. The level of difficulty is gradually increased. Participant receives one point per correct answer.

Associative memory was measured using another test from the Woodcock-Johnson Tests of Cognitive Abilities (Paleja, 2006; Woodcock et al., 2001) – "Memory of Names". This is an audio-visual task that requires the participant to learn names of twelve "aliens" – previously unknown information. The participant is first presented with the picture of an alien and then given its name. Afterwards the participant must point to the alien, whose name has been called.

Processing speed measures

Two approaches were used for measuring processing speed – based on reaction time and based on production.

Reaction time was measured using two tasks from the digital Handball goalie reaction test (Molotanovs, 2013). The first task measures simple reaction. The participant is presented with a picture of goalie and a "Start" and "Stop" buttons on the screen. After pressing the “Start” button, a ball appears by the goalie’s right hand with irregular intervals. Participants were asked to press “Stop” as soon as the ball appeared. In the second task, participants were presented with the same goalie, but the in this case the ball would appear either by his hand or by the elbow. If the ball appeared by the hand, participants had to press the letter “E” on the keyboard, if the ball appeared by the elbow, the letter “U” should be pressed. For both tasks, first five practice trials were done and then 20 trials were recorded. Mean reaction time in ms were further used to create a composite score of processing speed, created from a sum of standardized values. The standardized score was created using a formula adapted from Malek-Ahmadi et al. (2018) that uses two standard deviations for identifying min and max values of the measure (see formula below (1)).

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

Processing speed measures based on production were obtained using the “Visual Matching task” – another test from the Woodcock-Johnson Tests of Cognitive Abilities (Paleja, 2006; Woodcock et al., 2001). In this task, participants are presented with 60 rows of numbers (six numbers per row) and they are asked to circle two identical numbers in each row. The difficulty level is gradually increased (from one to three number combinations).

Verbal abilities

Two measures of verbal abilities were obtained – vocabulary (general knowledge) and verbal fluency.

Vocabulary measures were conducted using the “Picture Glossary” task from the Woodcock-Johnson Test of Cognitive Abilities (Paleja, 2006; Woodcock et al., 2001). The participant is presented with a picture of an object and asked to name it. The difficulty is gradually increased (from well-known objects, e.g. a ball, to more complex object, e.g. pagodas).

Verbal fluency measures were obtained using a Verbal fluency subtest from Monreal Cognitive Assessment scale (Nasreddine et al., 2005). Participants are asked to name as many words beginning with letter "L" as possible. One point is given per each correct answer.

Executive functions and visuo-spatial abilities

Three subtests from the Montreal Cognitive Assessment test (Nasreddine et al., 2005) test were used for measuring executive functions and visuo-spatial abilities. In the "Trailing task" participants are asked to draw an arrow from a number to a letter and then continue to a number again (e.g. 1 → A → 2). The test is finished when the participant reaches letter "E". If all arrows are correctly used, one point is given. The "Cube" task requires the participant to copy a cube. If the drawing is three-dimensional and there are no spare lines, a point is given. The third task is the Clock-Drawing task, where the participant is asked to draw a contour of a clock, write all numbers and indicate the time – ten minutes past eleven. One point is given per correctly answered command.

2.2.3 Procedure

Data were acquired in two consecutive stages and in two weeks. All data were acquired from each participant individually and frontally. First, informed consent was obtained and participants were provided with information on the aim and objectives of the study, then the first part of cognitive assessment was conducted and structural brain MRI was conducted in the Pauls Stradiņš Clinical University Hospital. A week later, cognitive assessment was concluded and life-style measures obtained (see Figure 2.1).

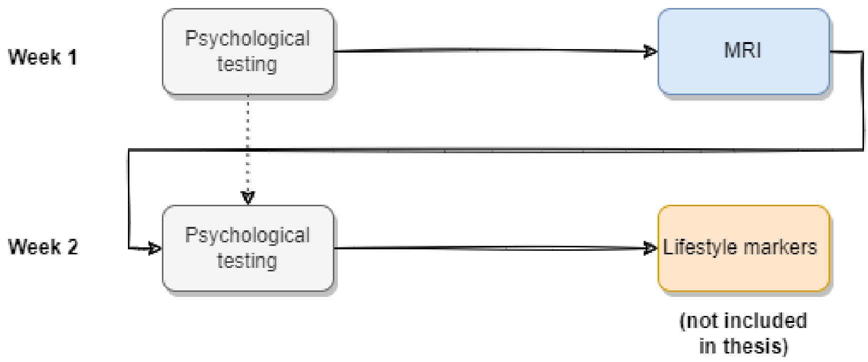

Figure 2.1 **Full procedural description of data acquisition**

All data were acquired adhering to the highest levels of research ethics and informed consent was signed prior to data acquisition. Within the ENABLE-LV project, approval from Rīga Stradiņš University Ethics Committee was obtained.

2.2.4 Data analysis

Descriptive statistics (mean, standard deviation, min and max values) were first calculated. To test the relationship between cognitive reserve and its subindices and cognitive functions, first Spearman's Rank Correlation analysis was conducted and afterwards Hierarchal Regression Analysis was conducted, controlling for the age of the participant.

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

Overall, 58 participants aged 65 – 85 (M = 71.83, SD = 5.016, 20.7 % male) were included in the analysis. All participants had at least 11 years of education and have been employed at some point in their life. Only Latvian speaking older adults aged from 65, 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 were further included in data analysis.

2.3.2 Measures and materials

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 = 15 degrees; voxel dimensions, 0.9 × 0.9 × 0.9 mm^3; acquisition time, 5 min].

Volumetric analysis

Volumetric data were acquired using Freesurfer 7.2. software. Volumes of thalamus and hippocampus were automatically segmented using regions of interest (ROI). For mapping cortical regions, Desikan-Killany-Tourville (DKT) atlas was used (Alexander et al., 2019).

2.3.3 Procedure

Data were acquired in two consecutive stages and in two weeks. The data on structural brain MRI was conducted in Pauls Stradiņš Clinical University Hospital and obtained on the first stage. For more detailed description of the procedure, see Subchapter 2.2.3. and Figure 2.1).

2.3.4 Data analysis

Descriptive statistics (mean, standard deviation, min and max values) were first calculated. To test the relationship between cognitive reserve and its subindices and cortical regions, hippocampus and thalamus, first Spearman's Rank Correlation analysis was conducted and afterwards Hierarchal Regression Analysis was conducted, controlling for the age and estimated intracranial volume (eTIV) of the participant.

2.4 The 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

There were 23 women aged from 68 – 83 (M = 74.13, SD = 4.70) recruited from the ENABLE-LV dataset. None of the participants reported having dementia diagnosis. Mean years between the measures were 3.391 years (SD = 0.656).

2.4.2 Measures and materials

Same measures used to test the second hypothesis was used (see Subchapter 2.2.2., and Table 2.2).

Table 2.2

Measures of cognitive reserve and cognitive functioning

Measure	Variable
Cognitive Reserve Index questionnaire	Cognitive reserve approximation based on socio-behavioural 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. Data were acquired in two consecutive stages and in two weeks. All data were acquired from each participant individually and frontally. First, informed consent was obtained and participants were provided with information on the aim and objectives of the study, then the first part of cognitive assessment was conducted and structural brain MRI was conducted in the Rīga 1st Hospital. A week later, cognitive assessment was concluded and life-style measures obtained.

Prior to data acquisition, Central Medical Ethics Committee approval was received (see Annex 4).

2.4.4 Data analysis

First, the differences between the baseline and follow-up cognitive function measures were tested, using Wilcoxon Signed Rank test. Only those variables that had statistically significant changes over the time were included further in data analysis. Next, to test whether cognitive reserve are associated with the changes in cognitive functions, partial correlation controlling for the time between measures, was conducted.

3 Results

The results in this chapter are summarized according to the second objective and considers: the relationship between cognitive reserve and cognitive functioning in a partially representative sample, the relationship between cognitive reserve and cognitive functioning in a sample of older Latvian adults, the relationship between cognitive reserve and neural correlates (cortex, hippocampus and thalamus) and the association between cognitive reserve and the change in cognitive performance.

3.1 The 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 verbal fluency, structural equation model was prepared.

3.1.1 Descriptive statistics

Mean, standard deviation, min and max values were calculated for education, memory and verbal fluency scores (see Table 3.1), frequency of the activity was calculated for leisure activities and employment and leisure activity.

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 employment status and leisure 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 (.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 moderate activities one to three times a month and only 8.4 % noted that they are involved in moderate physical activities hardly ever or never.

To test the relationship between variables, Spearman's Rank Correlation analysis was conducted. As a result, all variables indicating statistically significant relationship between at least one of the variables, were includes in the structural equation model. The chosen cut-off point was 0.10.

3.1.2 Creating Leisure Activity variable

In the next step, Leisure Activity composite score was created using confirmatory factor analysis. At first, a one scale Leisure Activity variable was proposed, composed of activities conducted in the last 12 months (Model 0). However, the model fit indices 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 Leisure Activity and Social Leisure Activity (Model 1). 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 (playing cards or board games) was removed and 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 3.3).

Table 3.3

Fit indices for the Leisure Activity composite model

	Model	RMSEA	SRMR	CFI	AIC	BIC
1	Model 0 – baseline	0.067	0.053	0.621	5893.7	5953.9
2	Model 1	0.048	0.044	0.884	−335.9	−271.3
3	**Model 2**	**0.055**	**0.045**	**0.899**	**258.5**	**314.4**

3.1.3 SEM analysis of the relationship between cognitive reserve and cognitive functioning

Two conceptual models were prepared, based on literature analysis and Spearman's Rank Correlation analysis. Both models included aforementioned socio-behavioural proxies of cognitive reserve (education, employment and leisure activities) and short- and long-term memory measures and verbal fluency measures (see Annex 5).

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 3.4).

Table 3.4

Model fit indices for the memory model

Model		RMSEA	SRMR	CFI	AIC	BIC
1	Model 0 – baseline	0.068	0.066	0.892	4120.9	4241.4
2	Model 1	0.066	0.066	0.893	4118.9	4235.1
3	Model 2	0.067	0.079	0.936	5101,9	5183.6
4	Model 3	0.068	0.078	0.933	5102.9	5180.3
5	Model 4	0.07	0.083	0.941	5111.7	5184.9
6	**Model 5**	**0.079**	**0.058**	**0.970**	**5117.7**	**5182.2**

The final model indicated that formal education is 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).

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 3.5).

Table 3.5

Model fit scores for verbal fluency

Model		RMSEA	SRMR	CFI	AIC	BIC
1	Model 0 – baseline	0.056	0.061	0.776	9232.7	9318.8
2	Model 1	0.051	0.059	0.829	9233.0	9314.8
3	Model 2	0.078	0.070	0.833	7240.4	7287.7
4	Model 3	0.056	0.061	0.847	8267.4	8340.6
5	Model 4	0.042	0.048	0.932	6990.9	7055.4
6	**Model 5**	**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.

3.2 The 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 3.6).

Table 3.6

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
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. CRI-Education was statistically significantly associated only with short-term memory ($r_s = 0.360$, $p < 0.01$) scores and vocabulary ($r_s = 0.274$, $p < 0.05$), while CRI-Occupation statistically significantly correlated with short-term memory ($r_s = 0.29$, $p < 0.05$), verbal fluency ($r_s = 0.353$, $p < 0.01$) and reaction time ($r_s = -0.346$, $p < 0.01$) scores. CRI-Leisure Activity did not correlate with any of the cognitive functions.

In the next step, hierarchal regression analysis controlling for age, was conducted. CRI-Education predicted short-term memory performance, explaining 15.3 % of the variation ($R^{2\,=}$ 0.154, $\Delta R^2 = 0.153$, $F(1, 60) = 9.541$, $p = 0.008$, $DW = 1.664$), as well as vocabulary scores explaining 14.8 % variation ($R^{2\,=}$ 0.148, $\Delta R^2 = 0.145$, $F(1, 60) = 5.039$, $p = 0.01$, $DW = 1.984$).

Even though CRI-Occupation previously correlated with short-term memory, after controlling for age, the relationship was no longer there. However, CRI-Occupation statistically significantly predicted reaction time, explaining 7.6 % of the variation ($R^{2 = 0.}099$, $\Delta R^2 = 0.076$, $F(1, 59) = 3.178$, $p = 0.049$, $DW = 1.690$). CRI-Occupation also predicted verbal fluency scores, explaining 8.5 % variation, though this model was not statistically significant ($R^{2 = 0.}091$, $\Delta R^2 = 0.085$, $F(1, 60) = 2.896$, $p = 0.063$, $DW = 1.625$).

CRI-Total statistically significantly predicted only verbal fluency scores, explaining 9.7 % of the variation ($R^{2 = 0.}103$, $\Delta R^2 = 0.097$, $F(1, 60) = 3.320$, $p = 0.043$, $DW = 1.518$).

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

To test the hypothesis, namely, that higher cognitive reserve will be associated with larger volume in brain cortex, hippocampus and thalamus, Spearman's Rank Correlation analysis and hierarchal regression analysis, controlling for age and estimated intracranial volume (eTIV) was used.

Due to only partial compliance with normal distribution, non-parametric correlation analysis method was chosen.

CRI-Education

CRI-Education statistically significantly correlated with the right hemisphere paracentral lobule ($r_s = -0.293$, $p = 0.026$), right hemisphere rostral anterior cingulate ($r_s = 0.272$, $p = 0.039$) and left hemisphere posterior cingulate ($r_s = 0.266$, $p = 0.043$). After controlling for age and eTIV, no association was found between the variables.

CRI-Occupation

CRI-Occupation correlated with right hemisphere entorhinal cortex (r_s = 0.336, $p < 0.01$), as well as, left and right hemisphere superior temporal gyrus ($r_s = 0.316$, $p = 0.008$ and $r_s = 0.316$, $p = 0.016$, respectively). Statistically significant relationship was also found with left hemisphere middle temporal gyrus ($r_s = 0.384$, $p = 0.003$) and transverse temporal gyrus ($r_s = 0.285$, $p = 0.03$). CRI-Occupation also significantly correlated with frontal regions, namely, left hemisphere rostral middle frontal gyrus ($r_s = 0.306$, $p = 0.02$), left and right hemisphere pars orbitalis ($r_s = 0.296$, $p = 0.024$ and $r_s = 0.323$, $p = 0.013$, respectively), left and right hemisphere orbitofrontal gyrus ($r_s = 0.327$, $p = 0.012$ and $r_s = 0.247$, $p = 0.037$, respectively) and right hemisphere medial orbitofrontal gyrus ($r_s = 0.285$, $p = 0.03$).

Association was also found between CRI-Occupation and parietal regions, namely, left hemisphere superior parietal lobule ($r_s = 0.262$, $p = 0.047$) and inferior parietal lobule ($r_s = 0.471$, $p < 0.001$), as well as, with cingulate cortex regions – left hemisphere caudal anterior cingulate ($r_s = 0.261$, $p = 0.44$) and left and right hemisphere rostral anterior cingulate ($r_s = 0.320$, $p = 0.014$ and $r_s = 0.301$, $p = 0.022$, respectively) and left hemisphere insula ($r_s = 0.361$, $p = 0.048$).

After controlling for age and eTIV, CRI-Occupation explained 6.3 % of the left hemisphere middle temporal gyrus volume variation ($R^2 = 0.396$, $\Delta R^2 = 0.063$, $F(1, 54) = 5.627$, $p = 0.021$), 9.6 % of the inferior temporal gyrus volume variation ($R^2 = 0.292$, $\Delta R^2 = 0.096$, $F(1, 54) = 7.336$, $p = 0.009$), 8.5 % of the right hemisphere inferior temporal gyrus ($R^2 = 0.406$, $\Delta R^2 = 0.085$, $F(1,54) = 7.765$, $p = 0.007$) and 13.8 % of left hemisphere inferior parietal lobule ($R^2 = 0.483$, $\Delta R^2 = 0.138$, $F(1, 54) = 14.404$, $p < 0.001$).

CRI-Total

The CRI-Total score statistically significantly correlated with left hemisphere middle temporal gyrus ($r_s = 0.259$, $p < 0.05$), right hemisphere pars orbitalis ($r_s = 0.411$, $p = 0.01$), left hemisphere inferior parietal lobule ($r_s = 0.387$, $p = 0.003$), right hemisphere pericalcarine ($r_s = 0.285$, $p = 0.030$) and rostral anterior cingulate cortex ($r_s = 0.274$, $p = 0.038$), as well as left and right hemisphere insula ($r_s = 0.294$, $p = 0.025$ and $r_s = 0.309$, $p = 0.18$, respectively).

After controlling for age and eTIV, CRI-Total statistically significantly predicted the volume of left hemisphere middle temporal gyrus, explaining 6.3 % variation ($R^2 = 0.396$, $\Delta R^2 = 0.063$, $F(1, 54) = 5.656$, $p = 0.021$), 12 % inferior parietal lobule volume variation ($R^2 = 0.465$, $\Delta R^2 = 0.120$, $F(1,54) = 12.107$, $p = 0.001$) and 8.4 % right hemisphere pars orbitalis volume variation ($R^2 = 0.127$, $\Delta R^2 = 0.084$, $F(1,54) = 5.223$, $p = 0.026$) (see visualization of the regions in Figure 3.1).

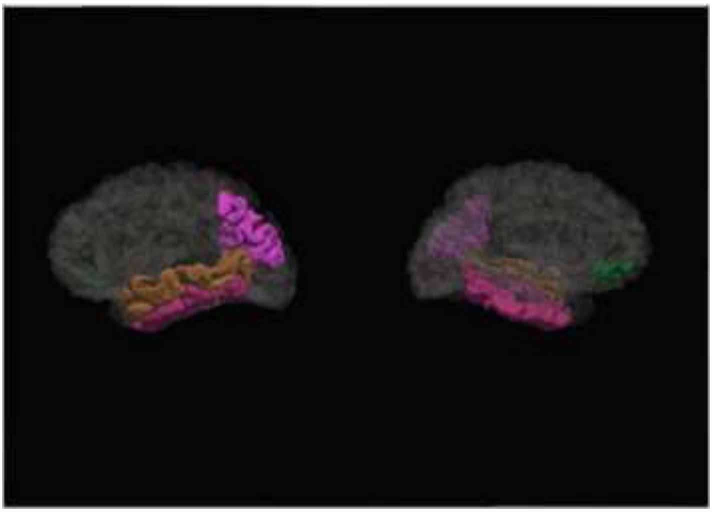

Figure 3.1 **Regions associated with proxies of cognitive reserve**

Association between cognitive reserve and hippocampus and thalamus volume

No statistically significant relationship was found between cognitive reserve and hippocampus and thalamus volumes (see correlation matrix in Annex 6).

3.4 The 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. Out of all cognitive variables, only long-term memory, reaction time and results in the Clock Drawing task indicated changes over time (see Table 3.7).

Table 3.7

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**	**<.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

In the next step, changes over time were calculated, subtracting first measure from the second measure, and partial correlation coefficient was calculated, controlling the time between measures. Statistically significant negative correlation was found only between CRI-Leisure Activity and changes in the reaction time ($r_p = -0.440$, $p = 0.041$).

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 scientific objectives were proposed: (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. This chapter further discusses the main implications of the results, as well as considers the limitations and future perspectives.

The relationship between cognitive reserve and cognitive functioning was tested in two different samples – a larger, partially representative sample of middle aged and older adults and a smaller sample of older adults. Results indicated that more years spent in education, current employment and occupational complexity as well as cognitive leisure activities could be associated with better cognitive functioning, especially – verbal abilities, short- and long-term verbal memory and processing speed, as measured by reaction time.

Education was also a significant predictor for memory scores, indicating that higher levels of formal education could be associated with better short- and long-term memory performance, previous studies have also shown a relationship between higher levels of education obtained early in life and non-verbal memory (Reifegerste et al., 2020). This is a rather consistent finding in the literature, noticeable in the findings by Yaakov Stern (Stern et al., 1999) and also in more recent studies (Yassuda et al., 2020).

Similarly, Lubrini and colleagues found that education was the best predictor of performance in both – phonetic and semantic verbal fluency tasks (Lubrini et al., 2022), while other studies have not yielded same results regarding this proxy of cognitive reserve (e.g. see Weng et al., 2018). Even though the results considering education and verbal fluency are contradictious, the association between higher levels of education and larger vocabulary were rather predicted and complemented the already existing literature on education in relation to verbal IQ (e.g. see Morin & Midlarsky, 2017).

Nevertheless, the association between the variables is often noticed together with occupational complexity and overall achievements. The role of employment status was identified in this study as well, highlighting that current employment could be associated with better memory and verbal fluency scores. This is largely consistent with other studies, for example, results of a study by Baowen Xue and colleagues showed that higher employment grade is protective against verbal memory decline; however, the effect was lost after retirement (Xue et al., 2018). This marks another important question when regarding cognitive reserve, namely, the length of the effect of occupation. Longitudinal studies would be beneficial to better understand this aspect of the reserve.

Even more, when considering the length and complexity of the employment experience (CRI-Occupation), the results indicated that more complex occupational activities were associated with better verbal fluency and faster reaction times. Overall, occupational complexity has been associated with better cognitive performance in general (e.g. see Mondini et al., 2022); however, some studies indicate a potential relationship between the type of the occupational activity and specific function. A study published by van der Elst and colleagues found that teachers had superior verbal fluency skills in comparison to their education, level of occupation, age and gender matched controls (Van Der Elst et al., 2012), later studies also showed a relationship between higher mental demands at work and better cognitive functioning independently from a specific occupation (Then et al., 2014).

Leisure activities were chosen to comply with activities integrated in the Cognitive Reserve Index questionnaire and initially planned to consider as one composite variable; however, CFI analysis indicated a need for separate subscales, thus three types of leisure activities were extracted – Cognitive Leisure (attending educational or training course, reading books or newspapers and playing word or number games), Social Leisure (doing voluntary or charity work, going to a sport, social or other kind of club, as well as, taking part in political or community-related organization) and Physical Activity (either vigorous or moderate).

While Cognitive Leisure and Physical activity predicted better memory and verbal fluency scores, Social Leisure activities did not. This was an unexpected result, as results from previous SHARE waves did indicate the opposite, showing a strong relationship between non-professional social activities and cognitive performance (Miceli et al., 2019). This, however, could be related to the relatively small sample of participants indicating that they have been involved in such activities.

In the final model, Cognitive Leisure included two activities – reading books or newspapers and playing word or number games. Studies on the relationship between word and number puzzles, such as Sudoku and crosswords, and cognitive functioning, have shown mixed results. 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 found a relationship between doing crossword puzzles and delayed onset of memory decline symptoms in participants who later developed dementia; however, it also increased the rate of decline after the onset of the symptoms (Pillai et al., 2011).

In addition to solving word and number puzzles, reading books and newspapers were also indirectly related to better verbal fluency and memory scores. Even in previous studies, more frequent reading has been associated with a lower risk of cognitive decline independent of education (Chang et al., 2021), and considering the time of acquiring reading skills (Peng et al., 2018). While both variables from the Cognitive Leisure scale indicated a correlation with memory and verbal fluency individually, the combination of both would possibly strengthen the association, thus a combined approach rather than individual activities could be more beneficial.

Finally, in both models moderate and vigorous activity was considered and the model indicated that more frequent participation in moderate physical activities, such as a quick walk or gardening, predicted better memory performance and verbal fluency scores. 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, many studies have shown that moderately intensive activities, such as regular walks or exercise, can be beneficial for cognitive health (Makizako et al., 2013; Sandroff et al., 2015; Varma et al., 2015).

Another scientific 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. Nevertheless, longitudinal studies would be beneficial to better understand the potential role of the reserve.

Results from previous research 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), thus similar findings were expected in this study. However, after controlling for age and eTIV such relationship was not present in this thesis. A number of factors could have contributed to this. First of all, 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). Furthermore, the limitations of the sample size should be considered. In addition, 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 volume in regions associated with social interaction and verbal abilities. Middle temporal gyrus has been found to be involved not only in verbal intelligence – an often used proxy of cognitive reserve (Heyer et al., 2021) –, but also in processing new information, as well as its functional connectivity with hippocampus in creating new and overriding old concepts (Ren et al., 2020). Inferior temporal regions have shown similar functions an show a potential role in creating new social relationships – especially regarding object, face and setting recognition (Conway, 2018; Yang & Bi, 2022).

Similarly, a correlation between right hemisphere pars orbitalis and total cognitive reserve scores were found. While the role of left hemisphere pars orbitalis is well documented, there is a lack of studies investigating its role in the other hemisphere. Nevertheless, a study by Belyk and colleagues have identified another social role for this region, highlighting that the left hemisphere pars orbitalis could be involved in recognising semantic and emotional reactions (Belyk et al., 2017).

The role of cognitive and social activities has also been identified in inferior parietal lobule. This region is considered to be one of the "rich club" hubs, showing that this region could be involved in overall improving the cognitive efficiency. Different segments of inferior parietal lobule have been involved in attention reorientation, as well as processing semantic information and are present in mentalization (Numssen et al., 2021). Even though the results of this study did not initially show a relationship between cognitive functions and social activities, it should be noted that during the life-span occupational activities are often the basis of daily socialisation.

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 throughout the 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 tendency shows that active employment would be retained even past the official retirement age.

There were no significant associations between cognitive reserve and thalamic volume. Earlier studies have implied the role of thalamus as a part of brain networks associated with cognitive reserve (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., as 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 an anatomical measure.

Similarly, hippocampal volume did not correlate with cognitive reserve, despite conclusions gained from previous studies (e.g., see Serra et al., 2019). Nevertheless, this could be attributed to the compensation through other structures, as several studies have also indicated the role of hippocampus as a moderator / mediator rather than an independent structure (Belleville et al., 2021; Vuoksimaa et al., 2013).

These findings must be interpreted with caution. Magnetic resonance images were obtained using a 1.5 Tesla machine; thus, reduced image quality can be expected. This is also significant considering that cortical structures can house several functions, depending on the segmentation. Further studies should involve functional connectivity measures, potentially using the identified brain regions as ROI.

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 three cognitive functions – long-term memory, reaction time and visuo-spatial abilities, showing a significant 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 that decrease in processing speed could function as a marker for cognitive decline (Salthouse, 1996). 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.

The results showed who participants that were more active in lifelong leisure activities (CRI-Leisure Activities) also showed lesser deceleration in reaction time. Surprisingly, such results were not found when using education and occupation as proxies; 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 or indicates the “intervention” aspect from STAC-r framework.

Nevertheless, caution should be taken when interpreting the data from this part of the study, as the sample size is insufficient to generalize any of the findings; thus, only potential tendencies can be discussed. Second, the sample includes 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.

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 role of cognitive reserve could be better explored and explained longitudinal study design. 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 directly comparable.

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 to be nationally representative, it was 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 additionally 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, 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.

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 have been examined from different angles, combining cross-sectional and longitudinal designs. It should also be stressed that this is a first study in Latvia investigating healthy ageing in a multidisciplinary setting, combining methodology from cognitive psychology with methods used in 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 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 are associated with better short-term memory scores and larger vocabulary, while higher occupational complexity and responsibility are associated with better processing speed and 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; nevertheless, hippocampal and thalamic volumes were not associated with none of the cognitive reserve sub-indices;

4) There are recognisable changes in such cognitive functions as long-term 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.

Proposals

The results of the Thesis offer an overview on the relationship between cognitive reserve and cognitive functioning and brain volume characteristics in Latvian adults. Based on the results, the following proposals are suggested:

1) To develop evidence-based strategy for promoting healthy cognitive ageing and lessening the burden of cognitive dysfunction;
2) In collaboration with non-governmental associations, to develop an informative material on main principles of healthy cognitive ageing;
3) To apply longitudinal design for the future studies, as well as integrate functional measures of the brain.

Publications

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.* 4, 480–490.
3. Šneidere, K., Mondini, S. & Stepens, A. 2020. Role of EEG in Measuring Cognitive Reserve: A Rapid Review. *Frontiers in Aging Neuroscience*. 12, 249.
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*. 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*. 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.
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Acknowledgements

No man is an island and no study can be started or finished without a support of a team. I would first like to thank my supervisors *PhD* Sara Mondini and assoc. prof. Ainārs Stepens for the work they have put in the often stubborn me, as well as the support I have received.

My biggest gratitude also goes to prof. Kristīne Mārtinsone, who has been guiding me through the world of research since 2012, to Viktorija Perepjolkina, who helped to see the data, not only to calculate them, to Jeļena Koļesņikova, who was always there to support me, and Sandra Mihailova, who was always a phone call away. I would also like to say thank you to my study friends – Inese Jokste, Sanita Šuriņa, Zane Ulmane, Elīna Zelčāne, Elīna Akmane, Inese Paiča and Gatis Upesleja for your support.

Finally, the Thesis would not be written without the support of my family, who encouraged me to do this from start to finish, provided me with chocolate and reminders to take a break from time to time.

The Thesis has been developed with financing from the European Social Fund and Latvian state budget within the project No 8.2.2.0/20/I/004 "Support for involving doctoral students in scientific research and studies" at Rīga Stradiņš University. In addition, data were obtained and analysed within projects The Effect of Lifetime Physical Activity on the Burden Caused by Cognitive Disfunction and Depression in Elderly, ELPA-COG (RSU Scientific Council Decision No 21-1/1/2019-3 of 07.03.2019), The Role of Motor Reserve in Cognitive Dysfunction in Older Adults (MORE-COG)", Modifiable Bio and Life-Style Markers in Predicting Cognitive Decline [MOBILE-COG]), 46-23/8/2021 and The Role of Motor Reserve in Cognitive Dysfunction in Older Adults (MORE-COG)", 6-ZD-22/27/2022.

Annexes

Annex 1

Permission to use SHARE project 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
- ☐ Clearly separate and independent research dept. of a public institution/non-profit organisation
- ☐ Other, **non**-scientific affiliation
  → *Note: Only if this option applies in your case you have to complete **PAGE 2** of this statement*

Declarations

I hereby acknowledge and agree to carry out work on data of the SHARE project in accordance with the ***SHARE Conditions of Use*** (available in the currently valid version at http://www.share-project.org/data-access/share-conditions-of-use.html) only.

Please note: The SHARE Conditions of Use create a legally binding contract between you and SHARE-ERIC. Please read them carefully.

☒ I confirm that I have read and fully understood the SHARE Conditions of Use.

In particular, I acknowledge and agree with the following conditions:

- The data may be used for scientific research only (commercial use is prohibited)
- No action aiming at a re-identification of SHARE participants may be taken
- The data may not be made available to any other person/third party
- Reference of all publications has to be provided to the SHARE coordination team
- The SHARE data set/s used must be referred to and the funding sources have to be acknowledged in all publications

☒ I agree to receive the ***SHARE newsletter*** via email.

Please note: Even though the SHARE newsletter is an optional service, subscribing is recommended in order to keep up to date with regard to the SHARE project on national and international levels. Unsubscribing is possible at any time.

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Signature: ....

Date: 29.07.2022 Place: Riga, Latvia

Please return this statement to: SHARE Research Data Center, c/o CentERdata, P.O. Box 90153, 5000 LE Tilburg, The Netherlands, or by email to: share-rdc@centerdata.nl

Survey of Health, Ageing and Retirement in Europe
European Research Infrastructure Consortium
Amalienstraße 33 · 80799 Munich · Germany
SHARE

SHARE coordination team
www.share-project.org
info@share-project.org

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SHARE Data Release CTRL <no-reply@centerdata.nl>

Your new SHARE Data Release CTRL account

To Kristīne Šneidere

Dear Kristīne Šneidere,

Priscilla Zhang has created a new account for you at SHARE Data Release CTRL. Please click the link below to set your new password.

Your username is: kristine.sneidere@rsu.lv

https://releases.sharedataportal.eu/users/activation/kristine.sneidere%40rsu.lv/3amvEdjuxL/1659086642

Best regards,
SHARE Data Release CTRL

Annex 2

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

Veidlapa Nr. E-9(3)
APSTIPRINĀTA
ar Rīgas Stradiņa universitātes rektora
2018. gada 26. septembra rīkojumu Nr. 5-1/238/2018

Rīgas Stradiņa universitātes
Pētījumu ētikas komitejas
LĒMUMS
Rīgā

15.12.2022 2-PĒK-4/601/2022

	Komitejas sastāvs	Kvalifikācija	Nodarbošanās
1	Profesors Jānis Vētra	Dr.habil. med.	Morfoloģijas katedra
2	Asoc. Prof. Zanda Daneberga	Dr.med.	OI Molekulārās ģenētikas laboratorijas vadītāja
3	Asoc. Prof. Anita Vētra	Dr.med.	Rehabilitācijas katedras vadītāja
4	Profesore Ingrīda Čēma	Dr.habil. med.	Mutes medicīnas katedras vadītāja
5	Docente Anna Junga	Dr.med.	Morfoloģijas laboratorijas vadītāja
6	Vadošā pētniece, docente Karina Palkova	Ph.D.	Advokāte, Doktora studiju programmas vadītāja
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. Kauke
Tālrunis: 26691306

Annex 3

Approval from Rīga Stradiņš University Ethics Committee (ENABLE-LV)

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 Liguts	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.

Annex 4

Approval from Central Medical Ethics Committee (ELPA-COG)

Centrālā medicīnas ētikas komiteja

Brīvības iela 72, Rīgā, LV-1011 • Tālr. 67876182 • Fakss 67876071 • E-pasts: vm@vm.gov.lv

Rīgā

30.05.2019. Nr.1/19-05-30

Rīgas Stradiņa universitātei

Atzinums par pētījumu
„Ilgtermiņa fiziskās aktivitātes ietekme
uz kognitīvās disfunkcijas un depresijas
radīto slogu senioriem"

Centrālā medicīnas ētikas komiteja 2019.gada 28.martā ir izskatījusi Rīgas Stradiņa Universitātes iesniegto pētījumu *„Ilgtermiņa fiziskās aktivitātes ietekme uz kognitīvās disfunkcijas un depresijas radīto slogu senioriem"*.

Pamatojoties uz Centrālās medicīnas ētikas komitejas 2019.gada 28.marta sēdes protokola Nr.2019-2 punktu Nr.6 un iesniegtajiem labojumiem, tiek izsniegts atzinums, ka Rīgas Stradiņa Universitātes iesniegtais pētījums *„ Ilgtermiņa fiziskās aktivitātes ietekme uz kognitīvās disfunkcijas un depresijas radīto slogu senioriem"* nav pretrunā ar bioētikas normām.

Centrālās medicīnas ētikas
komitejas priekšsēdētājs

Vents Sīlis

Strautiņš, 67876190
Edgars.Strautins@vm.gov.lv

Conceptual models

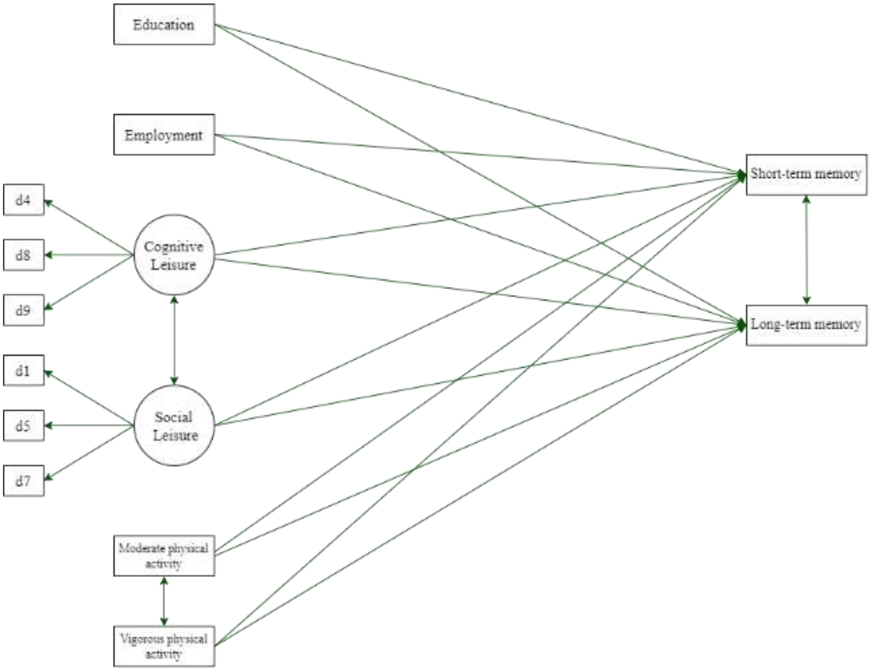

Figure 5.1 **Conceptual model of factors associated with memory in older adults**

Figure 5.2 **Conceptual model of factors associated with memory in older adults**

Annex 6

Relationship between cognitive reserve, hippocampus and thalamus volumes

Table 6.1

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. Hippocampus	0.098	0.084	−0.021	0.076	0.709**	0.697**	0.726**	0.959**	0.956**	–

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