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Research Article

Cognitive reserve as residual variance in cognitive performance: Latent dimensionality, correlates, and dementia prediction

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Abstract

Objectives: Cognitive reserve (CR) is typically operationalized as episodic memory residualized on brain health indices. The dimensionality of more generalized models of CR has rarely been examined. **Methods:** In a sample of $N = 113$ dementia-free older adults (ages 62–86 years at MRI scan; 58.4% women), the domain-specific representation of general cognition (COG) before vs. after residualization on brain indices (brain volume loss, cerebral blood flow, white matter hyperintensities) was compared (i.e., COG vs. CR). COG and CR were assessed by 15 tasks spanning five domains: processing speed, verbal memory, visuospatial memory, fluid reasoning, and vocabulary. Measurement invariance and item-construct representation were tested in a series of structural factor analyses. COG and CR were then examined in relation to 22 risk and protective factors and dementia status at time of death. **Results:** Item-factor loadings differed such that CR more strongly emphasized fluid reasoning. More years of education, higher occupational class, more hobbies/interests, and fewer difficulties with personal mobility similarly predicted better COG and CR. Only the sub-domain of visuospatial memory (both before and after residualization) was associated with conversion to dementia by end-of-life ($r = -.30$; $p = .01$). **Conclusions:** Results provide tentative support for the role of fluid reasoning (intelligence) as a potential compensatory factor for age- and/or neuropathology-related reductions in processing speed and memory. Intellectually stimulating work, efforts to preserve personal mobility, and a diversity of hobbies and interests may attenuate age- and/or pathology-related reductions in cognitive functioning prior to dementia onset.

Keywords: Fluid reasoning; factor analysis; MRI; mobility; Rey-Osterrieth complex figure; visuospatial memory

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Introduction

Different biological, psychological, and social factors can serve to delay or counteract losses in cognitive functioning linked to normative aging processes and/or neurodegenerative conditions. Two such factors relate to the concept of "reserve capacity," i.e., the ability to preserve functionally appropriate behavior despite the presence of neurocognitive impairment. Brain reserve refers to comparatively stable and nonmodifiable neuroanatomical features (e.g., larger brain volume and richer synaptic connectivity) that confer robustness to pathology-related depletion of neurobiological resources. In contrast, cognitive reserve (CR) is conceived as an active and dynamic process whereby the differential recruitment of cognitive strategies and/or neural networks underlying task performance allows individuals to compensate for accumulated brain injury and neurocognitive deficits (Stern, 2009; Stern et al., 2023).

CR as a conceptual framework was initially informed by converging clinical evidence showing that individuals with higher levels of education and intellectually stimulating life experiences were less likely to manifest symptoms of dementia and Alzheimer's disease (AD) despite conspicuous neuropathological burden. However, CR has since proven challenging to operationalize given that it cannot be measured directly (Stern et al., 2020). For this reason, CR is most commonly assessed by proxy measures of education level, occupational complexity, and intellectually enriching life experiences. However, such proxies are more appropriately viewed as protective factors for CR rather than as indicators of CR per se. This is because education and occupation are conflated with differences in socioeconomic status, access to healthcare and related behaviors, and other life experiences that may influence neuropsychological test performance via pathways other than proposed CR mechanisms (Jones et al., 2011; Satz et al., 2011).

A more objective and theoretically consistent approach to operationalizing CR treats it as the difference between observed cognitive performance vs. performance that would be expected given evidence of neuropathology (Reed et al., 2010; Stern et al., 2023). In this approach, cognitive performance is typically regressed on neuroanatomical indices (e.g., white matter hyperintensities, reduced hippocampal volume) such that the portion of

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performance unrelated to pathological burden (i.e., residual ability) is regarded as CR. Studies leveraging this methodology have usually focused on episodic memory due to its sensitivity to age- and pathology-related processes and given that impaired episodic memory is a hallmark of the early stages of AD (Bettcher et al., 2019; Reed et al., 2010; Zahodne et al., 2013, 2015;). However, limiting CR to memory performance may be insufficient for accurately predicting conversion from cognitive decline to AD, which has prompted some researchers to call for a more generalized model of CR (Serra et al., 2017).

Apart from factor analyses of CR proxy measures (e.g., Borella et al., 2023), the dimensionality of CR has rarely been examined. Thus, the degree to which CR reflects cognitive processes beyond memory remains an open question. Searches via Web of Science and Google Scholar for the terms "factor analysis, cognitive reserve, residualized" combined with reverse citation look-ups revealed a single structural factor analytic study of CR as a generalized construct (Reed et al., 2011). In this study, CR was indicated by processing speed, fluency, perceptual organization, and memory (episodic, semantic, and working) – which were regressed on autopsy-derived (rather than magnetic resonance imaging; MRI) brain indices. Results showed that these cognitive abilities were similarly strongly representative of a single higher-order CR factor. The authors further examined education, intellectual leisure activities, and socioeconomic status as predictors of CR, and they found that intellectual leisure activities in later adulthood were more important than early education for predicting CR.

Elman et al. (2022) have noted that for residualized cognitive performance to be a useful index of resilience, it should tell us something different than our original measure of cognitive performance. It follows that COG and CR as constructs may emphasize different cognitive abilities. Along these lines, adult developmental psychometric theory distinguishes cognitive abilities that are comparatively well-preserved with age (e.g., general intelligence) vs. abilities known to be more sensitive to age-related losses in brain health, such as processing speed and memory (Aichele et al., 2018; Baltes et al., 2006). Correspondingly, removal of variability in cognitive performance via residualization on indices of brain health (e.g., white matter lesion burden, brain volume loss) should result in adjusted measures of cognitive performance (i.e., CR) that reflect variability in general intelligence to a greater extent than variability in speed and memory. This assumption could be formally tested using a factor analytic approach to evaluate differences in patterns of associations in multiple cognitive abilities before vs. after residualization on brain indices, so as to compare the latent dimensionality of COG vs. CR.

In the current study, the domain-specific representation of general cognition before (COG) vs. after (CR) residualization on brain indices (brain volume loss, cerebral blood flow, white matter hyperintensities) was compared. Analyses were applied to data from participants from the Manchester Longitudinal Study of Cognition in Normal Healthy Old Age (MLSC; Rabbitt et al., 2004) who completed MRI scans in the years 1999–2000 ($N = 113$ dementia-free adults, ages 62–86 years at MRI scan; 58.4% women). COG/CR were assessed by 15 tasks spanning five domains: processing speed, verbal memory, visuospatial memory, fluid reasoning, and vocabulary. Measurement invariance and item-construct representation were tested in a series of structural factor analyses. COG and CR were further examined in relation to 22 risk/protective factors (prior to MRI) and dementia status (at time of death). It was hypothesized that intelligence measures (vs. speed and memory) would more strongly characterize CR than COG and, correspondingly, that intelligence-related factors typically used as proxy measures for CR (education, occupational class, intellectual hobbies) would show stronger predictive associations with CR than with COG.

Method

Participants

Data came from 66 women and 47 men (median age = 74.0 years, range = 62.0–86.0 years) who were participants in the Manchester Longitudinal Study of Cognition (MLSC; see Rabbitt et al., 2004, for detailed information) for 11–17 years prior to undergoing MRI scanning. The research was completed in accordance with the Helsinki Declaration, with ethical approval provided by the research ethics committee at The University of Manchester (Ref: 2021-11274-17829). All participants were independent community dwelling adults from Newcastle upon Tyne and Manchester, UK (and surrounding areas). Participants were recruited by local magazine, radio, and television advertisements. Physical and cognitive screening by two experienced geriatricians within the year prior to MRI showed no indication of dementia or neurological abnormality among participants (Rabbitt et al., 2007), and Mini Mental State Exam scores for all participants were above 24, the cutoff below which dementia may be indicated (MMSE; Folstein et al., 1975). Of the participants, 5 (4.5%) reported prior occurrence of stroke. Individuals with severe visual or auditory handicaps were excluded from the study. Individuals with mild, easily correctable sensory handicaps always used their prescribed lenses or hearing aids during testing.

Measures

Socio-demographics, lifestyle, and health

Variables included in analyses as covariates (22 in total) are summarized below in Table 1. Occupational class was based on the categorization system of the Office of Population Censuses and Surveys (1980). For the present analyses, being married and/or cohabitating with one's partner were treated as a single dichotomous variable. Tobacco smoker status was based on self-identification as a smoker, previously or currently. Functional limitations items were scored on a 3-point scale (0 = no difficulties, 1 = some difficulties, 2 = great difficulty). Two composite scores were calculated as the mean of item parcels as follows: Difficulty with Housework (items = "difficulty with household tasks", "difficulty doing things around the house," "difficulty cleaning the house," "difficulty doing laundry," and "difficulty preparing meals"); Difficulty with Personal Mobility (items = "difficulty bathing self," "difficulty dressing self," "difficulty cutting toenails," and "difficulty climbing stairs"). Physical activity was calculated as the sum of monthly hours of light exercise and strenuous exercise. Depressive symptoms were assessed using the Yesavage Geriatric Depression Scale (Yesavage et al., 1983).

Individuals' scores for each of these covariates were averaged across measurement waves prior to MRI (for most participants, MRI was conducted in the same year as wave 3), resulting in a single "baseline" score. Scores for functional limitations items were limited to those at study entry (wave 1) because scaling for these items at subsequent waves was changed to comparative endorsement (i.e., "more vs. less worse than before"). Prior occurrences of heart attack, hypertension, and diabetes were self-reported based on previous physician diagnoses. Mortality status (and coroner

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Table 1. Characteristics of the sample ($N = 113$)

Variable	Summary
Demographic	
Age at MRI (years)	*Mdn* = 74.0 [62.0–86.0]
Deceased (by 2018)	*n*=70 (53.1%)
Years from MRI to time of death (for deceased)	*Mdn* = 15.3 [3.3–20.4]
Women	*n* = 66 (58.4%)
APOE *e*4 (yes)	*n* = 26 (23.0%)
Years of formal education	*Mdn*=10.0 [8.0–24.0]
Post-secondary education (yes)	*n* = 83 (73.5%)
Occupational class	
Professional	*n* = 16 (14.2%)
Intermediate (managerial & technical)	*n* = 47 (41.6%)
Skilled (nonmanual)	*n* = 11 (9.7%)
Skilled (manual)	*n* = 29 (25.7%)
Partly skilled	*n* = 7 (6.2%)
Unskilled/Other	*n* = 3 (2.7%)
Socio-relational	
Married or Cohabitating (yes)	*n* = 90 (79.6%)
Number of children seen regularly	*Mdn*=1 [0–5]
Number of others in the home	*Mdn*=1 [0–3]
Socializing and visiting friends (hr/mo)	*Mdn*=40.5 [2.5–139.0]
Have one or more pets (yes)	*n* = 40 (35.4%)
Lifestyle	
Tobacco smoker (yes)	*n* = 61 (54.0%)
Units of alcohol per week	*Mdn*=3 [0–45]
Difficulty w/ housework	*Mdn*=0.0 [0–1.2]
Difficulty w/ personal mobility	*Mdn*=0.0 [0–0.5]
Physical Activity (hr/mo light & strenuous exercise)	*Mdn* = *22.0* [0.0–196.0]
Number of hobbies	*Mdn*=4 [0–10]
Hours of sleep per night	*Mdn*=7.2 [3.5–10.0]
Usually sleep through the night (yes)	*n* = 85 (75.2%)
Health & Medical	
Heart attack diagnosis	*n* = 14 (12.4%)
Hypertension diagnosis	*n* = 71 (62.8%)
Diabetes diagnosis	*n* = 10 (8.8%)
Dementia (reported on death certificate)	*n* = 15 of 70 (21.4%)
Geriatric depressive symptoms	*Mdn*=5.7 [0–27]
Brain Measures	
White matter hyperintensities (Scheltens')	*Mdn*=5, *IQR* = 2–8, *n* = 112 obs.
White matter hyperintensities (Erkinjuntti)	
(0) no lesions	*n* = 11
(1) <5 small focal and/or<2 large focal lesions	*n* = 17
(2) 5-12 small focal and/or 2-4 large focal lesions	*n* = 28
(3) >12 small focal and/or>4 large focal lesions	*n* = 46
(4) predominantly confluent lesions	*n* = 10
Brain volume loss (skull size-normed)	*Mdn*=.082 [.041–.137], *n* = 94 obs.
Cerebral blood flow (skull size-normed)	*Mdn*=1.78^{e-04} [9.37^{e-05}–2.53^{e-04}], *n* = 92 obs.

Note: [] indicates range. IQR = inter-quartile (25%-75%) range.

reported dementia status at time of death) were obtained by a search of death certificates performed by Her Majesty's General Registry Office.

Cognitive abilities

Cognitive performance was evaluated across five domains of ability: processing speed, verbal memory, visuospatial memory, fluid reasoning (i.e., abstract reasoning), and vocabulary. Three tasks were administered within each domain. Vocabulary tests were administered approximately 12–18 months prior to MRI scanning (Rabbitt et al., 2004). The remaining cognitive tasks were administered within the 6-week period prior to MRI scanning. These latter tests were carried out by the same investigator in a quiet room across two 75-minute sessions at the University of Manchester Age and Cognitive Performance Research Centre.

Processing speed was assessed by visual search, letter-digit coding, and alphabet coding tasks. For the visual search task, participants scanned sheets of capital letters of the alphabet (printed in random order and with equal frequency) to locate and mark as many instances of "I" or "O" as possible within a 2-minute period. Scores were total letters correctly identified. Letter-digit coding was a pencil-and-paper digit-symbol task adapted from the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1986). Participants were presented with a letter-digit key at the top of a page followed by rows of "unmatched" letters for which they were required to match as many digits as possible within a one-minute period. Scores were total correct letter-digit pairs. The alphabet coding task (Savage, 1984) was a letter-letter substitution task similar to the letter-digit task described above but with scores calculated as correct matches across four 2-minute runs.

Verbal memory was assessed by immediate free recall of 30 words, recall of "propositions about people" (PaP), and the digit span backwards task. Taken together, these tasks leveraged immediate recall, episodic memory, and working memory sub-domains. For the verbal free recall task, participants were sequentially presented with 30 six-letter nouns (matched for frequency and concreteness) at 1.5s intervals. Scores were total number of words correctly recalled in any order. For the PaP task, participants were visually presented with the names of five individuals, where each name was accompanied by three additional items of information. This information was then removed, and participants were immediately prompted to recall the pieces of information associated with each name. Scores were total correctly matched recall items. For the digit span backwards task (a subtest of the WAIS that has been used extensively to assess verbal working memory; Chai et al., 2018), participants were required to encode and then repeat in reverse-order number sequences of increasing length. Scores were based on the longest sequence correctly recalled.

Visuospatial memory similarly spanned recall, episodic memory, and working memory sub-domains and was assessed by the Rey-Osterrieth Complex Figure (ROCF; Osterrieth, 1944; Rey, 1941; Shin et al., 2006), delayed matching to sample (DMS), and a "circle objects/positions" task (COP). The ROCF presents participants with a figure that they first copy and then reproduce from memory both immediately and again following a delay of 30 minutes. Scores are based on the type and position of sub-components (18) correctly drawn, for a maximum possible score of 36 points. Here, scores were based on immediate recall of the ROCF. The DMS task came from the Cambridge Neuropsycholoigcal Test Automated Battery and is described at length in Robbins et al. (1994). In brief, participants were presented with a sequence of complex abstract patterns consisting of four quadrants, each differing in color and form, for 4.5s. Then, following a delay, they were presented with 4 choice patterns and tasked with selecting the correct match. Scores were based on total correct matches (max possible = 16). For the COP task, participants were given 15s to inspect a circle divided into 12 equal sectors, each of which contained a line drawing of an easily namable common object. This image was replaced with a blank circle, and participants were tasked with writing within the appropriate sectors the names of as many objects as they could remember (total score = total correct object/location pairs).

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Fluid reasoning was assessed by the Alice Heim Group Ability Tests (AH4-1 and AH4-2; Heim, 1970) and by the Culture Fair test (Cattell & Cattell, 1960). The AH4-1 consists of logic, arithmetic, number series completion, and verbal comparison items. The AH4-2 consists of nonverbal logical problems defined by progressive mental rotation, addition and subtraction, or other comparisons of line-drawn shapes. Both tests comprise 65 items. The Culture Fair is a nonverbal test in which participants must deduce rules to correctly recognize and insert missing elements in 50 different line-drawn matrices.

Vocabulary was assessed by the Raven (1965) Mill Hill A and Mill Hill B tests and by the WAIS (Wechsler, 1986). The Mill Hill A vocabulary test required participants to select the most exact synonym for each of 33 words from among 6 alternatives. The Mill Hill B required production of exact definitions for each of 32 different seldom-used words. The WAIS vocabulary test required selection of the appropriate definition out of 4 possibilities supplied for each of 74 words.

Brain indices

Brain anatomical and quantitative blood flow images were obtained through magnetic resonance imaging (MRI). All participants provided informed consent within 24 hours of undergoing MRI scanning. Global neurophysiological measures included age-related loss of brain volume (ARLBV), cerebral blood flow (CBF), and white matter hyperintensities (WMH).

ARLBV and CBF measures are described at length in Rabbitt et al. (2006). Anatomical images required for brain volume estimation were acquired using an axial fast spin-echo inversion recovery sequence (TR _ 6,850 ms, TE _ 18 ms, TI _ 300 ms, echo train length _ 9). Contiguous 3-mm slices were obtained throughout the brain with an in-plane resolution of 0.89 mm2 (matrix _ 256 _ 204, field of view _ 230 mm _ 184 mm). ARLBV was estimated using the volume of cerebrospinal fluid (CSF) as a surrogate: As the brain shrinks, CSF volume increases. Thus, measurement of CSF volume provides a good indication of relative brain volume loss over the lifespan. CSF volume was obtained using a fully automated procedure and corrected for head size (interior surface of the skull), according to the method described by Thacker et al. (2002). Losses measured this way reflect both the normal aging process and also additional causes of atrophy sustained throughout a person's lifetime. CBF was calculated as total sum of blood flow into the head via the left and right carotid arteries and via the basilar artery. Measurements of carotid and basilar arterial flow were made using a cardiac gated phase contrast quantitative flow sequence (TE _ 3 ms, TR _ 6 ms, flip angle _ 15°, in-plane resolution _ 1.17 mm _ 1.17 mm, slice thickness _ 5 mm). The arteries were imaged in one slice perpendicular to the direction of the arteries (direction of greatest flow). The final value was again corrected for interior skull surface area.

To determine WMH prevalence, MRI was performed with a 1.5 tesla whole-body scanner (Philips Medical Systems, Best, Netherlands) at the University of Manchester. Imaging sequences included fluid attenuated inversion recovery (FLAIR; TR = 11,000 ms, TE = 140 ms, TI = 2600 ms, field of view (FOV) = 230 mm^2, matrix 256; slice thickness 3.0 mm) and axial T1-weighted inversion recovery images (TIR; TR = 6850 ms, TE = 18 ms, TI = 300 ms, FOV = 230 mm^2; matrix 256; slice thickness 3.0 mm). Images were acquired in the transverse plane perpendicular to the lower borders of the genu and splenium of the corpus callosum and covered the entire head from the vertex to the foramen magnum. White matter lesion burden was based on visual ratings by an experienced neuroradiologist, Alan Jackson, whose inter-rater reliability with other experienced practitioners was previously shown to be excellent (Cohen's κ = 0.82–1.00) and using EFilm viewstation software (EFilm Medical Ltd, Toronto, Ontario, Canada). Total white matter lesion burden was calculated based on two different scales (Mäntylä et al.,). Erkinjuntti's scale ranks WMH severity based on counts of small vs. large, focal vs. confluent WMH. Final scores range from 0 (absent) to 4 (predominantly confluent lesions). Scheltens' scale (Scheltens et al., 1993) determines cortical deep white matter lesion burden based on counts of hyperintensities rated between 0 (low) and 6 (high) in frontal, parietal, occipital, and temporal lobes.

Statistical analyses

Statistical analyses were conducted using the R software environment (R Core Team, 2023). Descriptive statistics were calculated using R's base (built-in) functionality. Structural factor analyses and regressions were conducted using the R add-on package Lavaan (Rosseel, 2012) with full information maximum likelihood (FIML) estimation to handle missing data (Schafer & Graham, 2002). Overall model fit was based on established metrics, e.g., the comparative fit index > .90 and the root mean square error of approximation (RMSEA) < 0.10 (Hu & Bentler, 1999). Relative model fit was based on likelihood ratio tests (change in chi-square per change in degrees of freedom across nested models).

A multi-stage approach was taken. First, a "brain status" factor was modeled as indicated by ARLBV, CBF, and WMH. Two models were fit: one with WMH prevalence based on Erkinjuntti's scale (M1a) and one based on Scheltens' scaling (M1b). Individuals' brain status factor scores were extracted from the model with the stronger factor loadings. Individuals' scores for each of the 15 observed cognitive measures were regressed on this brain factor, and residualized cognitive scores (i.e., performance unrelated to the brain pathology markers) were extracted for subsequent analyses. Note that a single "brain factor" was initially estimated (a) to accommodate missing values in some of the brain measures for some of the participants to ensure that cognitive performance was residualized on the same brain construct and (b) for comparative purposes in determining which WMH rating method was most reliably associated with the other brain indices (volume loss, blood flow).

Two second-order structural factor models (Figure 1) were then fit. In the first model (M2a), the observed cognitive scores (level 1) indicated performance across five latent cognitive domains (level 2): processing speed, verbal memory, visuospatial memory, fluid reasoning, and vocabulary. In turn, these domain-specific cognitive factors were modeled as indicators of global cognitive functioning (level 3). The second model (M2b) was identical to the first, except that level 1 items were the residualized cognitive scores; therefore, level 2 and level 3 factors were construed as CR. A third model (M3) combining these two models (i.e., to concurrently estimate COG and CR as second-order constructs) was then tested. Following this, tests of factorial invariance (Widaman & Reise, 1997) were conducted to determine differences in dimensionality and scaling across the COG vs. CR constructs (models M4a–M4d).

Finally, covariates were tested as predictive of the COG and CR constructs, both directly and after statistical adjustment for differences in chronological age, biological sex, and APOE e4 status. Predictive associations were estimated with correction for multiple tests using the false discovery rate method (Benjamini &

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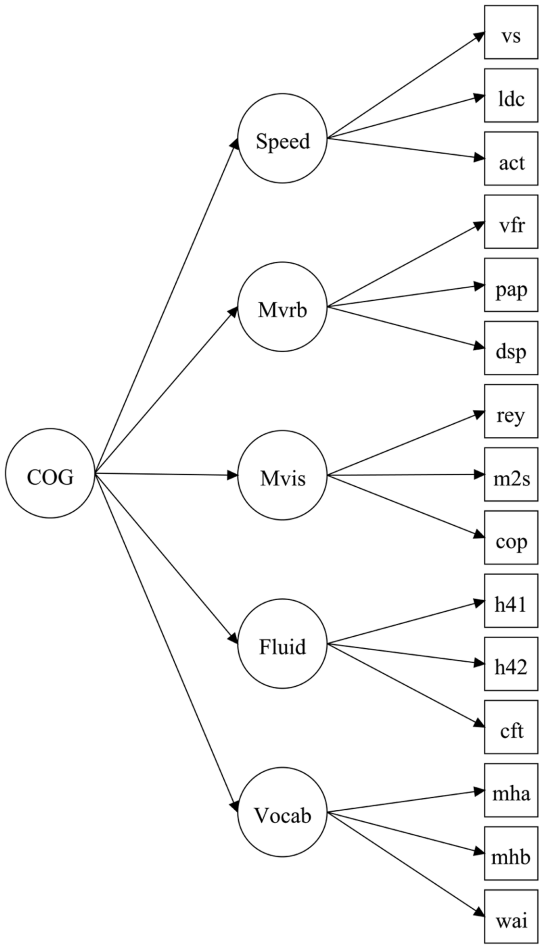

Level Three (Global Factor)

COG	Cognition

Level Two (Domain-Specific Factors)

Speed	Processing Speed
Mvrb	Verbal Memory
Mvis	Visuospatial Memory
Fluid	General Fluid Intelligence
Vocab	Vocabulary

Level One (Observed Tasks)

vs	Visual Search
ldc	Letter-Digit Coding
act	Alphabet Coding
vfr	Verbal Free Recall (Immediate)
pap	Propositions About People
dsp	Digit-Span Backwards
rey	Rey-Osterrieth Figure (Immediate)
m2s	Delayed Match-to-Sample
cop	Circle Objects/Positions
h41	Heim Intelligence Test (41)
h42	Heim Intelligence Test (42)
cft	Culture-Fair Intelligence Test
mha	Mill-Hill Vocabulary (A)
mhb	Mill-Hill Vocabulary (B)
wai	Wechsler Adult Intelligence Scale

Figure 1. Second-order structural factor model (M2a) of cognition. An identical model (M2b) was fit to cognitive scores residualized on brain status in order to estimate global cognitive reserve (CR) at level three and domain-specific CR factors at level two.

Hochberg, 1995). Differences in covariates' predictive effects on COG vs. CR (for variables with significant associations) were then tested using log-likelihood ratio tests (i.e., comparing fit of a model where the regression coefficients were constrained to equality vs. a model where they were unconstrained). "All-inclusive" models were then fit to estimate total explained variance in both COG and CR. Associations between global and domain-specific CR factors with dementia at time of death were estimated as point-biserial correlations.

Results

Sample descriptive statistics are reported in Table 1. Most participants (73.5%) had completed at least some post-secondary education (e.g., college, university, or vocational training). Individuals classified as having managerial or technical occupations constituted the majority (41.6%) of the sample (and thus served as the reference group for comparison purposes). Married/cohabitating participants comprised 79.6% of the sample. Most lived with one other person. Median time spent socializing with family and friends was approximately 10 hours per week. More than half of participants (54%) self-identified as a tobacco smoker currently and/or in the past. There was substantial variation in alcohol consumption, but on average participants consumed a few drinks (alcohol units) per week. On average, participants endorsed having few difficulties with activities of daily living and slept approximately seven hours per night.

Brain status factor and residualized cognitive scores

Observed brain status indicators are summarized in Table 1. White matter hyperintensities categorized according to Erkinjuntti's scale showed that 56 participants (49.6%) had evidence of extensive/confluent white matter lesions, with 10 individuals (7.5%) in the most severe category. WMH prevalence rankings based on Scheltens' vs. Erkinjuntti's scales were very strongly correlated, $\rho = 0.87$ (Spearman's rank-order correlation). Brain volume loss and cerebral blood flow variables were rescaled (standardized) for factor modeling purposes.

The brain status structural factor model was first applied to WMH data scaled using Erkinjuntti's method. This latter variable was initially modeled as an ordinal variable (using weighted least squares estimation with theta parameterization) and then as a continuous variable (with FIML estimation). Standardized factor loadings based on both scalings (ordinal vs. continuous) were acceptable (>.40 for all indicators; Brown, 2015), and the factor scores extracted from each method were nearly perfectly correlated at $r = .995$. Standardized factor loadings were: $\lambda_{b1} = 0.611$ (ARLBV), $\lambda_{b2} = -0.739$ (CBF), and $\lambda_{b3} = 0.412$ (WMH) for the model estimated using FIML (model fit statistics are provided in

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Table 2. Factor model fit statistics and tests for factorial invariance

Model	Nprm	χ^2	*df*	CFI	RMSEA	RMSEA [95% CI]	SRMR	AIC
Singular Top-Level Factor Models								
M1a. Brain Status (Erkinjuntti)	9	32	3	1.000	0.000	[0.000, 0.000]	0.000	855
M1b. Brain Status (Scheltens)	9	28	3	1.000	0.000	[0.000, 0.000]	0.000	832
M2a. COG	50	105	85	0.978	0.046	[0.000, 0.073]	0.056	9899
M2b. CR	50	106	85	0.973	0.046	[0.000, 0.073]	0.060	9840
COG + CR Models (two-stage estimation, with increasing invariance constraints)								
M4a. Configural Inv.	36	83	29	0.977	0.128	[0.096, 0.161]	0.154	3835
M4b. Weak Inv.	32	211	33	0.933	0.218	[0.191, 0.247]	0.345	3955
M4c. Strong Inv.	27	213	38	0.943	0.202	[0.176, 0.229]	0.345	3947
M4d. Strict Inv.	22	574	43	0.846	0.330	[0.307, 0.355]	0.167	4298

Note: Nprm = number of model parameters. CFI = comparative fit index. RMSEA = root mean square error of approximation. SRMR = Standardized root mean squared residual. AIC = Akaike information criterion. The model with both COG and CR as second-order factors (M3) did not converge and so is not reported. COG and CR were correlated at $r = .841$ in M4a.

Table 2).[1] Standardized factor loadings for the model applied to WMH data based on Scheltens' scaling were: $\lambda_{b1} = 0.512$ (ARLBV), $\lambda_{b2} = -0.892$ (CBF), and $\lambda_{b3} = 0.309$ (WMH). Thus, factor scores from the model applied to WMH prevalence based on Erkinjuntti's scaling were used due to its superior representation (stronger loadings for both WMH and ARLBV) of the brain status factor.

Finally, individuals' residualized cognitive scores were obtained by regressing each of their 15 cognitive scores on the brain status factor score and retaining the residual term. Correlations between the original cognitive scores and the residualized scores ranged from $r = .854$ (letter-digit coding task) to $r = .986$ (Culture Fair task). In general, differences in cognitive scores pre- vs. post-residualization were most pronounced for processing speed items and least pronounced with respect to fluid reasoning items.

COG and CR structural factor models

Fit statistics for COG and for CR (estimated independently as second-order factor models) indicated acceptable fit for both models (Table 2). Combining these models to concurrently estimate COG and CR as second-order constructs resulted in model nonconvergence. Therefore, for the purpose of conducting tests of factorial invariance, a two-stage approach was used: Domain-specific factor scores were first extracted from the independent models of COG and CR (i.e., scores for processing speed, verbal memory, visuospatial memory, fluid reasoning, and vocabulary – and the corresponding "reserve" scores). COG and CR were then modeled as latent variables indicated by these domain-specific factor scores, applying a standard sequence of tests for factorial invariance. Likelihood ratio tests showed that constraining factor loadings across these constructs (configural vs. weak invariance) resulted in significantly worse model fit ($\Delta\chi^2 = 128$, $\Delta df = 4$, $p < .001$), rendering subsequent tests moot. In other words, tests of factorial invariance showed that the five cognitive sub-domains were differentially representative of COG vs. CR, highlighting qualitative differences across the constructs.

Moreover, model fit statistics indicated that even the least restrictive two-stage COG + CR model (configural invariance) did not fit the data well: RMSEA > 0.10 and SRMR > .08. So interpretation was based on patterns of factor loadings from the independent second-order models (M2a and M2b; Table 3). For COG, standardized loadings for domain-specific factors were: 0.76 (processing speed), 0.83 (verbal memory), 0.86 (visuospatial memory), 0.92 (fluid reasoning), and 0.80 (vocabulary). For CR, domain-specific loadings were: 0.69 (processing speed), 0.77 (verbal memory), 0.80 (visuospatial memory), 0.95 (fluid reasoning), and 0.77 (vocabulary). Thus, compared with COG, CR showed a stronger emphasis on fluid reasoning and less emphases on the other domains.

[1]Shared common variance among the brain factor indicators was approximated by averaging their squared factor loadings, $\mu(\lambda^2) = .36$

Table 3. Summary statistics and factor loadings for cognition variables

	Summary		Standardized Factor Loadings	
Latent and observed variables	*M*	*SD*	COG (M2a)	CR (M2b)
Processing Speed			0.76	0.69
Visual Search	106.08	20.65	0.66	0.55
Letter-Digit Coding	60.15	16.25	0.84	0.77
Alphabet Coding	215.25	56.16	0.96	0.96
Verbal Memory			0.83	0.77
Verbal Free Recall	9.04	3.72	0.83	0.81
Propositions About People	4.87	2.52	0.73	0.70
Digit Span Backwards	4.51	1.45	0.44	0.35
Visuospatial Memory			0.86	0.80
Rey-Osterrieth Figure	22.48	7.58	0.75	0.71
Delayed Match-to-Sample	11.80	3.76	0.70	0.66
Circle/Object	6.98	2.79	0.74	0.70
Fluid Reasoning			0.92	0.95
Heim 4-1	38.59	10.69	0.92	0.90
Heim 4-2	37.97	11.23	0.82	0.82
Culture-Fair Intelligence	29.30	7.06	0.76	0.77
Vocabulary			0.80	0.77
Mill Hill A	23.50	4.03	0.82	0.83
Mill Hill B	18.20	5.44	0.88	0.86
WAIS	54.68	10.77	0.87	0.86

Note: COG = cognition, CR = cognitive reserve. Summary statistics (mean, standard deviation) are based on original (non-residualized) cognitive measures. M2a = factor loadings estimated from the second-order model of COG. M2b = factor loadings estimated from the second-order model of cognitive reserve. Loadings of domain-specific cognitive factors (i.e., processing speed, verbal memory, visuospatial memory, fluid reasoning, and vocabulary) onto COG and CR are shown in the corresponding rows/columns. (e.g., the standardized loading of processing speed onto CR = 0.69).

Associations with COG and CR

Results from structural regression models are presented in Table 4. Combined, the predictors accounted for about 70% of variability in COG and 60% of variability in CR. Patterns of statistically significant predictive associations were identical for COG and CR. Variables that were significantly predictive after adjustment for demographic covariates (age, biological sex, APOE status) were years of formal education (strong positive association), occupational class (lower skilled showed worse COG and CR), hobbies (moderate positive association), and mobility difficulties (weak-to-moderate negative association). Follow-up tests of differences in

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Table 4. Predictors and proxies of cognition (COG) and cognitive reserve (CR)

Predictor	Outcome	COG		CR	
		β	β_{adj}	β	β_{adj}
Demographic covariates					
Age at MRI		−0.583*		−0.458*	
Biological sex (= female)		0.130		−0.057	
APOE e4 (yes)		0.117		0.186	
Education and Occupation					
Years of formal education		0.618*	0.503*	0.600*	0.510*
Occupational class					
Professional		0.211	0.207	0.205	0.197
Skilled (nonmanual)		−0.299*	−0.245*	−0.409*	−0.358*
Skilled (manual)		−0.185	−0.169	−0.233*	−0.199
Partly skilled		−0.297*	−0.257*	−0.322*	−0.295*
Socio-relational variables					
Married or Cohabitating (yes)		0.183	0.118	0.130	0.042
Number of children seen regularly		0.020	−0.029	0.078	−0.007
Number of others in the home		0.244	0.066	0.194	0.017
Socializing (hr/mo)		−0.118	−0.053	−0.126	−0.083
Have one or more pets (yes)		0.332*	0.021	0.239*	−0.008
Lifestyle					
Tobacco smoker (yes)		−0.145	−0.095	−0.067	−0.093
Units of alcohol per week		0.138	0.130	0.137	0.070
Difficulty with housework		−0.166	−0.149	−0.147	−0.132
Difficulty with personal mobility		−0.327*	−0.246*	−0.373*	−0.281*
Physical activity (hr/mo)		0.139	0.004	0.160	−0.005
Number of hobbies		0.443*	0.407*	0.410*	0.412*
Hours of sleep per night		0.062	0.019	0.072	0.010
Usually sleep through the night (yes)		0.035	−0.004	0.080	0.031
Health					
Heart attack		−0.076	0.020	−0.076	−0.058
Hypertension		0.023	0.016	0.072	0.067
Diabetes		−0.169	−0.206	−0.105	−0.134
Depressive symptoms (GDS)		−0.209	−0.149	−0.187	−0.135

Note. β_{adj} = Standardized effect after adjustment for age, biological sex, and APOE e4 status.
*= $p < .05$, with false discovery rate correction. R-square values from models combining all predictors were .703 (COG) and .602 (CR).

the effects (on COG vs. CR) of these latter predictors were in all cases nonsignificant ($\Delta\chi^2 = 0.08–3.52$; padj = .24–.78).

Point-biserial correlations between CR factor scores (global and domain-specific) and dementia status at death ranged from −.301 to −.017 and were all nonsignificant except for visuospatial memory ($r = -.301$, $p = .01$). Follow-up tests of residualized scores for each of the visuospatial memory tasks showed that none on their own was significantly predictive of conversion to dementia: ROCF ($r = -.27$, $p = .07$), DMS ($r = -.17$, $p = .25$), COP ($r = -.19$, $p = .12$).[2]

Discussion

Cognitive scores across five domains (processing speed, verbal memory, visuospatial memory, fluid reasoning, and vocabulary) were differentially representative of COG and CR. Fluid reasoning most strongly represented both COG and CR. Fluid reasoning became even more prominent in CR (i.e., after residualization on brain status) relative to COG, whereas the converse was true for all other abilities. Despite this evidence of differential representation, COG and CR were very strongly correlated ($r = .841$), and all cognitive abilities were in general strongly representative of both COG and CR. Key predictive associations were nearly identical for COG and CR and implicated education, occupational class, number of hobbies, and mobility. With respect to predicting dementia status at time of death, only visuospatial memory (both before and after residualization) was significantly informative.

[2]The pattern of associations of dementia status with nonresidualized cognitive factors was identical with respect to statistical significance, but the estimated correlation between visuospatial memory and dementia was slightly reduced ($r = .29$).

These results partially conformed to the hypothesized outcome that measures of intelligence would be more prominent in CR than in COG. The basis for this hypothesis was that processing speed and memory measures are known to be comparatively sensitive to the effects both of normal healthy aging and brain-related pathological processes, whereas measures of intelligence are more robust to such effects. Thus, it was expected that intelligence would be comparatively more representative of CR insofar as residualization on brain indices (WMH, cerebral blood flow, and cerebral volume loss) would "dampen" individual variation in memory and speed measures. The current outcome implicating fluid reasoning, although modest, is important given that CR based on residualization has most often been operationalized in relation to episodic memory, whereas both adult developmental psychometric theory and common CR proxies (education, occupation, intellectual stimulation) implicate intelligence as key to CR's robustness.

That fluid reasoning showed increased representation in CR whereas vocabulary (crystallized intelligence) showed decreased representation in CR departed somewhat from this expectation. However, fluid reasoning may also benefit more (than crystallized intelligence) from ongoing engagement in intellectually stimulating activities (Stankov & Chen, 1988), such as cognitively demanding occupational roles, which here were correspondingly more closely associated with CR than with COG. The particular importance of *ongoing* intellectual stimulation for promoting CR was previously noted by Reed et al., (2010) in one of few studies to similarly operationalize CR as a multidimensional construct. It follows that efforts targeting fluid reasoning and related executive

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functioning skills may prove efficacious for the prevention and/or mitigation of the effects of reduced brain health on the manifestation of cognitive impairment and dementia (Ploughman et al., 2019; Nguyen et al., 2019).

Beyond the expected significant predictive associations with common CR proxies (education, occupation, hobbies; Stern, 2009), difficulty with mobility also predicted COG and CR. Mobility may serve as a protective factor in cognitive aging insofar as it facilitates cardiovascular exercise and, by extension, cerebrovascular health (Zhao et al., 2014). However, we also examined the effects of physical activity (light and strenuous exercise) on COG and CR, and these were nonsignificant. Limited mobility is associated with numerous chronic disease states, and these may reflect and/or influence brain health in ways beyond vascular functioning. For example, peripheral neuropathy has been linked to brain connectivity abnormalities (Rocca et al., 2014). Reduced mobility may also limit social participation, with downstream adverse effects on cognitive health (Evans et al., 2018; Kalu et al., 2022). Here, we found no evidence that social relations or socializing benefited COG or CR.

With respect to correlations of COG and CR with dementia status at time of death, only visuospatial memory performance was significantly (moderately, negatively) predictive of transition to dementia. Visuospatial memory has previously been shown to be diagnostic of AD, dementia of Lewy bodies (LB), and vascular dementia (Pal et al., 2016). Visuospatial memory (vs. verbal memory) has also been shown to be selectively sensitive to LB and "combined pathology" dementia (Johnson et al., 2005). Moreover, a systematic search of studies (1960–2016) investigating visuospatial dysfunction in dementia concluded that visuo-constructional tasks (and particularly the ROCF task, included here) showed "the greatest diagnostic potential in dementia" (Salimi et al., 2018). Unfortunately, dementia status in the current study was limited to coroner reports, which lacked specificity in dementia classification. Had more diagnostically nuanced measures of dementia been available, it is likely that associations with other cognitive domains, which may be more selectively associated with specific dementia profiles, would have emerged.

There were several limitations. First, we had a small sample size (hindering our ability to accurately detect smaller effects). WMH prevalence was based on physician visual ratings using older metrics (we selected the more reliable of two approaches). Cognitive performance was residualized on a single "brain factor" rather than on individual brain measures (see justification in Methods), which may have reduced the total brain-related variability removed from cognitive performance. The study was cross-sectional, so we could not examine associations with rate of progression of dementia symptoms or "dynamic" features of CR. Dementia status was limited to information provided on death certificates and so was nonspecific as to type of pathology. We also lacked information regarding age at dementia onset, so we were unable to determine whether CR measures and related protective factors moderated rate of progression.

Notwithstanding, results were in line with our hypothesis that intelligence (vs. memory or speed) would be comparatively more salient in relation to CR than in relation to general cognition. Predictive associations were highly consistent with prior studies implicating education, occupational complexity, and engagement in intellectually stimulating hobbies as CR proxies/protective factors. Moving forward, it will be important to confirm the roles of fluid reasoning and related executive functioning capacities in CR, which as a construct informed by psychometric theory implicates cognitive abilities beyond episodic memory as an isolated process. Additionally, fortification of CR through cognitive training and related intervention strategies targeting fluid abilities appears to be an especially promising area for future inquiry.

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