심리학석사 학위논문

# Microstructural White Matter Correlates of Cognitive Reserve

## 인지 예비능의 미세 백질 구조적 기전

2019년 2월

서울대학교 대학원

심리학과 임상심리 전공

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이 논문을 심리학석사 학위논문으로 제출함
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# Abstract

# Microstructural White Matter Correlates of Cognitive Reserve

The protective effects of cognitive reserve on late-life cognitive decline have been demonstrated in previous literatures. However, neural mechanisms of how cognitive reserve exhibit such roles are unclear. This study was designed to explore the microstructural white matter correlates of cognitive reserve and to test the mediating role of the correlates in the relationship between cognitive reserve and cognition. One hundred and seventeen healthy older adults completed neuropsychological assessments and MRI scanning. Tract-based spatial statistics was applied to test the association with white matter fractional anisotropy (FA) and cognitive reserve proxy estimated with education and vocabulary test of K-WAIS-IV. The results identified several clusters with statistically significant correlation, which comprised of left corticospinal tract, left superior longitudinal fasciculus, and forceps major. Furthermore, FA of the tracts partially mediated the relationship between cognitive reserve and cognition. These findings suggest life-time intellectual experiences enrich late-life cognitive functions through more integrated white matter fiber.

**keywords : cognitive reserve (CR), neural reserve, white matter integrity, neuropathology, late-life cognition, mediation analysis**
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# Table of Contents

# List of Tables



# List of Figures

# INTRODUCTION

Population aging has been a global phenomenon around the world over a few decades (Mathers, Stevens, Boerma, White, & Tobias, 2015) and Korea is one of the fastest countries to show an increase in the rate of aging. Along with the demographic change, domestic dementia prevalence is growing rapidly. This trend is expected to accelerate over time. In 2030, the number of domestic dementia patients is predicted to be around one million (Statistics, 2013). Accordingly, the importance of investigating the risk factors and protective factors for the cognitive decline resulting from aging or late-life pathology is arising.

The cognitive decline in elderly population is associated with diverse aspects of life. It has been known that individuals experiencing cognitive decline have diminished life satisfaction (St John & Montgomery, 2010), quality of life (Abrahamson, Clark, Perkins, & Arling, 2012), overall well-being (Wilson et al., 2013), and social functioning (Kuiper et al., 2016). However, such decline does not occur at the same rate among elders. Some older adults show a faster rate of impairment to others despite of the same age or similar amount of brain pathology. The concept of cognitive reserve attempts to explain such individual differences in cognitive decline.

## 1. Cognitive Reserve

Cognitive reserve refers to an active ability to cope with brain pathology and optimize performance through alternative cognitive processing approaches or recruitment of compensatory brain networks (Stern, 2009). It attempts to explain the difference between the brain's neuropathology and clinically expressed symptoms. According to the cognitive reserve hypothesis, if the brain's pathological degeneration occurs at the same rate in two individuals, it will take a longer period of time for clinical symptoms to be expressed in a person with high cognitive reserve compared to a person with low cognitive reserve (Stern, 2002). That is to say that a greater amount of pathology needs to be piled up in the brain before cognitive decline begins in individuals with high cognitive reserve, which can delay the diagnosis of neuropathological disease (Barulli & Stern, 2013). The role of cognitive reserve as compensatory resources is not limited to a later onset of neuropathological diseases (Brayne et al., 2010; Hall et al., 2006), but also include a reduction in the effect of brain pathology on cognitive function (Bennett et al., 2003a; 2003b; Rentz et al., 2010) and protective influence on cognitive decline in normal aging (Zahodne, Stern, & Manly, 2015). The theoretical mechanisms of cognitive reserve are compensatory brain networks and the efficient use of neural reserve that allow for more flexible coping against brain pathology (Barulli & Stern, 2013; Valenzuela & Sachdev, 2006).

Since cognitive reserve is a theoretical construct, the amount of cognitive reserve one possesses cannot be directly measured. Generally, it is indirectly estimated through proxy variables (Siedlecki et al., 2009; Stern, 2009). Proxy variables are presumably composed of cognitively-stimulating, intellectual experience one has accumulated throughout the lifetime. The most frequently used proxy variables are years of education (Bennet et al., 2003a; Le Carret et al., 2003; Stern, Alexander, Prohovnik, & Mayeux, 1992) and premorbid IQ (Alexander et al., 1997), while occupational characteristics (Richards & Sacker, 2003; Staff, Murray, Deary, & Whalley, 2004; Stern et al., 1994), participation in cognitively stimulating activities (Aartsen, Smits, van Tilburg, Knipscheer, & Deeg, 2002; Colombo, Balzarotti, & Greenwood, 2018; Wilson et al., 2002), and the cohesion of social networks (Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000) are also used (Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012). Each proxy variable is known to have both differential and synergistic contributions to cognitive reserve (Foubert-Samier et al., 2012). The convergent and discriminant validity of the proxy variables have been confirmed (Siedlecki et al., 2009).

## 2. Neural mechanisms of cognitive reserve

### *2.1 Neural reserve and neural compensation*

Although the importance of cognitive reserve in the

maintenance of cognitive functioning in late-life has been documented in plenty of literature, the neural implementation of how cognitive reserve allows individuals to counter the brain pathology is still unclear. In Stern (2009)'s review paper, two components of the possible neural mechanisms of cognitive reserve are suggested. One is neural reserve, defined as differences between individuals in the employment of brain networks or cognitive paradigms for task performance. Individuals with better efficiency, greater capacity, and more flexibility would be able to better deal with brain pathology and maintain cognitive function. Another component is neural compensation, representing the process by which alternative brain networks that are not typically utilized in normal functioning individuals are recruited to maintain the cognitive performance in those with brain pathology or older age. Such idea is on the same line with the HAROLD model, in which older adults who recruited contralateral hemispheric brain regions showed better cognitive performance (Cabeza, 2002). These two forms might be distinguished depending on the research designs of imaging studies. In a situation where the neural mechanism of cognitive reserve is explored in one group, the resulting brain networks are to be interpreted as neural reserve. If, on the other hand, one group with less impairment or younger age and another group with more impairment or older age were compared and the usage of different networks is examined,

neural compensation would be a more suitable term to use (Stern, 2009).

*2.2 Previous literature on neural correlates of cognitive reserve*

Since the identification of the neural mechanism of cognitive reserve is associated with the clues for delaying the effect of aging and neuropathology, many previous literature have examined this topic. However, a large portion of exploration was conducted with pathologic populations that studies in healthy older adults are relatively lacking (Bartres-Faz & Arenaza-Urquijo, 2011). Studying the healthy elderly population is needed because cognitive reserve in healthy and pathological aging have different brain correlates (Colangeli et al., 2016). Also, it can provide insight to the protective mechanisms of cognitive reserve in normal brain aging, while studying patient groups can investigate the compensatory mechanisms after pathology has already damaged the brain (Bartres-Faz & Arenaza-Urquijo, 2011). Thus, the investigation of neural reserve in healthy elderly would be able to provide evidence toward the underlying mechanism of cognitive reserve in aging.

Accumulated research on the topic of neural mechanisms of cognitive reserve in healthy older adults utilized either functional or structural imaging techniques to investigate the effect of cognitive reserve proxy on brain parameters. In the perspective of functional

brain, several studies examined the relationship between education and measures of brain activity or connectivity at rest (Arenaza-Urquijo et al., 2013; Bastin et al., 2012; Franzmeier, Duering, Weiner, Dichgans, & Ewers 2017a; Perneczky et al., 2006; Scarmeas et al., 2003a). For example, the study by Arenaza-Urquijo and her colleagues (2013) found that higher years of education predicted greater metabolism in the anterior cingulate cortex (ACC) and increased functional connectivity between ACC and brain regions in frontal, temporal and parietal lobes. On the other hand, task-based functional studies found that higher cognitive reserve proxies are associated with compensatory brain networks (Ansado et al., 2013; Boller, Mellah, Ducharme-Laliberte, & Belleville, 2017; Scarmeas et al., 2003b; Springer, McIntosh, Winocur, & Grady, 2005; Stern et al., 2008), better brain efficiency (Batres-Faz et al., 2009; Bosch et al., 2010; Carreiras et al., 2009; Franzmeier et al., 2018; Lopez et al., 2014; Sole-Padulles et al., 2009), and increased connectivity of the left frontal cortex hub (Franzmeier et al., 2017b).

In the perspective of structural brain, positive associations between brain structural measures and cognitive reserve proxies have been a general trend in structural imaging studies (see Bartres-Faz & Arenaza-Urquijo, 2011 for a review), while a few had shown negative or null relationship (Arenaza-Urquijo et al., 2011; Bastin et al., 2012; Christensen et al., 2009). Greater grey matter volume (Arenaza-Urquijo

et al., 2013; Batres-Faz et al., 2009; Boller, Mellah, Ducharme-Laliberte, & Belleville, 2017; Carreiras et al., 2009; Chey, Kim, Stern, Shin, Byun, & Habeck, 2016; Foubert-Samier et al., 2012; Liu et al., 2012; Sole-Padulles et al., 2009), cortical thickness (Liu et al., 2012), and microstructural white matter diffusivity and its efficiency (Arfanakis et al., 2016; Piras, Cherubini, Caltagirone, & Spalletta, 2011; Teipel et al., 2009; Yoo et al., 2015) were associated with higher cognitive reserve proxy.

However, as reviewed, while a number of studies have been conducted on grey matter and functional brain correlates of cognitive reserve, studies regarding microstructural white matter are scant. Microstructural white matter is a brain structure that acts as pathways between grey matter structures, reflecting the strength and efficiency of anatomical connectivity (Mori, 2007). Compared to functional connectivity, white matter connections have advantages in that they are direct connectivity measures, while functional connectivity is an indirect measure that estimates the connections through co-activation between brain regions. Furthermore, according to Jbabdi, Sotiropoulos, Haber, Essen, and Behrens (2015), white matter connections are prerequisites for the fast and effective interaction of functional connectivity. Despite of such strengths, studies on the microstructural white matter correlates of cognitive reserve are limited.

*2.3 Microstructural white matter as neural mechanism*

In studying microstructural white matter, diffusion tensor imaging (DTI) is the most commonly used imaging technique. DTI reflects the diffusion patterns of water molecules and the likelihood of water molecule displacements at the voxel by measuring the dephasing of spins of protons in the gradient (O'Donnell & Westin, 2011; Jones, Knosche, & Turner, 2013). Of many different parameters derivable from DTI, fractional anisotropy (FA) is the most frequently used index to represent the efficiency of white matter connections that contains information regarding the quantitative integrity of microstructural white matter fiber tracts (Mori, 2007).

Up to date, only a few studies have investigated the association between FA and cognitive reserve proxy in healthy elders. The first study was done by Teipel and his colleagues (2009), where they reported a positive association of higher years of education with greater FA in medial temporal lobes and association fibers. Further, Arenaza-Urquito and her colleagues (2011) observed a negative relationship between years of education and white matter tracts vulnerable to aging, mainly the genum of the corpus callosum. The authors interpreted tis negative correlation as cognitive reserve acting directly on age-related brain burden while maintaining cognitive function, which supports a theoretical model of "neuroprotection" (see Arenaza-Urquijo, Wirth, & Chetelat (2015) for more details). Most

recently, Arfanakis and his colleagues (2016) found that more frequent late-life cognitive activity is associated with higher FA in left superior and inferior longitudinal fasciculi, left fornix, and corpus callosum. Although only little evidence is present, considering two of three previous research and the general trend of the positive correlations in structural imaging studies (Bartres-Faz & Arenaza-Urquijo, 2011), it is not unreasonable to hypothesize that higher FA is associated with higher cognitive reserve proxies in healthy older adults.

Moreover, the relationship between the microstructural white matter correlates of cognitive reserve and cognitive function is remaining as an unclear area of research. The only study that examined on this topic was by Arfanakis and his colleagues (2016), in which higher FA and lower trace of fiber tracts associated with late-life cognitive activity partially mediated the relationship between late-life cognitive activity and cognition. Though conducted in different modality, Arenaza-Urquijo and her colleagues (2013) found out that older adults with more education had increased functional connectivity, which in turn was correlated with better performance in memory and executive function. The authors suggested that this complementary analysis provides supports on the increased functional connectivity as the brain mechanism of the maintenance of cognitive performance in elders with higher education that might have a critical impact on healthy aging. One of the models that can be used for the

investigation on this issue is provided by Steffener and Stern (2012). They suggested a mediation model comprising of cognitive reserve as an independent variable, neural reserve as a mediator, and clinical measures as dependent variables.

### 3. Objectives and Hypothesis

Previous studies have limitations in their scant number on research of white matter correlates of cognitive reserve and its relation with cognitive function. Thus, the primary goal of this study is to explore the microstructural white matter correlates of cognitive reserve and its relationship with cognition. The mediation model suggested by Steffener and Stern (2012) will be used for the latter analysis. If white matter correlates partially mediate the relationship between cognitive reserve and neuropsychological measures, such finding will be able to provide an additional insight on what brain characteristics allow for the delay of clinical expression of neuropathology. In other words, it can be predicted that cognitive reserve will be associated with brain diffusion characteristics, and identified white matter tracts will have significant correlation with cognitive outcomes.

The hypotheses of this study are as follows. First, higher cognitive reserve is associated with higher FA, which represents the integrity of white matter tracts. Second, higher FA is associated with

better performance on neuropsychological tests. Third, FA of white matter partially mediates the associations of cognitive reserve with cognition.

# METHODS AND MATERIALS

## 1. Subjects

Participants of this study were recruited from the Korean Social Life, Health and Aging Project (KSHAP). There were two stages of screening for people with age of 60 years or older who volunteered to participate in the study. The first stage of screening was taken place prior to neuropsychological tests based on the Health Screening Exclusion Criteria, which was previously recommended by Christensen, Multhaup, Nordstrom, and Voss (1991). Accordingly, individuals with any history of brain surgery, neuropsychiatric or neurocognitive disorders, psychiatric or neurological conditions, vision or hearing problems, hypertension or diabetes incapable of being managed with drugs or insulin, or a history of losing consciousness other than during surgery for more than 1 hour, were excluded. The second stage of screening was based on the results of the Elderly Memory disorder Scale (EMS; Chey, 2007), the Mini-Mental State Examination for Dementia Screening (MMSE-DS; Han et al., 2010), and the self-rated and parental semi-structured interview based on the Korean Dementia Screening Questionnaire (KDSQ; Yang, Cho, Chey, Kim, & Kim, 2002) to exclude older adults with cognitive impairment. If either the total score of EMS was less than 5%, the

total score of MMSE-DS was less than 1.5 SD, or severe cognitive decline was reported through semi-structured interviews, individuals were excluded. In addition, of the screened individuals, only those who can safely participate in magnetic resonance imaging (MRI) scans were selected based on the following screening criteria: possession of unremovable metals in the body, left-handed or both-handed, and the presence of any neurological conditions or radiological problem.

As a result, one hundred and twenty-six older adults went through both neuropsychological tests and MRI scanning. Three were excluded because they failed to complete a few neuropsychological tests due to illiteracy. One failed to complete MRI scanning because of claustrophobia. Five were excluded because of neurological conditions. The remaining 117 individuals (70 females and 47 males) were included in the data analysis. Mean age was 71.96 (SD = 6.761) and mean years of education was 7.34 (SD = 4.305). All participants were given with the informed consent regarding the nature and possible risks of the study. After the completion of neuropsychological test and MRI scanning, financial remuneration was provided for their participation at the end of the session. This study was reviewed and approved by the Institutional Review Board (IRB) of the Seoul National University.

## 2. Cognitive Reserve

A composite measure of cognitive reserve was calculated based on participants' years of education and premorbid intelligence measured with the vocabulary test of Korean Wechsler Adult Intelligence Scale-IV (K-WAIS-IV; Wechsler, 2008; Hwang, Kim, Park, Chey, & Hong, 2012). Years of education has been known as a cognitive reserve proxy variable that best explains the individual differences in cognitive function in elders (Opdebeeck, Martyr, & Clare, 2016). The vocabulary test of K-WAIS-IV reflects life-time intellectual experiences that cannot be measured with years of education (Hwang, Kim, Park, Chey, & Hong, 2012). Principle Component Analysis was performed to calculate the composite score of these two proxy variables.

## 3. Neuropsychological Assessment

Subtests of Elderly Memory Disorder Scale (EMS; Chey, 2007) were used to assess the performance in memory, attention, and working memory.

*Verbal Episodic Memory*

Elderly Verbal Learning Test (EVLT) was used to measure verbal episodic memory. It basically follows the paradigm of California Verbal Learning Test with nine words as stimulus (Chey,

Na, Tae, Ryoo, & Hong, 2006). Participants learn nine words for each trial that can be classified into either furniture, animal, or fruit category. It is composed of 5 different subtests, which include five trials of immediate recall using the original word list, one trial of immediate recall with an interference word list, short free and cued recall with the original word list, delayed free and cued recall with the original word list after 15 to 30 minutes, and a recognition test that asks to identify rather a given word was in the original word list or not. For the analysis, scores for short free recall, delayed free recall, and recognition were used to represent verbal episodic memory.

*Attention and Working Memory*

For attention and working memory, digit span and symbol span test were administered. There are two different conditions in each test: forward and backward.

In digit span test, participants are asked to repeat back the list of numbers in correct order immediately, either forward or backward. In symbol span test, they have to tap the corsi-block in the same order the examiner tapped, either forward or backward.

Forward condition measures attention and backward condition measures working memory. For this study, the sum of the longest correct forward digit span and Corsi-block tapping were used to measure attention. On the other hand, the longest correct backward

scores were used to measure working memory (Song & Chey, 2006).

*Executive Function*

Category fluency test (Kang, Jang, & Na, 2012), Stroop test (Golden & Freshwater, 1978; Kang, Jang, & Na, 2012), and Trail Making Test (TMT; Park & Chey, 2003) were used to assess executive function. In category fluency test, participants are asked to produce words from a given category within a minute, as quickly as possible. In this study, the results from two categories were used: supermarket and animal.

In Stroop test, two different tasks are performed. In word condition, individuals are asked to read the written letters of the colored words as quickly as possible. In color condition, they are required to name the ink color of the colored words as quickly as possible. The performance of this condition requires individuals to overcome a mismatch between ink color and word. A Stroop interference index was calculated by subtracting the number of correct trials from the word condition to the color condition (Word condition – color condition) and was used to measure executive function.

Trail Making Test (TMT) is composed of three forms: TMTa, TMTb, and TMTc. In TMTa, targets are numbers in a circle randomly distributed along the sheet. Participants are asked to connect them in sequential order as quickly as possible. In TMTb, targets are

randomly distributed triangles and squares. Participants are asked to connect them in turn as quickly as possible. Finally, in TMTc, targets are both numbers and shapes. In this form, participants are asked to alternate between numbers and shapes, with numbers in sequential order and shapes in turn as practiced from TMTa and TMTb. TMTa and TMTb are usually used to measure processing speed and TMTc is used to measure the ability to flexibly react on altering rules. A TMT interference index was calculated by subtracting the completion time of TMTc to TMTa and was used to measure executive function.

*Vocabulary (Premorbid IQ)*

To measure premorbid IQ, the vocabulary test of K-WAIS-IV was used. This assessment requires participants to explain the meaning of a given vocabulary. The vocabulary word list is composed of both specific and abstract words. If the participant successfully explains the core meaning of the vocabulary, they earn 2 points. If the explanation is insufficient or does not include the core meaning, they earn 1 point. For all others, they earn 0 point. Vocabulary test is known to reflect the cultural and educational experience an individual had throughout the lifetime. Furthermore, it is one of the least influenced neuropsychological tests by aging or neuropathology (Hwang, Kim, Park, Chey, & Hong, 2012). Therefore, the vocabulary test is often used as a proxy for premorbid IQ. The score of this test was used as

one of the cognitive reserve proxies in this analysis.

**4. MRI Data Acquisition**

MRI imaging was conducted using a 3.0 Telsa MRI scanner (Magnetom TrioTim, Siemens, Erlangen, Germany), with a 12 channel head coil. To attenuate the scanner noise, participants were provided with ear plugs. Using a head coil, their heads were fixed and an additional foam pad was placed in between head coil and subjects' heads to minimize the head motion. A single-shot echo planar diffusion data acquisition was performed using the following parameter: 76 slices, one b = 0 s/mm$^2$ volume, b = 1000 s/mm$^2$ for 64 directions, TE = 93 ms, TR = 9,000 ms, FOV = 224 mm x 224 mm, Flip Angle = 90 $^\circ$, voxel size = 2mm x 2mm x 2mm.

**5. Data Analysis**

*Preprocessing*

The diffusion data were processed with the FSL software package (http://www.fmrib.ox.ac.uk/fsl). The procedure included brain-tissue extraction and eddy currents and motion correction. First, automatic segmentation of brain and non-brain tissue was applied to obtain brain mask without non-brain tissue. Next, the diffusion weighted images were aligned to the b0 image to correct for eddy current distortions and head motion on DTI sequences. This step

corrects for stretches and shears in the diffusion weighted images induced from eddy currents in the gradient coils. After these steps, a diffusion tensor model was fitted at each voxel and fractional anisotropy (FA) maps were generated for each subject

*Tract-Based Spatial Statistics*

Once the preprocessing is done, tract-based spatial statistics (TBSS; Smith et al., 2006) was employed. TBSS enables voxel-wise analysis of FA data and has its strength in aligning FA images from multiple subjects. First, each subject's FA image was non-linearly registered to the 1 mm x 1 mm x 1 mm FMRIB58_FA standard-space image as the target image. Next the target image was affine transformed to the 1 mm x 1 mm x 1 mm MNI space (Montreal Neurologic Institute, Montreal, Canada). Then, mean FA image was created by averaging aligned individual FA images with a threshold of 0.2. Finally, the FA image was thinned to create a mean FA skeleton.

**6. Statistical Analysis**

To test the hypothesis that high cognitive reserve is associated with higher brain fractional anisotropy, a multiple linear regression model was applied, controlling for age and sex. The "randomise" tool in FSL was used to build the null distribution (FMRIB, University of

Oxford, UK) and 5000 permutations of the data. The associations were considered significant at $p<0.05$, Family Wise Error (FWE) corrected. Clusters with statistically significant associations were found using the Threshold-Free Cluster Enhancement method (Smith & Nichols, 2009). The voxels that showed the significant correlations of FA with the cognitive reserve composite score in the voxel-wise analysis were extracted using FSL's Cluster tool. For anatomical labelling of these clusters, FSL Atlas Query (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlasquery) was used. FA values of each cluster were extracted for further analysis.

In the next stage, the relationship between FA of a cluster and cognition was tested. Partial correlation between the FA value of each cluster and neuropsychological assessments was examined using SPSS, version 23, controlling for age and sex. Finally, the mediation analysis was conducted to test whether the relationship between cognitive reserve (X; independent variable) and cognition (Y; dependent variable) is mediated by FA of each cluster (M; Mediator). Process macro for SPSS (v3.1; http://www.processmacro.org/index.html) was used for the analysis, controlling for age and sex. The conditions for testing the mediation are as follows. First, the relationship between X and Y should be significant in a simple regression model. Second, the correlation between M and X should be significant. Third, the correlation between M and Y should be significant. Lastly, the effect

of X on Y should be significantly reduced once M is added to the model.

Since the correlations between X and Y, M and X, and M and Y were analyzed in previous statistical analysis, the mediation model could be tested using Process macro for SPSS. In the case of generating bootstrap confidence intervals for the indirect effect, 5,000 bootstrap samples were used.

# RESULTS

## Estimation of cognitive reserve composite score

Cognitive reserve composite score was estimated through a principal component analysis of two cognitive reserve proxies, education and vocabulary score of K-WAIS-IV. One component was extracted and total variance explained was 84.437%. In other word, cognitive reserve composite score accounts for 84.437% of the variability in education and vocabulary score of K-WAIS-IV.

## Demographics and cognitive reserve

The correlation analysis was performed to examine the relationship between basic demographics and cognitive reserve composite score (Table 3). Greater age was associated with higher cognitive reserve composite score ($r=-.205$, $p=.026$). In addition, males tended to have higher cognitive reserve composite score than females ($r=.319$, $p<.001$). No significant relationship was observed between age and sex ($r=.101$, $p=.278$).

## Demographics, cognitive reserve and cognition

The influence of age, sex, and cognitive reserve on cognition was examined with correlation analysis (Table 1). Age was associated with lower performance on short free recall ($r=-.257$, $p=0.005$),

delayed free recall (r=-.261, p=.004), and recognition (r=-.301, p=0.001) tests of elderly verbal learning test, which measures verbal episodic memory function. Also, greater age predicted lower executive functioning. It had significant negative relationship with animal fluency (r=-.290, p=0.002), store fluency (r=-.347, p<.001), trail making test (r=.427, p<.001), and stroop test (r=.246, p=.008).

Sex was associated mainly with lower performance on attention and working memory tests. Being male predicted greater performance on digit span forward (r=.359, p<.001), digit span backward (r=.188, p=.042), symbol span forward (r=.206, p=026), and symbol span backward (r=.388, p<.001). Other relationships observed included delayed free of EVLT (r=-.237, p=.010) and store fluency (r=-.200, p=.031). The results of these two tests were better in females than males.

Higher cognitive reserve predicted better performance on every 11 neuropsychological tests (p<.001). These relationships were significant for all the tests even after controlling for age and sex (p<001). In other words, cognitive reserve was associated with all 4 cognitive domains examined in this study, which are verbal episodic memory, attention, working memory, and executive function.

Table 1. Correlations between age, sex, cognitive reserve and cognition

| | Age | Sex | CR | CR(partial)[a] |
|---|---|---|---|---|
| EVLT Short Free | **-.257**** | -.171 | **.273**** | **.277**** |
| EVLT Delayed Free | **-.261**** | **-.237*** | **.264**** | **.298**** |
| EVLT Recognition | **-.301**** | -.090 | **.241**** | **.203*** |
| Digit Span Forward | -.150 | **.359**** | **.668**** | **.600**** |
| Digit Span Backward | -.138 | **.188*** | **.511**** | **.462**** |
| Symbol Span Forward | -.036 | **.206*** | **.309**** | **.258**** |
| Symbol Span Backward | -.136 | **.388**** | **.431**** | **.300**** |
| Animal Fluency | **-.290**** | .151 | **.429**** | **.374**** |
| Store Fluency | **-.347**** | **-.200*** | **.366**** | **.404**** |
| Trail Making Test | **.427**** | -.083 | **-.309**** | **-.231*** |
| Stroop Test | **-.246**** | .174 | **.458**** | **.390**** |

Note. *p<.05, **p<.01. [a]Age, sex controlled partial correlation

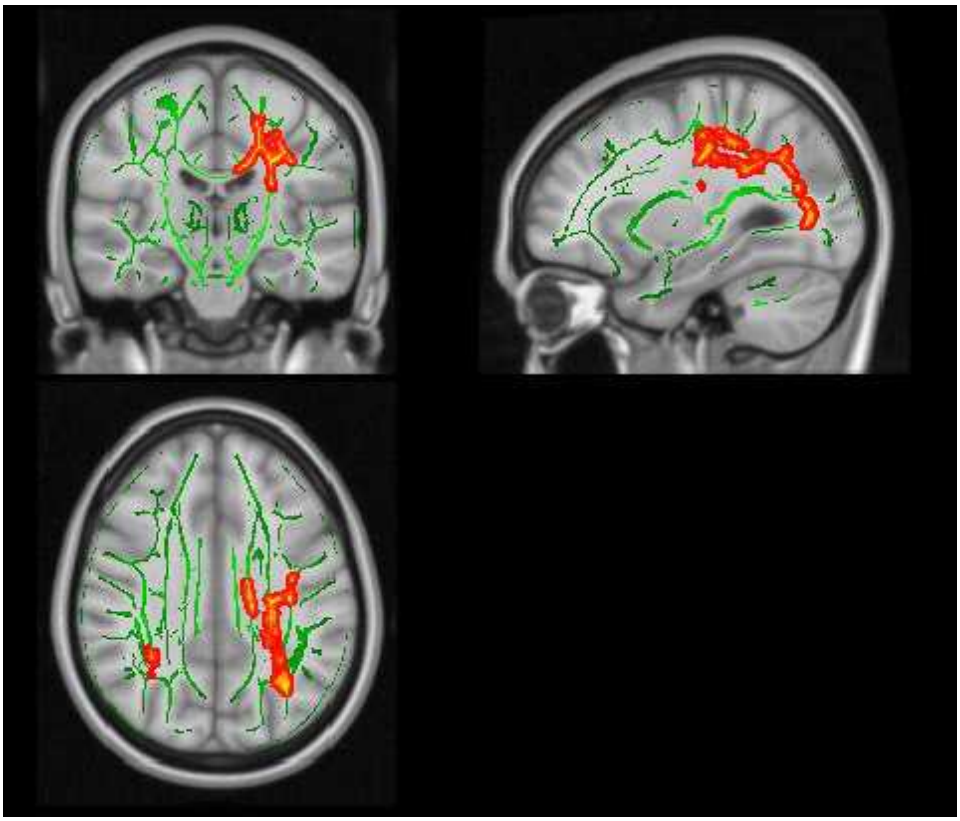
EVLT = Elderly Verbal Learning Test; CR = Cognitive Reserve Composite Score;

**Cognitive reserve and fractional anisotropy**

To examine whether cognitive reserve is associated with higher FA in the brain, a general linear model was created with FA as dependent variable and cognitive reserve as independent variable, controlling for age and sex. In a positive contrast between FA and cognitive reserve, where corrections were applied for multiple comparisons across the brain, three clusters were identified and labelled based on the Johns Hopkins University White-Matter Tractography Atlas (Table 2). The largest cluster comprised of left corticospinal tract, left superior longitudinal fasciculus, and temporal

part of left superior longitudinal fasciculus. The second, smaller cluster was identified as left superior longitudinal fasciculus and the last, smallest cluster was identified mainly as forceps major, while left inferior fronto-occipital fasciculus and left inferior longitudinal fasciculus were also included. No regions were identified to have significant negative association with CR.

Figure 1. Regions showing association between FA and CR



Note. Regions of the white matter skeleton in which higher CR was related to higher FA, controlling for age and sex, are shown in red ($p<0.05$, corrected for multiple comparison)
Green color = white matter skeleton

Table 2. Probabilistic labels for clusters associated with higher CR

| Cluster | JHU Labels | Hemi (L/R) | Cluster size (voxels) |
|---|---|---|---|
| Cluster 1 | Cortico-spinal tract | L | 1606 |
| Cluster 2 | Superior longitudinal fasciculus | L | 290 |
| Cluster 3 | Forceps Major | - | 268 |

Note. Anatomical labels taken from Johns Hopkins University White-Matter Tractography Atlas.

Labels are only reported from regions which survived multiple correction at the voxel level

Furthermore, correlations between demographics, cognitive reserve, and three identified clusters were examined (Table 3). Age was associated with lower FA in all three clusters ($p<.005$). Being female was associated with higher FA in cluster 2 but not with cluster 1 or cluster 3. As these clusters were identified based on the positive correlation with cognitive reserve composite score, all clusters had significant associations with cognitive reserve. In addition, around .5 to .6 positive correlations were found between clusters ($p<.001$).

Table 3. Correlations between age, sex, cognitive reserve and FA clusters

| | Age | Sex | CR | Cluster 1 FA | Cluster 2 FA | Cluster 3 FA |
|---|---|---|---|---|---|---|
| Age | 1.000 | .101 | **-.205*** | **-.285**** | **-.322**** | **-.407**** |
| Sex | .101 | 1.000 | **.319**** | -.105 | **-.250**** | -.145 |
| CR | **-.205*** | **.319**** | 1.000 | **.401**** | **.376**** | **.306**** |
| Cluster 1 FA | **-.285**** | -.105 | **.401**** | 1.000 | **.570**** | **.580**** |
| Cluster 2 FA | **-.322**** | **-.250**** | **.376**** | **.570**** | 1.000 | **.565**** |
| Cluster 3 FA | **-.407**** | -.145 | **.306**** | **.580**** | **.565**** | 1.000 |

Note. *p<.05, **p<.01.

EVLT = Elderly Verbal Learning Test; CR = Cognitive Reserve Composite Score; FA = Fractional Anisotropy

**Fractional anisotropy and cognition**

The relationships between FA of identified clusters and cognition were examined through partial correlation analysis, controlling for age and sex. Cluster 1 FA showed positive associations with digit span forward (r=.381, p<.001), digit span backward (r=.255, p=.007), symbol span backward (r=.317, p=.001), animal fluency (r=.309, p=.001), and store fluency (r=.423, p<.001), which belong to cognitive domains of attention, working memory, and executive function. Higher cluster 2 FA predicted better performance on digit span forward (r=.217, p=.021), symbol span backward (r=.229,

p=.015), animal fluency (r=.296, p=.002), store fluency (r=.386, p<.001), and stroop test (r=.221, p=.019). These neurocognitive tests belong to the same cognitive domains as results from cluster 1 FA. Cluster 3 had significant positive relationships with delayed free of EVLT (r=.190, p=.045), digit span forward (r=.236, p=.012), and store fluency (r=.336, p<.001). The cognitive domains include verbal episodic memory, attention, and executive function.

Table 4. Partial correlation between cluster FA and cognition, controlling for age and sex

| | Cluster 1 FA | Cluster 2 FA | Cluster 3 FA |
|---|---|---|---|
| EVLT Short Free | .160 | .145 | .132 |
| EVLT Delayed Free | .095 | .122 | **.190*** |
| EVLT Recognition | -.105 | -.030 | .011 |
| Digit Span Forward | **.381**** | **.217*** | **.236*** |
| Digit Span Backward | **.255**** | .176 | .124 |
| Symbol Span Forward | .017 | .047 | .042 |
| Symbol Span Backward | **.317**** | **.229*** | .169 |
| Animal Fluency | **.309**** | **.296**** | .095 |
| Store Fluency | **.423**** | **.386**** | **.336**** |
| Trail Making Test | -.114 | .022 | -.138 |
| Stroop Test | .168 | **.221*** | .097 |

Note. *p<.05, **p<.01.

EVLT = Elderly Verbal Learning Test; FA = Fractional Anisotropy

**Cognitive reserve, cognition, and fractional anisotropy**

To test the hypothesis that FA partially mediates the association of cognitive reserve with cognition, the mediation model was tested (Figure 2). Since correlation analysis was already completed, only cognitive functions and clusters that showed significant correlations with each other were tested (Table 4). Of all, five mediation models were found to be statistically significant.

The results indicated that when controlling for cluster 1 FA and covarying age and sex, the path coefficients of the relationship between cognitive reserve and digit span forward, symbol span backward, and store fluency were reduced, where for cluster 2 and 3 FA, only the association with store fluency was reduced (Table 5; Figure 2).

Table 5. The effect of FA clusters in the relationship between CR and cognition

(a) A model with cluster 1 FA as a mediator and digit span forward as a dependent variable

| Path | Coefficient | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| Total effect (c) | 1.3159 | <0.0001** | .9940 | 1.6377 |
| Direct effect (c') | 1.1588 | <0.0001** | .8093 | 1.5082 |
| a | .0128 | <0.0001** | .0076 | .0179 |
| b | 12.3057 | 0.0364* | 0.7904 | 23.8209 |
| Indirect effect | | | | |
| ab | .1571 | - | .0092 | .3296 |

Note. *p<.05, **p<.01; Bootstrapped with 5,000 samples.

a, b, c, c', and ab are path coefficients (unstandardized regression coefficients): path a (X -> M), path b (M ->Y), path c (total effect; direct + indirect; X -> Y), path c' (direct effect; X -> Y), and path ab (indirect effect; X -> M -> Y) respectively.

(b) A model with cluster 1 FA as a mediator and symbol span backward as a dependent variable

| Path | Coefficient | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| Total effect (c) | .5755 | 0.0005** | .2575 | .8935 |
| Direct effect (c') | .3813 | 0.0289* | .0399 | .7226 |
| a | .0128 | <0.0001** | .0076 | .0179 |
| b | 15.2759 | .0085** | 3.9669 | 26.4648 |
| Indirect effect | | | | |
| ab | .1942 | - | .0403 | .3721 |

Note. *p<.05, **p<.01; Bootstrapped with 5,000 samples.

a, b, c, c', and ab are path coefficients (unstandardized regression coefficients): path a (X -> M), path b (M ->Y), path c (total effect; direct + indirect; X -> Y), path c' (direct effect; X -> Y), and path ab (indirect effect; X -> M -> Y) respectively.

(c) A model with cluster 1 FA as a mediator and store fluency as a dependent variable

| Path | Coefficient | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| Total effect (c) | 2.6254 | <0.0001** | 1.5519 | 3.699 |
| Direct effect (c') | 1.8012 | 0.0021** | .6704 | 2.9319 |
| a | .0128 | <0.0001** | .0076 | .0179 |
| b | 64.5660 | .0008** | 27.3050 | 101.827 |
| Indirect effect | | | | |
| ab | .8243 | - | .3048 | 1.4395 |

Note. *p<.05, **p<.01; Bootstrapped with 5,000 samples.

a, b, c, c', and ab are path coefficients (unstandardized regression coefficients): path a (X -> M), path b (M ->Y), path c (total effect; direct + indirect; X -> Y), path c' (direct effect; X -> Y), and path ab (indirect effect; X -> M -> Y) respectively.

(d) A model with cluster 2 FA as a mediator and store fluency as a dependent variable

| Path | Coefficient | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| Total effect (c) | 2.6254 | <0.0001** | 1.5519 | 3.699 |
| Direct effect (c') | 1.887 | 0.0018** | .7148 | 3.0592 |
| a | .0176 | <0.0001** | .0112 | .0240 |
| b | 42.0189 | .0071** | 11.6772 | 72.3606 |
| Indirect effect | | | | |
| ab | .7385 | - | .2884 | 1.2601 |

Note. *p<.05, **p<.01; Bootstrapped with 5,000 samples.

a, b, c, c', and ab are path coefficients (unstandardized regression coefficients): path a (X -> M), path b (M ->Y), path c (total effect; direct + indirect; X -> Y), path c' (direct effect; X -> Y), and path ab (indirect effect; X -> M -> Y) respectively.

(e) A model with cluster 3 FA as a mediator and store fluency as a dependent variable

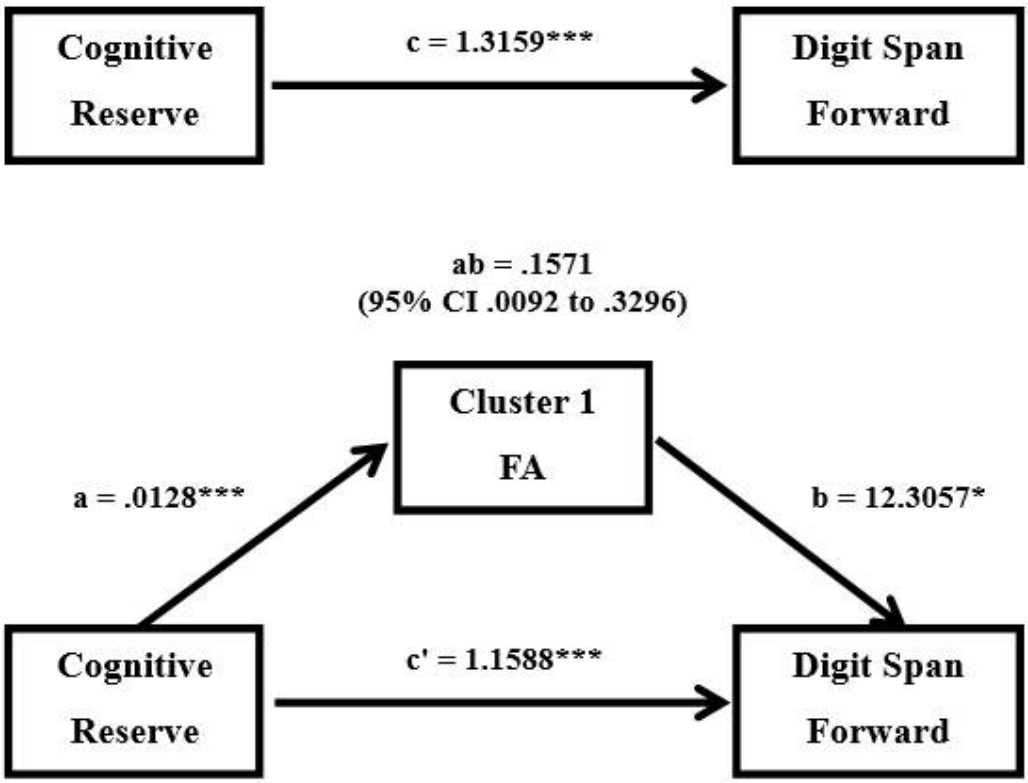
| Path | Coefficient | p-value | 95% Confidence Interval | |
|---|---|---|---|---|
| Total effect (c) | 2.6254 | <0.0001** | 1.5519 | 3.699 |
| Direct effect (c') | 2.1782 | 0.0002** | 1.0761 | 3.2803 |
| a | .0141 | 0.0007** | .0060 | .0221 |
| b | 31.7769 | .0109* | 7.4521 | 56.1018 |
| Indirect effect | | | | |
| ab | .4473 | - | .0954 | .9250 |

Note. Bootstrapped with 5,000 samples

a, b, c, c', and ab are path coefficients (unstandardized regression coefficients): path a (X -> M), path b (M ->Y), path c (total effect; direct + indirect; X -> Y), path c' (direct effect; X -> Y), and path ab (indirect effect; X -> M -> Y) respectively.

Figure 2. Summary coefficients for mediation model

(a) A model with cluster 1 FA as a mediator and digit span forward as a dependent variable

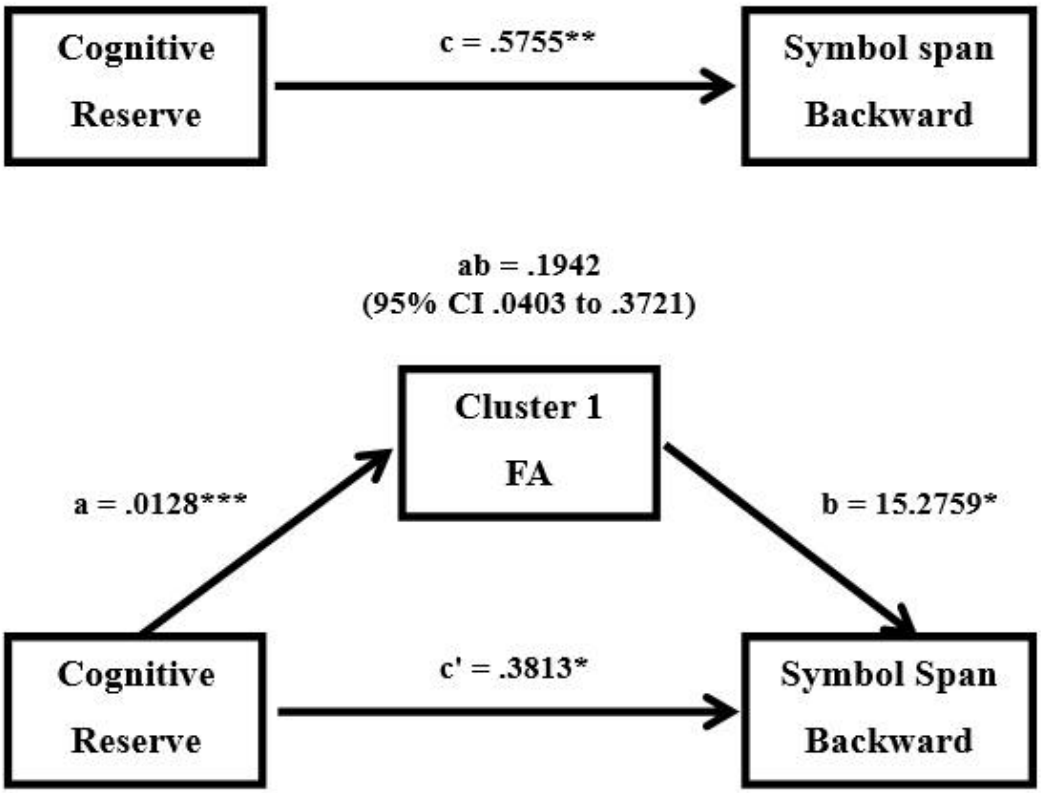



Note. *p<.05, **p<.01, ***p<0.0001

FA = fractional anisotropy; CI = confidence interval

A top model represents cognitive reserve predicting digit span forward without considering mediation effect. A bottom model represents an indirect model considering mediation effect.

(b) A model with cluster 1 FA as a mediator and symbol span backward as a dependent variable

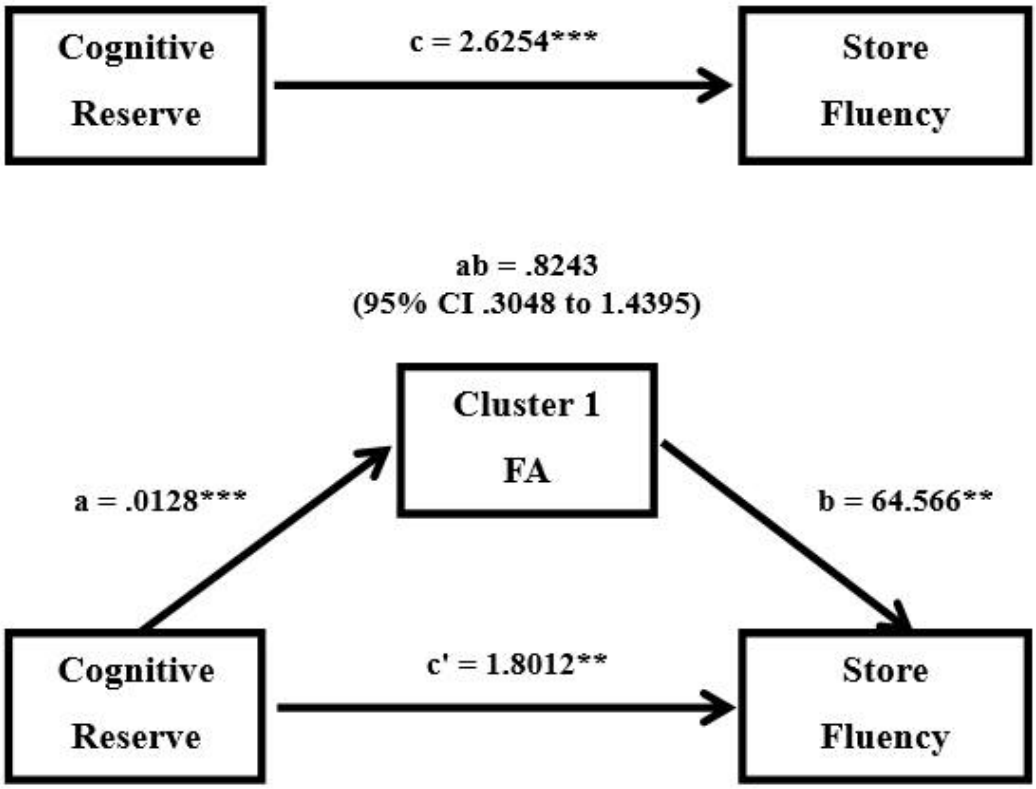



Note. *p<.05, **p<.01, ***p<0.0001

FA = fractional anisotropy; CI = confidence interval

A top model represents cognitive reserve predicting symbol span backward without considering mediation effect. A bottom model represents an indirect model considering mediation effect.

(c) A model with cluster 1 FA as a mediator and store fluency as a dependent variable

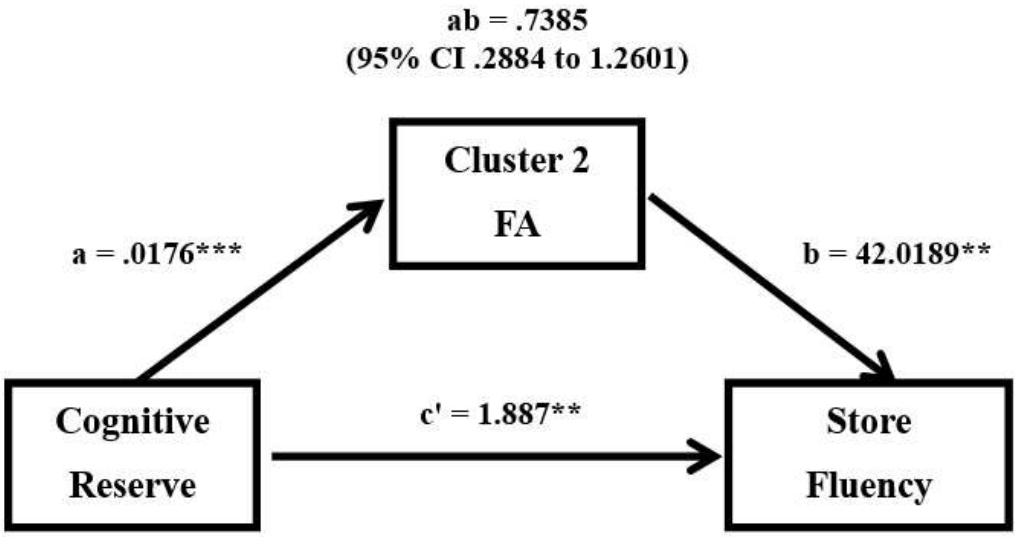



Note. *p<.05, **p<.01, ***p<0.0001

FA = fractional anisotropy; CI = confidence interval

A top model represents cognitive reserve predicting store fluency without considering mediation effect. A bottom model represents an indirect model considering mediation effect.

(d) A model with cluster 2 FA as a mediator and store fluency as a dependent variable

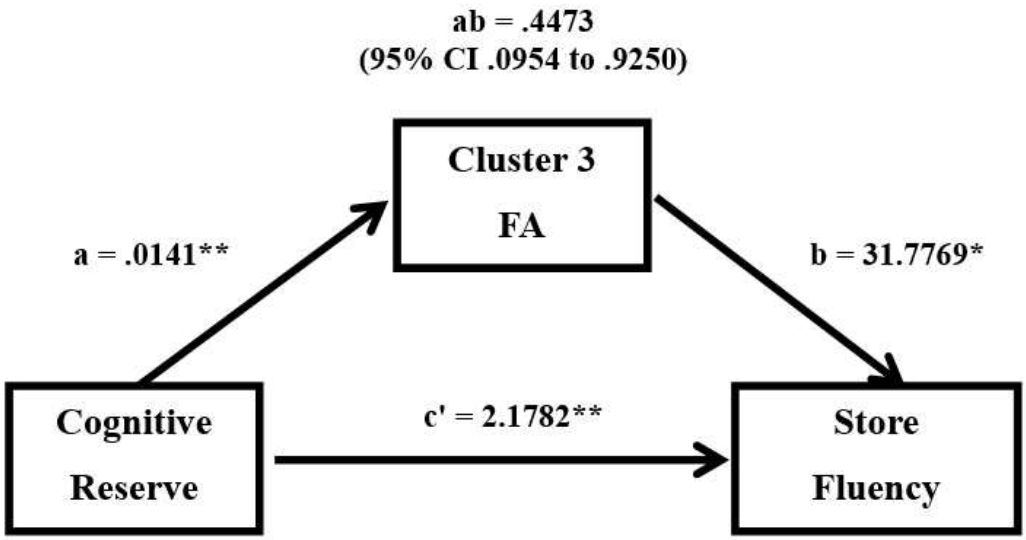



Note. *p<.05, **p<.01, ***p<0.0001

FA = fractional anisotropy; CI = confidence interval

A model represents cognitive reserve predicting store fluency considering mediation effect.

(e) A model with cluster 3 FA as a mediator and store fluency as a dependent variable




Note. *p<.05, **p<.01, ***p<0.0001

FA = fractional anisotropy; CI = confidence interval

A model represents cognitive reserve predicting store fluency considering mediation effect.

# Discussion

The main purpose of this study was to explore the microstructural white matter correlates of cognitive reserve and how they relate to cognitive function. The major findings were that higher cognitive reserve was associated with higher FA in the left corticospinal tract, left superior longitudinal fasciculus, and forceps major. Furthermore, FA clusters of each tract partially mediated the association of cognitive reserve with cognition.

**Neural Reserve**

The cognitive reserve proxy estimated by education and premorbid IQ showed significant positive relationships with every eleven neuropsychological tests from four different cognitive domains of verbal episodic memory, attention, working memory, and executive function even after controlling for age and sex. This result is supported by cognitive reserve hypothesis, where individuals with high cognitive reserve can maintain cognitive functions in late life (Stern, 2009). Furthermore, only positive associations between FA and cognitive reserve proxy were observed, which goes along with the general trend of structural correlates studies (Batres-Faz & Arenaza-Urquito, 2011) and previous research using FA (Teipel et al., 2009; Arfanakis et al., 2016).

The remarkable, novel finding of the present study is that FA partially mediated the association between cognitive reserve proxy and cognition. This suggests that FA supports the link between cognitive reserve proxy and cognition. Based on the results, it can be interpreted that more integrated microstructural white matter is one of the components of neural reserve that allows healthy older adults with more lifetime intellectual experience to maintain cognitive functioning. Thus, intellectually enriching experience throughout the lifetime may enhance white matter integrity, increasing capacity and efficiency of cognitive strategies and brain networks, which in turn, allowing for the maintenance of cognitive performance (Steffener & Stern, 2012).

While interpreting FA as white matter integrity has been natural in the field, the uncertainty of what the index actually reflects has to be noted. FA is a normalized measure that reflects multiple tissue properties including the axonal orientation within the voxel, the myelination, the packing density, permeability of the cell membrane, and isotropic partial volume effects (Jones, Knosche, & Tumer, 2013). Therefore, changes in FA might reflect any one of or all of the above factors so that interpretation should be done in cautious. In such consideration, recent research studies suggested that brain plasticity in a tissue level, including synaptogenesis, axonal sprouting, and myelination, may be detectable by FA (Blumenfeld-Katzir, Pastemak, Dagan, & Assaf, 2011; Markham & Greenough, 2004; Sagi

et al., 2012). The concept of neural reserve itself is also closely related to brain plasticity (Mahncke, Bronstone, & Merzenich, 2006). Thus, the results of this study may be reflecting plasticity in brain tissue induced by intellectually stimulating experience throughout the lifetime. Studying white matter in deeper level through advanced imaging techniques (e.g. myelin imaging) would provide further insight into the interpretation.

**Tracts within each cluster**

The tracts in each cluster identified as microstructural white matter correlates of cognitive reserve in this study have previously known associations with cognitive function. In cluster 1, three different tracts were included: left corticospinal tract (CST), which has projection to primary motor cortex (Wakana, 2004) and association with processing speed (Duering et al., 2011), left superior longitudinal fasciculus (SLF), involved in visual space perception and attention (Makris et al., 2005), and left temporal part of SLF, engaged in articulation of language (Makris et al., 2005). Cluster 2 included additional voxels from SLF. The voxels of cluster 1 and cluster 2 were closely located to each other. Finally, cluster 3 included forceps major, which participates in the maintenance of verbal stimuli (Van der Ham, Raemaekers, Van Wezel, Oleksiak, & Postma, 2009), left inferior fronto-occipital fasciculus (IFOF) that is important in reading,

attention, and visual processing (Catani & Thiebaut de Schotten, 2008), and left inferior longitudinal fasciculus (ILF), which has been linked to visual perception, visual memory, and language-related functions (Catani & Thiebaut de Schotten, 2008). The investigation of the relationship between identified clusters and cognitive functions revealed that FA of each cluster has positive correlations with different cognitive domains, which goes along with previous research (Arfanakis et al., 2016). However, any further interpretation will have to be done in cautious because this study did not include FA of the full tract but only the clusters. Therefore, repeating the study using apriori regions of interests (ROI) defined by deterministic or probabilistic tractography would be needed for an accurate inference. Nevertheless, overall results suggest that engagement in intellectual activities throughout the lifetime enhance the structural integrity of brain, strengthening cognitive systems in multiple cognitive domains.

Furthermore, although the availability of only one study limits strong reasoning, it is notable that left SLF has been identified as neural reserve. Arfanakis and colleagues (2016) have previously identified left SLF as neural reserve through similar statistical analysis of this study. The difference is that their study used participation in late-life cognitive activities as a proxy variable for cognitive variable, while education and premorbid IQ were used in this study. Cognitive reserve proxy variables are known to have both independent and

overlapping roles to each other (Siedlecki et al., 2009). Therefore, such identification of the same tract using different proxy variables provides support on interpreting the tract as neural mechanism of cognitive reserve, neural reserve. However, more research would have to be repeated to make a stronger inference.

**Limitations and Future Considerations**

Several limitations exist in this study. First, there is a few months of gap between data collection of neuropsychological tests and MRI scanning. Since the analysis of the present study was conducted in cross-sectional design, such time interval was not considered. Conducting the study in longitudinal design or performing neuropsychological tests and brain imaging at the same period of time would be needed.

Second limitation is in the characteristics of samples. The samples of this study are all from the same cohort in the common township in Korea. Therefore, the results may not be generalizable to residents in the city or those with different social and cultural background. In addition, there is a danger that samples might be biased because the absence of Alzheimer's disease pathology has not been directly confirmed. Previous studies have reported that amyloid-free older adults and those who are not amyloid-free exhibit difference in the structure and function of the brain (Hedden et al.,

2009) and in the resistance toward dementia pathology (Ewers et al., 2013). Therefore, some individuals in the samples might be in a preclinical stage, which can bias the results. Screening amyloid-free elders would enhance the validity of the results in the future study.

Third, because FA of the tracts were clusters, regional interpretation of white matter tracts are limited. As noted above, repeating the study using apriori region of interests (ROI) would provide more accurate results. Furthermore, using different DTI index than FA would lead to the deeper understanding of the microstructural white matter correlates of cognitive reserve.

Finally, although two different proxy variables were used to estimate cognitive reserve, they cannot perfectly represent cognitive reserve. Proxy variables have shared variances that are likely to be characteristics of cognitive reserve (Siedlecki et al., 2009). However, such variances also include external factors such as socioeconomic status. Therefore, repeating the analysis using other proxy variables such as occupational characteristic, would be recommended to establish reliability. In addition, recently, a residual method of estimating cognitive reserve is receiving a great deal of attention (Habeck et al, 2017; Marques et al., 2016; Reed et al., 2010; Zahodne et al., 2013). A residual cognitive reserve is defined as a statistical discrepancy between brain pathology and cognitive impairment. It is measured by statistically decomposing the variance

of cognitive measure using brain measures and sometimes demographics. Repeating the study design with the residual method is likely to provide additional insights into the neural mechanisms of cognitive reserve.

Nevertheless, this study was the first study to explore the microstructural white matter correlates of cognitive reserve through TBSS method, using years of education and premorbid IQ. It has implications in enhancing the understanding of how intellectual experiences throughout the life-time can contribute on preserving cognitive performance to the late-life via the more integrated white matter fibers. Future works will have to be done using different DTI index and cognitive reserve proxy variables. Studying the neural mechanisms of cognitive reserve would provide insights on how individuals with high cognitive reserve can counter the late-life neuropathological burden through neural reserve, which can ultimately contribute on exploring the keys to delay cognitive decline due to aging and dementia.

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# 국문 초록

# 인지 예비능의 미세 백질 구조적 기전

노년기 인지 감퇴에 대한 인지 예비능의 보호 효과는 선행 연구들에서 반복적으로 보고되었다. 하지만, 그 기저에 어떠한 신경학적 매커니즘이 있는 가에 대하여는 알려진 바가 적다. 본 연구에서는 117명의 정상 노인들을 대상으로 인지 예비능의 미세 백질 구조적 기전을 탐색하고 이 기전이 인지 예비능과 인지 기능 간의 관계를 매개하는 역할을 하는 지에 대하여 검증하였다. 참가자들은 신경심리검사들과 MRI 촬영을 완료하였고, 백질 구조의 분할 이등방성 지표와 교육과 병전 지능으로 추정된 인지 예비능 대리지표의 관계를 분석하기 위해 경로 기반 공간 패턴 분석(TBSS; Tract-based spatial statistics)을 사용하였다. 그 결과, 통계적으로 유의한 상관을 보이는 3개의 군집이 확인되었다. 이 중, 좌측 피질척수로, 좌측 위세로다발, 좌측 위세로다발의 측두 부분을 포함하는 군집의 분할 이등방성이 인지 예비능과 인지 기능 간의 관계를 부분적으로 매개하는 것으로 나타났다. 본 연구 결과는 생애에 걸친 지적인 경험들이 백질 통합성을 통해 노년기 인지 기능을 유지하는 것에 기여한다는 것을 시사한다.

**주요어 : 인지 예비능, 신경적 예비능, 미세 백질 통합성, 신경병리, 노년기 인지 기능, 매개 분석**
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