Associations of cognitive reserve and psychological resilience with cognitive functioning in subjects with cerebral white matter hyperintensities

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Abstract

Background and purpose: Cerebral small vessel disease is characterized by progressive white matter hyperintensities (WMH) and cognitive decline. However, variability exists in how individuals maintain cognitive capabilities despite significant neuropathology. The relationships between individual cognitive reserve, psychological resilience and cognitive functioning were examined in subjects with varying degrees of WMH.

Methods: In the Helsinki Small Vessel Disease Study, 152 subjects (aged 65–75 years) underwent a comprehensive neuropsychological assessment, evaluation of subjective cognitive complaints and brain magnetic resonance imaging with volumetric WMH evaluation. Cognitive reserve was determined by education (years) and the modified Cognitive Reserve Scale (mCRS). Psychological resilience was evaluated with the Resilience Scale 14.

Results: The mCRS total score correlated significantly with years of education ($r = 0.23$, $p < 0.01$), but it was not related to age, sex or WMH volume. Together, mCRS score and education were associated with performance in a wide range of cognitive domains including processing speed, executive functions, working memory, verbal memory, visuospatial perception and verbal reasoning. Independently of education, the mCRS score had incremental predictive value on delayed verbal recall and subjective cognitive complaints. Psychological resilience was not significantly related to age, education, sex, WMH severity or cognitive test scores, but it was associated with subjective cognitive complaints.

Conclusions: Cognitive reserve has strong and consistent associations with cognitive functioning in subjects with WMH. Education is widely associated with objective cognitive functioning, whereas lifetime engagement in cognitively stimulating leisure activities (mCRS) has independent predictive value on memory performance and subjective cognitive complaints. Psychological resilience is strongly associated with subjective, but not objective, cognitive functioning.
INTRODUCTION

Cerebral small vessel disease (SVD) is the most common cause of vascular cognitive impairment and a major burden on global healthcare [1]. The key neuroimaging findings in SVD are white matter hyperintensities (WMH) along with lacunar infarcts, microbleeds and brain atrophy [2]. Although the aforementioned changes can stay symptomless for years, they affect brain areas and networks that are critical for cognitive functioning [3]. The cognitive profile of SVD is characterized by impairment in executive functions and processing speed, whereas memory stays relatively intact [4,5]. There is evidence, however, to suggest a more global and complex relationship between SVD brain changes and cognitive functioning highlighting the need for a comprehensive cognitive assessment [6,7].

Paradoxically, there is high individual variability in cognitive functioning despite substantial brain pathology [8,9] suggesting a need to examine individual factors that might protect from cognitive decline such as cognitive reserve and psychological resilience. According to the cognitive reserve hypothesis, active and varied engagement in cognitively stimulating activities across lifetime leads to more cognitive resources, which in turn results in less cognitive impairment despite significant brain pathology [10,11]. Higher cognitive reserve, measured with education and occupation as proxies, has been identified as a potential protective factor for cognitive decline in SVD despite brain imaging findings [12,13]. The most commonly used proxy measure of cognitive reserve has been educational attainment [12]. Albeit important, education represents a fixed measure of cognitive reserve and thus does not encompass lifetime buildup of resources. Novel ways to measure cognitive reserve are necessary to provide insight on a more dynamic characterization of these resources.

Another factor that may affect the high variability in cognitive functioning despite brain pathology is psychological resilience, which refers to the ability to mentally recover after adverse life events [14]. It is a personal resource, which has been associated with a better functional independence in daily activities as defined by a modified Rankin Scale score [22] of 0–2; and (e) fluent Finnish language skills.

Exclusion criteria were (a) significant neurological disease (e.g., symptomatic stroke, multiple sclerosis or treatment resistant epilepsy); (b) severe diagnosed psychiatric disorder; (c) current substance abuse; (d) other severe medical condition preventing participation; (e) traumatic brain injury that has required hospitalization; (f) severe sight or hearing impairments hindering administration of cognitive tests; (g) severe intellectual disability; and (h) inability or refusal to undergo brain MRI. Additional exclusion criteria based on MRI findings were defined as follows: (a) cortical infarct; (b) subcortical infarct larger than 15 mm (20 mm on diffusion-weighted images); (c) haemorrhage larger than microbleed (over 10 mm); (d) brain tumour; and (e) contusion, traumatic subarachnoid or intracranial haemorrhage, distinct diffuse axonal injury.
Magnetic resonance imaging

Imaging was performed with a 3 T MRI scanner with 32-channel head coil. The imaging protocol consisted of fast three plane localizer, 3D fluid-attenuated inversion recovery (FLAIR) SPACE, 3D T2 SPACE, 3D T1 magnetization-prepared rapid acquisition with gradient echo, 3D gradient echo susceptibility weighted imaging sequence, 3D gradient echo sequence with magnetization transfer pulse on and off.

As the core SVD imaging finding, WMH of presumed vascular origin were defined on FLAIR sequences as hyperintense areas in the white matter without cavitation. WMH were first evaluated visually by a board certified neuroradiologist using the modified Fazekas scale [23] with scores 0 = none, 1 = mild, 2 = moderate and 3 = severe, taking into account deep and subcortical WMH. Based on the aforementioned scores, two groups were formed to compare the characteristics of subjects with low versus high WMH burden (WMH1 = Fazekas 0–1, WMH2 = Fazekas 2–3). WMH were also segmented on FLAIR images using an automated multi-stage segmentation method that is based on the expectation-maximization algorithm [24]. The segmentation was done in three steps as described earlier [25]. Total WMH volume (ml) was normalized for intracranial volume and logarithmic transformation was applied to account for non-normality of the distribution.

Evaluation of cognitive reserve

Cognitive reserve was assessed using years of education and the modified Cognitive Reserve Scale (mCRS), a self-report questionnaire developed to determine lifetime involvement in cognitively stimulating activities [26,27]. The questionnaire has been shown to have high internal consistency and reliability [26,27]. It includes three age-specific versions, of which those intended for persons 36–64 and ≥65 years of age were used. Each subject was asked to fill in both versions to determine their activities during these ages. The mCRS has 20 questions in each age version, responses ranging from 0 to 4, resulting in a total mCRS score from 0 to 80. Items include topics in three categories: training and information, hobbies and social life. Examples include taking a course or speaking a non-native language, playing games or a musical instrument and visiting relatives/friends/neighbours or volunteering [27]. There were a few sporadic missing responses, which were replaced by the subject’s median response within the same age-specific questionnaire. Then each mCRS age group version was summed for a total score/age group/person. Finally, the mean of the two questionnaires was used as the final mCRS score. A total of 151 subjects completed the mCRS.

Evaluation of psychological resilience

Psychological resilience was assessed with the Resilience Scale 14 (RS14), a 14-item self-report questionnaire reflecting individual adaptation to adverse situations [28,29]. Responses in the RS14 range from 1 (strongly disagree) to 7 (strongly agree) and the final score is the sum of the 14 items (with a potential range from 14 to 98). Items include statements such as ‘I usually manage one way or another’, ‘I feel proud that I have accomplished things in my life’ and ‘When I’m in a difficult situation, I can usually find my way out of it’ [28]. RS14 has been shown to have good internal consistency and reliability in a Finnish sample of healthy subjects [28]. The few sporadic missing responses within a subject’s RS14 questionnaire were replaced by the neutral response 4 (neither agree nor disagree). All subjects completed the RS14.

Neuropsychological evaluation

The comprehensive neuropsychological assessment included multiple tests covering the cognitive domains of processing speed, executive functions, working memory, verbal memory, visuospatial perception and verbal reasoning. The tests, as detailed with references in Table S1, included the Wechsler Adult Memory Scale III (WMS-III; letter number sequencing, digit span backward, word lists immediate and delayed), the Wechsler Adult Intelligence Scale IV (WAIS-IV; coding, block design and similarities), the Stroop test, verbal fluency test and Hayling sentence completion test. Standard instructions and scoring were followed. All subjects had complete data of cognitive test scores. In addition, the Montreal Cognitive Assessment was used as a measure of general cognitive status and was completed by 150 subjects [30].

Subjective cognitive complaints were assessed using two questionnaires, one evaluating memory difficulties (the Prospective and Retrospective Memory Questionnaire, PRMQ) [31] and the other evaluating executive functioning (the Dysexecutive Questionnaire, DEX) [32]. The total scores of these scales were used, where higher scores reflect a greater amount of subjective complaints. The PRMQ was completed by 151 subjects and the DEX by 150 subjects.

Statistical analyses

Data were analysed in three parts. First, the bivariate associations between mCRS, RS14, age, education (in years), WMH volume and cognitive test scores were examined with Pearson’s correlations. Secondly, the associations of the predictor variables with neuropsychological test scores or subjective cognitive complaints (PRMQ and DEX scores) as dependent variables were studied with hierarchical
linear regression models. The first step included education and mCRS or RS14 (model 1) and the second step added WMH volume (model 2) as predictor variables. Thirdly, interactions between the predictor variables on cognitive functioning were examined in separate linear regression analyses (cognitive reserve × WMH, RS14 × WMH; centred variables) adjusting for the main effects. For the cognitive reserve interaction term, years of education and mCRS total score were combined by taking the mean of their standardized z scores. Multicollinearity diagnostics showed no multicollinearity amongst the predictor variables. Basic assumptions of linear regressions were reasonably met (most relevant partial effect figures can be found in Figures S1–S14). As a sensitivity analysis all models were also repeated using heteroscedasticity-consistent standard error estimators (HCSE estimators) [33]. For the results which differed in either direction the more conservative approach was opted for and the null hypothesis was kept. A p value <0.05 was regarded as statistically significant and the false discovery rate (FDR) correction was applied due to multiple comparisons (11 neuropsychological test variables) [34].

RESULTS

The demographic and clinical information of the subjects can be found in Table 1. WMH Fazekas scores were the following: none (14), mild (76), moderate (42) and severe (20). The mCRS had a mean of 40.40 (SD = 8.47, min 15, max 68). The mCRS scores were approximately normally distributed (skewness 0.15, SE = 0.20, kurtosis 0.62, SE = 0.39). mCRS was significantly associated with education (r = 0.23, p = 0.005), but not with age (r = −0.05, p = 0.518), sex (t(149) = −1.16, p = 0.247) or WMH volume (r = −0.05, p = 0.550). The distribution of the RS14 scores had moderate negative skewness (skewness −1.29, SE = 0.20, kurtosis 2.73, SE = 0.39). RS14 scores did not significantly correlate with age (r = −0.04, p = 0.633), education (r = 0.12, p = 0.143) or WMH volume (r = −0.13, p = 0.102). There were no significant differences in RS14 scores based on sex (t = −1.59, p = 0.114).

As indicated in Table 2, education correlated significantly with all of the cognitive tests, mCRS with specific measures of processing speed, executive functions, working memory, verbal memory as well as verbal reasoning, whereas RS14 correlated weakly and only with one measure of processing speed (not surviving FDR correction). mCRS correlated significantly with PRMQ scores (r = −0.26, p = 0.002) and DEX scores (r = −0.26, p = 0.002). RS14 correlated significantly with PRMQ scores (r = −0.61, p < 0.001) and DEX scores (r = 0.46, p < 0.001).

Linear regression analyses revealed that education and mCRS as entered together accounted for a significant amount of variance in all of the cognitive tests examined (Table 3; model 1, R²). Education was independently associated with each test (Table 3; model 1, standardized β coefficients). In addition to education, mCRS total score had independent associations with verbal fluency scores, Hayling sentence completion test 2 time and immediate as well as delayed word list scores (Table 3; model 1, standardized β coefficients). After FDR correction, the association between mCRS and the delayed word list score remained statistically significant. WMH had independent predictive associations with WAIS-IV coding, verbal fluency, WMS-III word lists immediate score and WAIS-IV block design, but adding WMH to the regression models did not influence the associations between cognitive reserve and cognitive test scores (Table 3; model 2, standardized β coefficients). Moreover, mCRS independently accounted for a significant amount of variance in PRMQ scores (standardized β = −0.23, p = 0.005) and DEX scores (standardized β = −0.22, p = 0.007), whereas the effects of education or WMH volume on these self-assessments were not significant. None of the interactions between cognitive reserve and WMH volume on cognitive test scores and subjective cognitive complaints were significant (all p values >0.05). HCSE estimators were run as a sensitivity analysis. With HCSE estimators the results remained mainly unchanged except for slight differences in the predictive value of education on WMS-III word lists delayed, of mCRS on verbal fluency, Hayling sentence completion test 2 time and WMS-III word lists immediate score.
TABLE 2  Pearson correlations between cognitive test scores and years of education, Modified Cognitive Reserve Scale (mCRS) score, Resilience Scale (RS14) score and white matter hyperintensities (WMH) volume

| Neuropsychological test scores                  | Education | mCRS     | RS14     | WMH     |
|------------------------------------------------|-----------|----------|----------|---------|
| Processing speed                               |           |          |          |         |
| WAIS-IV coding                                 | 0.37***   | 0.19**   | −0.02    | −0.26***|
| Stroop colour-congruent                        | 0.27***   | 0.11     | 0.17     | −0.22***|
| Executive functions                            |           |          |          |         |
| Stroop colour-incongruent                      | 0.26***   | 0.09     | 0.08     | −0.21***|
| Verbal fluency test                            | 0.34***   | 0.26***  | 0.15     | −0.25***|
| Hayling sentence completion test 2, time       | −0.29***  | −0.24*** | −0.05    | 0.01    |
| Working memory                                 |           |          |          |         |
| WMS-III letter number sequencing               | 0.37***   | 0.17*    | 0.01     | −0.20***|
| WMS-III digit span backward                    | 0.29***   | 0.19***  | 0.00     | −0.01   |
| Verbal memory                                  |           |          |          |         |
| WMS-III word lists immediate                   | 0.36***   | 0.27***  | 0.14     | −0.28***|
| WMS-III word lists delayed                    | 0.25***   | 0.29***  | 0.13     | −0.18***|
| Visuospatial perception                        |           |          |          |         |
| WAIS-IV block design                           | 0.26***   | 0.12     | 0.02     | −0.25***|
| Verbal reasoning                               |           |          |          |         |
| WAIS-IV similarities                           | 0.47***   | 0.20***  | 0.15     | −0.14   |

Abbreviations: WAIS-IV, Wechsler Adult Intelligence Scale; WMS-III, Wechsler Memory Scale.

*p < 0.05.

**p < 0.01.

***p < 0.001.

The impact of cognitive reserve and psychological resilience on cognitive functioning was investigated in subjects with varying levels of WMH. Cognitive reserve (years of education and lifetime participation in cognitively stimulating activities combined) was associated with performance on several cognitive domains including processing speed, executive functions, working memory, verbal memory, visuospatial perception and verbal reasoning. Education was the strongest individual predictor of objective cognitive functioning. In addition, self-evaluated lifetime participation in cognitively stimulating activities had independent predictive value on memory performance, namely delayed verbal recall and subjective cognitive complaints.

These results are in line with other studies showing the pivotal influence of education on cognitive performance [35,36]. Instead, the association between lifetime engagement in cognitively stimulating activities and cognitive functioning has not been investigated in subjects with SVD or other cerebrovascular diseases. Similarly to our results, mCRS has been found to significantly relate to verbal learning as well as short and long term memory in a cohort of healthy subjects [26]. Unlike León et al., however, no association between mCRS and visuospatial perception was found, which could be explained by differences in the study samples (healthy subjects vs. older adults with varying degrees of WMH). In a community-based longitudinal study, lifespan accumulation of cognitive reserve was...
TABLE 3 Relationship between cognitive reserve, white matter hyperintensities (WMH) volume and cognitive test scores

|                      | Model 1 |                      | Model 2 |                      |
|----------------------|---------|----------------------|---------|----------------------|
|                      | Education | mCRS | $R^2$ (p value) | Education | mCRS | WMH | $R^2$ (p value) |
| Processing speed     |          |      |             |          |      |      |             |
| WAIS-IV coding       | 0.34 (<0.001)$^a$ | 0.11 (0.144) | 0.15 (<0.001)$^a$ | 0.31 (<0.001)$^a$ | 0.11 (0.146) | −0.22 (0.003)$^a$ | 0.20 (<0.001)$^a$ |
| Stroop colour-congruent | 0.26 (0.002)$^a$ | 0.05 (0.509) | 0.08 (0.003)$^a$ | 0.23 (0.004)$^a$ | 0.05 (0.524) | −0.18 (0.024) | 0.11 (<0.001)$^a$ |
| Executive functions  |          |      |             |          |      |      |             |
| Stroop colour-incongruent | 0.26 (0.001)$^a$ | 0.03 (0.707) | 0.07 (0.005)$^a$ | 0.23 (0.006)$^a$ | 0.03 (0.728) | −0.19 (0.021) | 0.10 (0.001)$^a$ |
| Verbal fluency       | 0.30 (<0.001)$^a$ | 0.19 (0.015) | 0.15 (<0.001)$^a$ | 0.26 (<0.001)$^a$ | 0.19 (0.014) | −0.22 (0.005)$^a$ | 0.20 (<0.001)$^a$ |
| Hayling sentence completion test 2 time | −0.25 (0.002)$^a$ | −0.18 (0.024) | 0.12 (<0.001)$^a$ | −0.26 (0.002)$^a$ | −0.18 (0.024) | −0.04 (0.653) | 0.12 (<0.001) |
| Working memory       |          |      |             |          |      |      |             |
| WMS-III letter number sequencing | 0.35 (<0.001)$^a$ | 0.09 (0.244) | 0.14 (<0.001)$^a$ | 0.33 (<0.001)$^a$ | 0.09 (0.251) | −0.14 (0.069) | 0.16 (<0.001)$^a$ |
| WMS-III digit span backward | 0.26 (0.002)$^a$ | 0.13 (0.112) | 0.10 (<0.001)$^a$ | 0.26 (0.002)$^a$ | 0.13 (0.11) | 0.03 (0.750) | 0.10 (0.001)$^a$ |
| Verbal learning      |          |      |             |          |      |      |             |
| WMS-III word lists immediate | 0.31 (<0.001)$^a$ | 0.20 (0.010) | 0.17 (<0.001)$^a$ | 0.28 (<0.001)$^a$ | 0.20 (0.009) | −0.25 (0.001)$^a$ | 0.23 (<0.001)$^a$ |
| WMS-III word lists delayed | 0.19 (0.016)$^a$ | 0.25 (0.002)$^a$ | 0.12 (<0.001)$^a$ | 0.17 (0.035)$^a$ | 0.24 (0.003)$^a$ | −0.15 (0.058) | 0.14 (<0.001)$^a$ |
| Visuospatial perception |          |      |             |          |      |      |             |
| WAIS-IV block design | 0.24 (0.004)$^a$ | 0.06 (0.435) | 0.07 (0.005)$^a$ | 0.21 (0.010)$^a$ | 0.06 (0.449) | −0.22 (0.006)$^†$ | 0.12 (<0.001)$^a$ |
| Verbal reasoning     |          |      |             |          |      |      |             |
| WAIS-IV similarities | 0.44 (<0.001)$^a$ | 0.10 (0.172) | 0.23 (<0.001)$^a$ | 0.43 (<0.001)$^a$ | 0.10 (0.176) | −0.07 (0.339) | 0.23 (<0.001)$^a$ |

Notes: Hierarchical regression analyses with the following predictor variables: model 1, cognitive reserve (years of education and modified Cognitive Reserve Scale [mCRS] score); model 2, cognitive reserve with white matter hyperintensities (WMH) volume.

Standardized $\beta$ coefficients indicate the independent predictive values of education, mCRS and WMH on cognitive performance. $R^2$ represents the significance of the model.

Abbreviations: WAIS-IV, Wechsler Adult Intelligence Scale; WMS-III, Wechsler Memory Scale.

$^a$Associations significant after false discovery rate corrections.
associated with a reduced risk of dementia [37]. Lifespan cognitive reserve was estimated using a composite measure of education and cognitive and social activities, making it hard to assess which aspects of cognitive reserve accounted for the result.

Subjective cognitive complaints have previously been associated with more severe WMH in SVD [38,39] and with cognitive reserve as defined by a composite score including lifetime participation, occupation and education [40]. Interestingly in our study, specifically lifetime cognitive engagement and not education or WMH was associated with subjective cognitive complaints. A cognitively active lifestyle may result in an enhanced confidence in one's cognitive abilities, which in turn does not necessarily translate to overall cognitive performance.

No evidence was found of cognitive reserve modulating the impact of WMH on cognitive performance, unlike in some previous research in SVD [12,13]. Higher levels of education and occupational attainment have predicted a slower rate of cognitive decline in a 3-year follow-up of patients with WMH [13]. Our cross-sectional design might explain the differing results. Then again, studies on cognitive reserve in ageing and Alzheimer’s disease research have had somewhat mixed findings [41]. There is an association between higher cognitive reserve, higher baseline cognition and a reduced risk of mild cognitive impairment symptom onset, but cognitive reserve does not necessarily protect from the effects of vascular risk factors or SVD [42]. In a community-based longitudinal study, education attenuated the effect of WMH on memory performance in a sample with less brain pathology, whereas it had the opposite effect in a sample with more pathology, suggesting possible limits to the protective effect of cognitive reserve [43]. Taken together, these mixed results show that cognitive reserve may have a different impact on cognition depending on the severity of brain pathology and the scale of cognitive impairment.

Psychological resilience was found to have strong associations with subjective memory and executive functioning complaints. However, psychological resilience was unrelated to objective cognitive functioning and did not modulate the association between WMH and cognitive functioning. Our results on psychological resilience are unique since its relationship with cognitive functioning has previously been largely unexplored in SVD. Psychological resilience has been most consistently identified as an important factor related to specific psychological and quality of life outcome measures [44]. Higher levels of resilience might protect from depressive symptoms over time in ageing with disability [45]. Shi et al. found a positive association between psychological resilience and brain activity related to the self-evaluation process, flexible use of emotional resources and flexible control in processing affective information [46]. There was a negative connection between psychological resilience and rumination in negative self-related thoughts. Positive mood was found to facilitate psychological resilience. Consistent with these previous studies, a strong association was found between psychological resilience and subjective cognitive complaints, where higher levels of psychological resilience were related to lower levels of subjective complaints in both memory and executive functioning. It appears that psychological resilience is important for subjective wellbeing despite adversity, but it does not have an impact on objective functioning when measured with a comprehensive cognitive assessment.

White matter hyperintensities were used as the surrogate of SVD severity in this study since previous studies have shown them to be the strongest imaging predictor of cognitive and functional outcomes [47,48]. The age range for our cohort was 65–75 years and was chosen to minimize the likelihood of coexisting neurodegenerative disorders, which become more prevalent in the oldest age groups. The subjects were recruited from a clinical setting based on brain imaging findings representing cases with covert SVD. However, the results cannot be directly generalized to other elderly populations. The strengths of our study include the use of a comprehensive neuropsychological assessment with complete data from all subjects. This enabled us to evaluate the association of cognitive reserve and psychological resilience with a wide spectrum of cognitive functioning. Previous research of vascular cognitive impairment and specifically SVD has largely used education as the sole proxy of cognitive reserve [12,41]. Education was looked at independently from lifetime engagement in cognitive activity and thus it was possible to gain a deeper understanding of the strength of these two measures.

The present study contributes to the literature by identifying individual factors that have a marked impact on cognitive functioning in SVD. Based on our results, it is concluded that cognitive reserve has consistent associations with both objective and subjective cognitive functioning in subjects with varying degrees of WMH. Education has strong associations with a wide range of cognitive domains. Engagement in cognitively stimulating activities across the lifetime is independently associated with delayed verbal memory and subjective cognitive complaints. Finally, psychological resilience is important for subjective, but not objective, cognitive functioning. More research is needed to determine the effects of cognitive reserve and psychological resilience on cognitive decline over time and how these factors are related to the clinical progression of SVD.

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CONFLICT OF INTERESTS
JK and JL are shareholders at Combinostics Oy. JL has received lecture fees from Merck and Sanofi (paid to the employer). The other authors report no conflicts.

AUTHOR CONTRIBUTIONS
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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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