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# Is residual memory variance a valid method for quantifying cognitive reserve? A longitudinal application

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ABSTRACT

Cognitive reserve describes the mismatch between brain integrity and cognitive performance. Older adults with high cognitive reserve are more resilient to age-related brain pathology. Traditionally, cognitive reserve is indexed indirectly via static proxy variables (e.g., years of education). More recently, cross-sectional studies have suggested that reserve can be expressed as residual variance in episodic memory performance that remains after accounting for demographic factors and brain pathology (whole brain, hippocampal, and white matter hyperintensity volumes). The present study extends these methods to a longitudinal framework in a community-based cohort of 244 older adults who underwent two comprehensive neuropsychological and structural magnetic resonance imaging sessions over 4.6 years. On average, residual memory variance decreased over time, consistent with the idea that cognitive reserve is depleted over time. Individual differences in change in residual memory variance predicted incident dementia, independent of baseline residual memory variance. Multiple-group latent difference score models revealed tighter coupling between brain and language changes among individuals with decreasing residual memory variance. These results suggest that changes in residual memory variance may capture a dynamic aspect of cognitive reserve and could be a useful way to summarize individual cognitive responses to brain changes. Change in residual memory variance among initially non-demented older adults was a better predictor of incident dementia than residual memory variance measured at one time-point.



## 1. Introduction

The theory of cognitive reserve posits that some older adults are more resilient to age-related neuropathology than others due to more adaptive use of neural networks (Stern, 2002, 2009). This mismatch between brain structural integrity and cognitive performance is associated with various experiences acquired over the life course, including formal education, occupational complexity, and cognitively-stimulating leisure activities (Stern, 2009). Older adults with more of these experiences exhibit better cognitive performance than older adults with similar levels of brain pathology but fewer of these experiences. Practically, cognitive aging research has treated these experiential variables as proxies for cognitive reserve in analyses. Such indirect measurement of cognitive reserve is problematic for a variety of reasons (Jones et al., 2011; Satz et al., 2011). For example, education also correlates with childhood IQ, socioeconomic status, risk of disease, and health behaviors (Reed et al., 2010). In addition, the same value of a proxy variable (e.g., 12 years of education) does not reflect the same experiences in all people (Manly et al., 2002; Jones, 2003). Using a single proxy variable also fails to measure the entirety of the construct, as cognitive reserve is conceptualized as a confluence of life experiences, many of which are difficult to measure retrospectively. Finally, most proxy measures of cognitive reserve are static and cannot be measured over time despite the potential for modifying one's level of cognitive reserve (Borenstein et al., 2006).

Reed and colleagues proposed an alternative method for quantifying cognitive reserve based on the decomposition of episodic memory variance (Reed et al., 2010). Specifically, cognitive reserve was quantified as residual variance in episodic memory performance that remains after accounting for demographic

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factors and structural magnetic resonance imaging (MRI) variables (Reed et al., 2010, 2011). This "residual" method is in line with a definition of cognitive reserve as the discrepancy between observed and expected performance. In this method, individuals who perform better than their brain structural integrity predicts will have high cognitive reserve, and individuals who perform worse than predicted will have low reserve. The utility of this cross-sectional measure of cognitive reserve has been demonstrated in multiple cohorts (Reed et al., 2010, 2011; Zahodne et al., 2013). For example, residual memory variance was found to moderate the association between memory performance attributable to brain variables and subsequent changes in executive functioning (Reed et al., 2010) and language (Zahodne et al., 2013). A key next step in applying this method is to learn how the residual variable changes over time (Zahodne et al., 2013).

The primary goal of the present study was to extend this approach to a longitudinal framework by calculating the difference between predicted memory performance (based on concurrent MRI) and actual memory performance at two time points. We then investigated whether changes in residual memory variance capture unique and meaningful information. Specific aims were to: (1) quantify changes in residual memory variance in relation to changes in structural MRI and cognitive changes, (2) determine whether changes in residual memory variance were associated with incident dementia independent of baseline residual memory variance, and (3) test whether changes in residual memory variance moderated the relationship between structural MRI changes and language changes.

## 2. Methods

### 2.1. Participants

The 244 older adults in this sample were participants in the Washington Heights/Hamilton Heights Inwood Columbia Aging Project (WHICAP), a prospective, community-based longitudinal study of aging and dementia in a racially and ethnically diverse sample of Medicare-eligible residents of northern Manhattan. Study procedures and a description of the larger sample have been described previously (Tang et al., 2001; Manly et al., 2005). Data were obtained in compliance with the Institutional Review Board of Columbia University Medical Center.

Beginning in 2004, 769 active WHICAP participants who were not demented at their previous visit received high resolution structural magnetic resonance imaging (MRI). These individuals were, on average, 1 year younger than WHICAP participants who refused MRI but were similar in other demographic characteristics (Brickman et al., 2008). The subset of 283 individuals eligible for the present study also underwent a second MRI 4.6 years (SD=1.0) after their baseline MRI. In addition, these individuals had a neuropsychological evaluation at the time of their baseline MRI, did not meet criteria for dementia during this evaluation, and had baseline images of sufficient quality to undergo FreeSurfer analysis (see below). Characteristics of the sample are provided in Table 1. Of these 283 individuals, 244 underwent a second neuropsychological evaluation that included memory testing at the time of their second MRI and had follow-up images of sufficient quality to undergo FreeSurfer analysis.

### 2.2. Magnetic resonance imaging

MRI was obtained on a 1.5 T Philips Intera scanner at Columbia University Medical Center at two time points separated by 4.6 years (SD=1.0 year). T1-weighted (repetition time=20 ms, echo time=2.1 ms, field of view 240 cm, 256 × 160 matrix, 1.3 mm slice thickness) and T2-weighted fluid attenuated inversion recovery (FLAIR; repetition time=11,000 ms, echo time=144.0 ms, inversion time=2800, field of view 25 cm, 2 nex, 256 × 192 matrix with 3 mm slice thickness) images were acquired in the axial orientation. Total gray matter volume, total intracranial volume (ICV), and total hippocampal volume (across hemispheres) were derived from T1-weighted images using the FreeSurfer longitudinal processing stream. For computation of residual memory variance, total brain and hippocampal volumes were corrected for total intracranial volume via regression and then scaled down by factors of 10,000 and 100, respectively. Total white matter hyperintensity (WMH) volume was derived from T2-weighted fluid attenuated inversion recovery images using previously-described procedures (Brickman et al., 2009, 2011, 2012). In brief, images were skull stripped, and a Gaussian curve was fit to map voxel intensity values. Voxels at least 2.0 standard deviations above the image mean were labeled as WMH. Labeled images were also visually inspected and corrected if errors were detected.

**Table 1**
Sample characteristics at baseline ($N$=283).

| | Mean (SD) or % |
|---|---|
| Age (years) | 79.4 (5.2) |
| Education (years) | 11.1 (4.8) |
| Sex | 67.6% Female |
| Race/ethnicity | 38.9% Black<br>33.2% Hispanic<br>27.9% Non-Hispanic White |
| Intracranial volume ($mm^3$) | 1301916.8 (152438.0) |
| Total gray matter volume ($mm^3$) | 524774.7 (48920.0) |
| Hippocampal volume ($mm^3$) | 6866.6 (828.9) |
| White matter hyperintensity volume ($cm^3$) | 8.6 (10.4) |
| Memory score (z-score metric) | 0.2 (0.7) |
| Language score (z-score metric) | 0.4 (0.6) |

SD=Standard deviation.

### 2.3. Neuropsychological measures

Following the methods outlined by Reed et al. (2010) and Zahodne et al. (2013), a memory composite was used in the decomposition. Reed et al. (2010) investigated whether residual memory variance predicted subsequent changes in a composite measure of executive functioning. Zahodne et al. (2013) investigated whether residual memory variance predicted subsequent changes in a composite measure of language functioning. Language was chosen because it is well-characterized by the WHICAP battery based on exploratory factor analysis (Siedlecki et al. 2010) and is sensitive to dementia pathology. In the current study, the language composite was used to determine whether associations between brain MRI changes and cognitive changes differed according to magnitude of change in residual memory variance.

Individual neuropsychological tests of memory and language were combined into their respective memory and language composite scores based on a previously-reported exploratory factor analysis (Siedlecki et al., 2010), in which resultant factor structure and factor loadings were found to be invariant across English and Spanish speakers. Composite scores were computed by converting all scores to z-scores based on baseline mean scores and standard deviations from the larger WHICAP sample and averaging these z-scores within each of the two domains. Z-scores were not corrected for demographics. The memory composite included the following subscores from the Selective Reminding Test (SRT; Buschke & Fuld, 1974): total recall, delayed recall, and delayed recognition. The language composite included tests of naming, letter fluency, animal fluency, verbal abstraction, repetition, and comprehension. Of note, some of these measures (e.g., letter fluency and verbal abstraction) tap certain executive skills.

### 2.4. Dementia diagnosis

After each visit in WHICAP, dementia diagnoses are made by consensus of neurologists and neuropsychologists based on *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria (American Psychiatric Association, 1987) using data from neuropsychological tests, functional interviews and medical interview, but not MRI data (Stern et al., 1992).

### 2.5. Statistical analyses

Statistical analysis was carried out in SPSS version 22 and Mplus version 7. Baseline residual memory variance was computed by regressing baseline memory composite scores onto sex, race, ethnicity, years of education, total gray matter volume (corrected for ICV via regression and reduced by a power of 4), total hippocampal volume (corrected for ICV via regression and reduced by a power of 2), and total WMH volume in the sample of 283 participants with complete baseline data. These unstandardized regression estimates (i.e., B-weights) were then applied to demographics and the follow-up MRI data to compute predicted memory scores at follow-up for the subset of 244 participants with complete follow-up data. Residual memory variance at follow-up reflects the difference between these predicted scores and actual memory scores obtained at the follow-up visit.

Changes in the variables of interest were evaluated with separate univariate latent difference score (LDS) models using maximum likelihood estimation in Mplus (McArdle and Nesselroade, 1994). Rather than calculating difference scores from the raw data, the LDS approach defines a latent variable as the portion of the follow-up value that is not identical to the initial value. In addition, features of change that are of interest (e.g., mean change, inter-individual variability in change,