Aging Brain 2 (2022) 100027

Contents lists available at ScienceDirect

Aging Brain

journal homepage: www.elsevier.com/locate/nbas

Model of brain maintenance reveals specific change-change association between medial-temporal lobe integrity and episodic memory

Jarkko Johansson [a,b,*], Anders Wåhlin [a,b], Anders Lundquist [b,c], Andreas M. Brandmaier [d,e], Ulman Lindenberger [d,e], Lars Nyberg [a,b,f,g]

[a] Department of Radiation Sciences, Diagnostic Radiology, Umeå University, S-90187 Umeå, Sweden
[b] Umeå Center for Functional Brain Imaging (UFBI), Umeå University, S-90187 Umeå, Sweden
[c] Department of Statistics, USBE, Umeå University, S-90187 Umeå, Sweden
[d] Center for Lifespan Psychology, Max Planck Institute for Human Development, Lentzeallee 94, D-14195 Berlin, Germany
[e] Max Planck UCL Centre for Computational Psychiatry and Ageing Research, Berlin Germany and London, UK
[f] Department of Integrative Medical Biology, Umeå University, S-90187 Umeå, Sweden
[g] Wallenberg Center for Molecular Medicine, Umeå University, Umeå, Sweden

ARTICLE INFO

Article history:
Received 4 August 2021
Revised 21 December 2021
Accepted 22 December 2021
Available online 10 January 2022

ABSTRACT

Brain maintenance has been identified as a major determinant of successful memory aging. However, the extent to which brain maintenance in support of successful memory aging is specific to memory-related brain regions or forms part of a brain-wide phenomenon is unresolved. Here, we used longitudinal brain-wide gray matter MRI volumes in 262 healthy participants aged 55 to 80 years at baseline to investigate separable dimensions of brain atrophy, and explored the links of these dimensions to different dimensions of cognitive change. We statistically adjusted for common causes of change in both brain and cognition to reveal a potentially unique signature of brain maintenance related to successful memory aging. Critically, medial temporal lobe (MTL)/hippocampal change and episodic memory change were characterized by unique, residual variance beyond general factors of change in brain and cognition, and a reliable association between these two residualized variables was established ($r = 0.36$, $p < 0.01$). The present study is the first to provide solid evidence for a specific association between changes in (MTL)/hippocampus and episodic memory in normal human aging. We conclude that hippocampus-specific brain maintenance relates to the specific preservation of episodic memory in old age, in line with the notion that brain maintenance operates at both general and domain-specific levels.

Introduction

The aging brain is characterized by marked individual differences in rates of change. This fact serves as a cornerstone in the theory of *brain maintenance*, which states that "[*i*]*ndividual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related cognitive decline*" (Nyberg et al., 2012, p. 395). Supporting evidence for this notion have been observed in previous longitudinal studies, with samples partly overlapping the one from the present study [11,26], demonstrating positive change-change associations for hippocampus/medial-temporal lobe (MTL) atrophy and episodic memory [6,16,19,32]. A largely unresolved issue is whether older individuals displaying minimal hippocampal atrophy are characterized by

* Corresponding author at: Department of Radiation Sciences, Diagnostic Radiology, Umeå University, S-90187 Umeå, Sweden.
E-mail address: jarkko.johansson@umu.se (J. Johansson).

https://doi.org/10.1016/j.nbas.2021.100027
2589-9589/

preserved whole-brain gray matter volumes [22], and relatedly, whether individuals with well-preserved episodic-memory in aging also tend to have intact cognition more generally. Put somewhat differently, this issue relates to the fundamental question posed by Rabbitt (1993), "*does it all go together when it goes?*".

Previous longitudinal studies investigating age-related changes in brain volumes have found correlated changes for some brain regions [7,30]. Likewise, a high degree of shared variance in age-related changes across various cognitive abilities has been established [9,39]. As for change-change associations, Fletcher et al. [8] used multilevel latent modeling methods to measure individual differences in rates of change and found that global gray matter atrophy was the strongest predictor of general cognitive decline, whereas specific temporal lobe atrophy and baseline hippocampal volume showed incremental contributions. In a recent study, Cox et al. [1] identified three major dimensions of cortical change, of which the most general was associated with change in general cognition as well as the cognitive domains of memory, visuospatial ability, and processing speed. No additional associations across distinct spatial dimensions and cognition were observed [1], but it should be noted that subcortical structures such as the hippocampus were not part of their analysis. In sum, previous findings point to the existence of domain-general dimensions of both cortical change and cognitive change, with initial evidence that brain changes and cognitive changes are linked in a domain-general manner. It is an open question whether domain-specific links above the link at the general level can be observed. Conceptually, it is likely that brain maintenance operates at both general and domain-specific levels [22,28]. However, their joint existence in aging-induced change-change relations of brain and behavior has not been demonstrated thus far.

In the present study we investigated the potential existence of a specific relationship between hippocampus/MTL atrophy and episodic memory decline that extends beyond general dimensions of correlated change in brain (whole-brain gray matter) and cognition (episodic memory, processing speed, fluid intelligence, verbal fluency) [1,2,8,14,17,18,25,34]. To address this question, we used structural equation modeling [SEM; Kievit et al., [15]], which allows simultaneous modeling of both general and specific links between brain and cognitive changes, and thus allowed us to quantify specific associations between episodic memory changes and hippocampal volume changes while statistically adjusting for general brain changes and general cognitive changes.

Materials and Methods

Sample characteristics

The study participants in the present analyses were part of the longitudinal Betula Prospective Cohort Study on memory, health and aging [21]). Informed consent was given by all participants, in accordance with the guidelines of the Swedish Council for Research in the Humanities and Social Sciences. Parts of these data have been reported previously [11], and we now reanalyze them by a statistical approach accounting for global dimensions within measures of both brain and cognition [34]. Within the project, seven waves of cognitive assessment and three waves of structural magnetic resonance (MR) imaging have been conducted. In this study, the sample was based on 262 healthy (no severe neurological disorders or dementia) older adults, who entered the study at first (1988–1990, T1) or second (1993–1995, T2) wave of data collection, and underwent MRI at fifth (2008 – 2010, T5) wave of data collection. The age of the participants at T5 ranged from 55 to 80 years (mean = 66.5, standard deviation [SD] = 7.8 years; 53.8% female). Absence of severe neurological findings was ascertained by a trained neuroradiologist at each wave of data collection, and clinically relevant signs of dementia were screened by a gero-psychiatrist also at each wave of data collection. Of the initially scanned 262 individuals, 155 remained healthy and underwent a follow-up MRI examination at the sixth (2013–2014, T6, age 59 – 84 years, mean = 68.8, SD = 7.0, 52.9 % female) wave of data collection, and 94 remained healthy and returned for the seventh (2018–2019, T7, age 63 – 88 years, mean = 72.5, SD = 6.4, 57.4 % female) wave of data collection. Drop out was not completely at random as described previously between T5 and T6 [11]. Briefly, the reasons for T5-T6 dropout were; decline to participate or no contact (n = 92), death (n = 8), and scanned but not healthy (n = 7). The healthy returnees were found to be younger (-3.5 years) than the dropouts [11]. Reasons for T6-T7 dropout were; decline to participate, no contact, or death (n = 58), and three individuals were scanned but not finally found to be meet the inclusion criteria (dementia).Lag between T5 and T6 data collection points were in average four years ± 2.5 months (SD), and between T6 and T7 in average three years ± 3 months (SD).

Cognitive measures

The cognitive tests and testing procedures have been described previously [11,20]. Episodic memory performance was measured by 5 episodic memory tasks. Two tasks involved immediate free recall of sentences (16 items each). In one condition participants enacted the sentences with objects provided by the test leader. In the other, the sentences were studied visually and verbally without enactment. After a delay, participants were asked to recall nouns from the enacted/studied sentences, with noun categories (e.g., fruits, animals) as cues. Nouns from the enacted and studied task conditions were counted as separate measures (16 items each). The fifth measure was immediate free recall of a list of 12 unrelated nouns. In order to reduce practice effects, counterbalancing was performed between test occasions such that the item-list that was studied with enactment at one test occasion, and was studied without enactment on the next test occasion 5 years later. In addition, there were 8 list-order variations of each list, which were counterbalanced over test occasions and participants.

The Block Design test from the revised form of Wechsler Adult Intelligence Scale [41] was used to assess visuospatial ability and fluid IQ. This test requires the participants to use colored blocks to recreate spatial patterns shown to them on cards. The raw score from Block Design (maximum 51) was used in the current analyses.

Word fluency was measured by 3 conditions in which participants orally generated as many words as possible, during 1 min, satisfying the following criteria: (1) starting with the letter A; (2) 5- letter words with the initial letter M; and (3) names of professions beginning with the letter B [20].

The measure of processing speed was based on three paper–pencil tests. The first was a letter-digit substitution test requiring participants to pair letters with digits according to a letter-digit transformation key, which was given on the top of the paper form. The score was the number of correct digits that the participant managed to fill in during 1 min (maximum 125). The second measure was letter comparison, in which participants were instructed to compare pairs of nonword strings of 3–9 letters, in order to judge whether they were the same or different. The score was the number of correctly judged pairs during 30 s (out of a maximum of 21). A similar test, figure comparison, was the final measure of speed. Here participants compared pairs of abstract line figures during 30 s (maximum 30). All three versions of the tests listed all test items simultaneously on one A4-sized paper.

For primary statistical analysis, composite scores of episodic memory, word fluency and processing speed were constructed as a sum of the scores from the individual tests. Earlier investigation using the same tests found significantly improved reliability of the composite scores over the subtest scores [11]. All available tests were included in the composite scores at each test wave, and changes to the composition of the episodic memory test battery at W3 were adjusted for as described earlier [12]. An individual scaling factor was determined using episodic memory test scores at W1 and W2 to translate a two-test composite score to a five-test composite score at W3.

MRI data acquisition and estimation of gray matter volumes

MRI data acquisition and procedures for estimation of gray matter volumes have been described previously [11]. MRI data were collected using the same 3 T General Electric magnet resonance tomograph, equipped with a 32 channel head coil, at all three scanning occasions. T1-weighted images were acquired with a 3D fast spoiled gradient echo sequence (180 slices with a 1 mm thickness; TR: 8.2 ms, TE: 3.2 ms, flip angle: 12 degrees, field of view: 25 × 25 cm). To obtain measures of GM volume, the T1-weighted images from three test occasions were first processed separately using the standard processing stream in FreeSurfer v.6.0 (http://surfer.nmr.mgh.harvard.edu/). Technical details of this procedure have been documented online and in previous publications [4]. Briefly, the processing includes motion correction, normalization of multiple T1-images, applying a hybrid watershed/surface deformation procedure to remove non-brain tissue, Talairach transformation, segmentation of subcortical WM and GM structures, intensity normalization, tessellation of the GM/ WM boundary, topology correction, as well as surface deformation to optimize placement of GM/WM and gray/cerebrospinal fluid border. Subsequently the images from baseline and follow-up were processed through the FreeSurfer longitudinal processing stream, which creates an unbiased within-subject template image of the longitudinal data, to increase reliability of the segmentation and parcellation of brain regions over time [31]. The reported data were derived from the longitudinal FreeSurfer pipeline. For the cortical regions of interests (ROIs) used in our analyses, the parcellation was based on the "Desikan-Killiany" atlas in FreeSurfer [3], while the subcortical segmentation was based on Fischl et al. (2002). Quality of all segmentations were visually controlled as described previously, and exclusions of separate regions were made when necessary [11]. This quality control led to exclusion of all data from one participant (uncurable segmentation errors), and from five additional participants one (non-hippocampal) region was excluded for each individual.

White matter lesion volumes were estimated as described previously [11], and they were included in control analysis assessing the influence of gray matter atrophy to cognition above-and-beyond the effects of cerebrovascular insults. T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR) images were acquired with a 2D T2 FLAIR sequence (48 slices with 3 mm thickness; TR: 8000 ms, TE: 120 ms, field of view: 24 × 24 cm). Lesions were segmented by the lesion growth algorithm [36] as implemented in the Lesion Segmentation Tool (LST) version 2.0.14 (http://www.statistical-modelling.de/lst. html) for SPM12, and threshold at kappa = 0.3.

Statistical analysis

Evaluation of mean change and inter-individual differences in change

Linear mixed effects models (LME) were configured to evaluate fixed effects of change over time, time by age interactions as well as participant-specific random effects of intercept and slope [5]. Participant-specific random effects were added to the model one-by-one, to form two nested models: one with participant-specific intercept only, and one with both participant-specific intercept and slope. The complete LME model including participant-specific intercepts and slopes was defined as follows.

$$y_{ij} = \beta_0 + \beta_1 age_i + \beta_2 time_{ij} + \beta_3 age_i \times time_{ij} + b_{0i} + b_{1i} time_{ij} + \varepsilon_{ij}$$

where, y_{ij} is either the regional gray matter volume or the cognitive score for *i*th participant at *j*th measurement occasion. βs denote fixed effect estimates, while *b*s denote participant-specific random effect estimates, and ε stands for residual error. *Age* was entered as "cohort age" in five year age segments (45,50, 55, etc.) at baseline and centered by the mean age, and *time* was the time elapsed from study entry. Fixed effects of this model captured the average longitudinal change across the participants, the effects of age,

and age by time interactions, reflecting potential differences in overall change dependent on baseline age. Participant-specific longitudinal effects were considered in a step-wise manner and model comparisons were conducted to evaluate the significance of individual slopes (b_{1i}). LME fits were conducted using R (version 4.0.3; https://www.r-project.org/) and package nlme (version 3.1; https://cran.r-project.org/web/packages/nlme), and model comparisons using a likelihood-ratio-test (LRT). Significance ($p < 0.05$) of the LRT comparing the complete model with a model excluding participant-specific slopes was interpreted as an indication of reliable inter-individual variance in change. The null hypothesis was that individual change over time would not differ from the group mean change at each corresponding age segment. *b*1i, the random effects of time were used as participant-specific estimates of change, and indicators for which the effect was not significant were excluded from subsequent analysis.

Modeling dimensionality in change

Previous studies suggest a strong general cognitive ability factor (*g*-factor) explaining a large portion of inter-individual differences in cognitive change in aging, accompanied by distinct dimension of, for example, memory change [2,39]. Notably, this organizational structure was established in an earlier investigation with a sample partly overlapping the present [23]. Based on these observations, a hierarchical model was constructed and structural equation modeling (SEM) in R [lavaan, version 0.6 [33] was conducted using LME-derived individual slopes as estimates of cognitive change, to statistically adjust for global cognitive change [2]. All domains with reliable inter-individual differences in change (as indicated by the LME fits) were used as indicators, and each domain was allowed to load on a common first-level global cognitive factor (g-factor). Loadings to the common g-factor were inspected to evaluate the soundness of this model configuration, and residual variances of domain-specific indicators were inspected to evaluate the reliability of inter-individual differences in each residualized variable. A z-test as provided in lavaan was used for this purpose, thresholded at $P(>|z|) < 0.05$. A factor model with three indicators is a saturated model hence we do not report measures of goodness-of-fit for this model.

Previous studies have indicated covariances across some regional estimates of gray matter change [30], suggesting common causes that explain part of inter-individual differences in the aging brain. To investigate the possibility that there are spatially distinct dimensions of gray matter change (beyond a common cause), we first conducted exploratory factor analysis (EFA) on regional estimates of brain change, which mirrors previous analysis reported by Cox et al. [1]. In analogy to the procedure applied for cognitive variables, all brain regions exhibiting reliable inter-individual differences in change (as indicated by the LME fits) were used as indicators. A bi-factor model was configured to examine the oblique factor structure beyond any common variance shared using the Schmid-Leiman transformation [35] in R (psych, version 2.0.9; https://CRAN.R-project.org/package = psych). This transformation was conducted simultaneously on left and right hemisphere ROIs and factor loadings were inspected to detect spatially distinct dimensions of change. Next, the cortical factor structure identified from Schmid-Leiman transformation was imposed into a bi-factor SEM configuration, allowing all indicators to load onto a general brain factor and additionally to spatially distinct and mutually uncorrelated factors of brain change. Owing to our specific hypothesis regarding hippocampus and related structures, left and right hippocampus and parahippocampal gyrus served as sole indicators of (residual) hippocampal/MTL latent, and their loadings were constrained to be equal to ascertain that the model is locally identified. Model fit parameters and loadings to the general brain factor and specific factors were inspected to evaluate the soundness of this model configuration. Associations among gray matter change variables and white matter lesion volumes at T5 were inspected to identify potential confounding factors due to concomitant cerebrovascular insults.

To analyze the degree to which cognitive change was associated with brain volume change, we then extended the SEMs to form a single multivariate model of coupled change in cognition and brain volume (see Fig. 3). The aggregate model was configured according to the above descriptions for cognitive and brain volume changes, allowing for correlations between the variables of interest. Our primary hypothesis concerned the coupling between residualized HC/MTL and residualized EM components of the model, but for the sake of completeness, the correlations were additionally tested across all the available change-change pairs (general-general, general-specific, specific-specific). Finally, the correlations were adjusted for concomitant effects of cerebrovascular integrity by regressing the white matter lesion volumes at T5 with the gray matter volume factors in the composite model.

Results

Cognitive changes

The results of the LME model estimations are presented in Table 1. A significant effect of age was observed for episodic memory, processing speed, and visuospatial ability (block design) but not for fluency. A significant mean effect of time was observed for all cognitive variables, together with significant negative age by time interaction effects, suggesting accelerated change at older ages. The likelihood-ratio tests across LME model configurations with and without participant-specific effects of time indicated robust inter-individual differences in change for episodic memory, processing speed, and visuospatial ability but not for fluency. Due to the lack of reliable inter-individual differences in change, fluency was excluded from subsequent analyses.

A preliminary principal component analysis was first conducted to assess the strength of the hypothesized general factor of cognitive change in the present data, using change in episodic memory, processing speed, and visu-

Table 1
Statistical results for fixed effects in linear mixed effects models estimating cognitive change over time, and results of model comparison (likelihood-ratio-test; LRT). Statistically significant effects ($p < 0.05$) are highlighted using bold font.

	Age	Time	Age × Time	LRT
Episodic memory	**T(289) = −5.14**	**T(889) = −9.64**	**T(889) = −5.82**	**34.72**
Fluency	T(289) = −0.85	**T(795) = −4.68**	**T(795) = −3.82**	0.38
Spatial ability	**T(289) = −7.96**	**T(894) = −15.92**	**T(894) = −2.57**	**20.8**
Processing speed	**T(289) = −8.56**	**T(894) = −19.08**	**T(894) = −4.84**	**21.18**

ospatial ability as indicators. This analysis corroborated a strong loading on the first principal component (46% of total variance explained), which is consistent with a general factor. Next, we specified a SEM with a first-level general cognitive factor, and freely estimated loadings for the three indicators. Standardized loadings onto the general factor were 0.44, 0.61 and 0.29 for episodic memory, processing speed, and visuospatial ability, respectively. This pattern indicated a fairly well-balanced general factor of change across cognitive domains, though visuospatial ability loaded less strongly, and confirmed the predicted factor structure in the present data. Residual variances in each of the cognitive indicators were statistically significant (z-values 3.31 – 10.5, p's < 0.001), allowing for investigating correlations with brain indicators in a domain-specific ('general-cleaned') manner.

Brain changes

The results of the LME model estimations are presented in Supplemental Table 1. Reliable inter-individual differences in gray matter volume change over time were observed in bilateral hippocampus and in a number of cortical regions. Spatial maps of cortical regions are presented in Fig. 1. Robust inter-individual differences in change were observed in bilateral prefrontal cortex, bilateral temporal cortex, and right parietal cortex, but not in sensorimotor cortex and occipital cortex.

Next, in order to identify common dimensions of brain atrophy, we conducted an EFA that included brain regions exhibiting reliable interindividual differences in change. In an initial principal component analysis, the first component accounted for 42% of the total variance, suggesting a general dimension of gray matter atrophy. Next, we conducted a bi-factor analysis using the Schmid-Leiman transform to investigate the structure of general and region-specific variation in change. This analysis identified a general factor of gray matter volume change [mean g-loading across regions was 0.40 (0.20–0.70)], and indications for one additional cortical dimension of specific change was found (see Supplementary Table 2 for factor loadings >0.5). This dimension of specific volume change involved the superior frontal cortex, including bilateral superior frontal, bilateral caudal middle frontal, and left rostral middle frontal ROIs (see column F3 in Supplementary Table 2, mean loading 0.64, eigenvalue 2.4). The other two oblique factors (F1 & F2 in Supplementary Table 2) exhibited lower eigenvalues (1.4 and 1.9, respectively) than F3, lower average loadings (0.3 and 0.4, respectively) than F3, and consisted of anatomically discontinuous areas, and were therefore not deemed as potential sources of specific variance in cortical atrophy.

A bi-factor SEM was specified in view of the results from the EFA in the cortex and *a priori* factor for hippocampus & medial temporal cortex. A latent variable of general brain volume change was defined by regions showing a loading greater than 0.25 to "g" in the Schmid-Leiman transformation (see Supplementary Table 2 for loadings), and orthogonal latent variables of change were defined for medial temporal lobe (bilateral hippocampus and bilateral parahippocampus), and for superior frontal cortex. Model fit parameters were as follows: RMSEA = 0.089, CFI = 0.80, χ^2 (df = 318) = 702 ($p < 10^{-3}$), indicating acceptable model configuration. A robust latent variable of general brain gray matter volume change was confirmed (mean loading to g = 0.48 [0.18 – 0.85]), as well as a specific HC/MTL latent variable (equal loadings of 0.45) and a specific superior frontal latent variable (mean loading 0.63 [0.45 – 0.70]). There was no evidence for correlation between the residual HC/MTL and residual superior frontal variables (correlation = 0.017, p = 0.89). Furthermore, the hypothesized model including the HC/MTL factor yielded significantly better representation of the data as compared to model omitting this factor ($\Delta\chi^2 = 36$, $p < 10^{-8}$). Control analysis using white matter lesion volumes as a covariate indicated only a trend-level correlation between residual superior frontal cortex change and lesion volume at T5 (Supplementary Table 3, r = −0.13, p = 0.14). No other correlations approached significance. These results confirmed that distinct dimensions of MTL/hippocampal and superior frontal cortex change exhibited significant residual variance beyond the general dimension of age-related brain atrophy, that was not strongly associated to cerebrovascular status.

Linking cognitive and brain changes

Brain-cognition change-change associations were assessed using a multivariate brain-cognition SEM, configured on the basis of univariate models by allowing correlations between variables of interest. A summary of the pairwise correlations is presented in Table 2 (see also Figs. 2 and 3).

We found a statistically significant correlation ($r = 0.35$, p = 0.042; Table 2) between the latent variables of general brain volume change and global change in cognition (Fig. 2A). Critically, a statistically significant correlation ($r = 0.36$, $p < 0.01$) was detected between the residualized variables of MTL/hippocampal change and episodic memory change (Fig. 2B). This result indicates that medial temporal lobe gray matter volume change was specifically

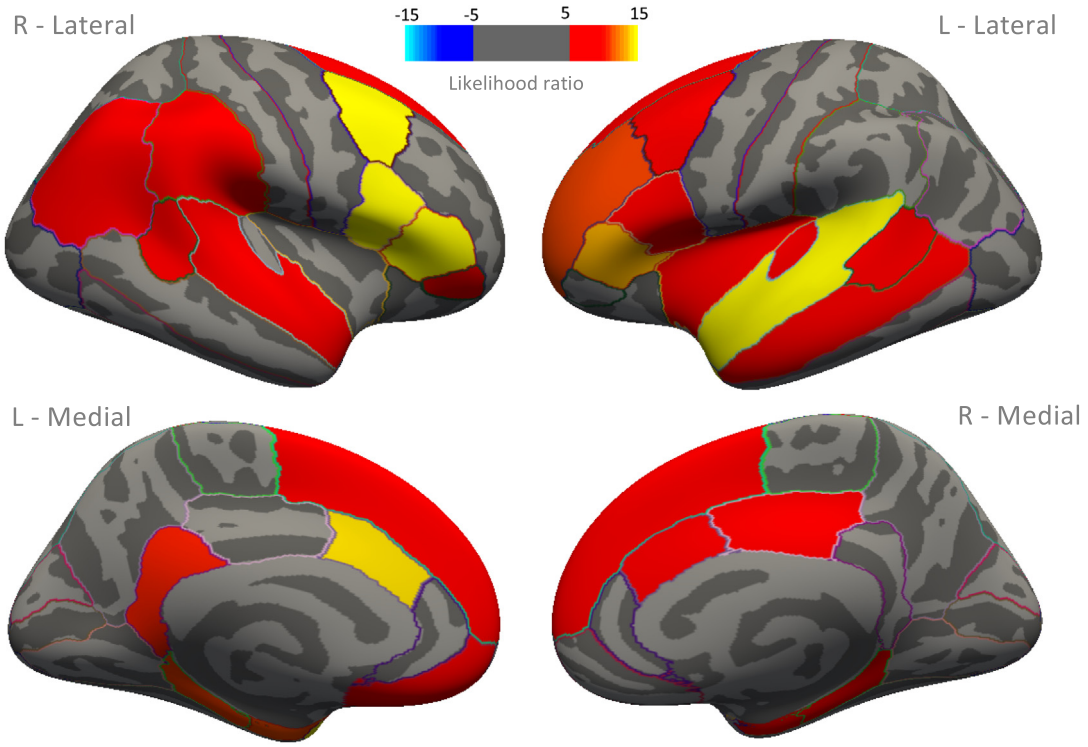

Fig. 1. Regions exhibiting reliable inter-individual differences in gray matter volume change over time. Hippocampus not shown. Warmer color corresponds to higher likelihood ratio in a model comparison between a reference model and a model including individual rates of change (see Methods for detail).

Table 2
Pair-wise correlations across the distinct factors of brain-cognition change. Multivariate SEM analysis was conducted as described in the Methods. Statistically significant correlations ($p < 0.05$) are highlighted using bold font.

	Global brain factor	Hippocampus/ MTL	superior-PFC
Global cognitive factor	**0.35 (p = 0.042)**	**0.52 (p = 0.01)**	0.30 (p = 0.15)
Episodic memory	0.09 (p = 0.32)	**0.36 (p = 0.0063)**	0.05 (p = 0.59)
Processing speed	**0.21 (p = 0.046)**	0.14 (p = 0.31)	−0.07 (p = 0.47)
Visuospatial ability	0.02 (p = 0.79)	−0.11 (p = 0.41)	**0.24 (p = 0.016)**

associated with change in episodic memory, beyond the general dimensions of gray matter volume and general cognitive change. In addition, global change in cognition was related to residualized MTL/hippocampal change ($r = 0.51$, $p = 0.01$, Table 2). Furthermore, a correlation of global brain change with processing speed change was detected ($r = 0.21$, $p = 0.046$; Table 2), as well as a correlation between residualized superior-PFC change and residualized change in visuospatial ability ($r = 0.24$, $p = 0.016$; Table 2). Control analysis including white matter lesion volumes at T5 as a regressor confirmed that the correlation between superior-PFC change and change in visuospatial ability was not driven by concomitant cerebrovascular insults ($r = 0.20$, $p = 0.032$; correlation adjusted for WML effect; Supplemental Table 4).

Discussion

We used a latent variable approach to separate general and specific dimensions of cerebral and cognitive changes and their interrelations. Specifically, we investigated the extent to which brain maintenance in support of successful memory aging is specific to memory-related brain regions. In line with earlier findings, we found that rates of change across three cognitive domains and across multiple brain regions are substantially correlated, generalizing the notion of the positive manifold [37] from cognitive abilities to cognitive decline and cerebral atrophy in adulthood and old age. At the same time, we were able to confirm the postulated specificity of changes in grey-matter volumes for different cognitive domains. As hypothesized [22], we found evidence for specificity in the relationship between changes in hippocampus/MTL volume and changes in episodic memory.

The presence of a strong factor of general cognitive change in adulthood and old age [39] has led to the assertion that many of "the underlying biological causes of cognitive change tend to operate at broad levels affecting cognition in many forms" [40]. In line with this assertion, we found that general brain volume change and general cognitive change are positively correlated. At the same

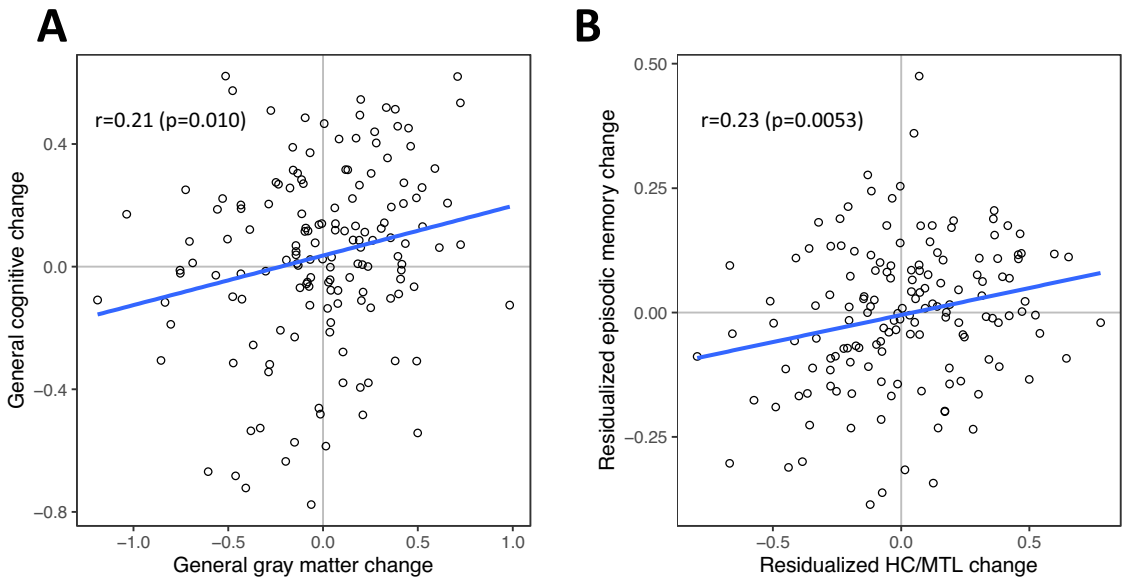

Fig. 2. Scatter-plots representing a selection of the significant brain-cognition associations in the SEM-analysis (c.f. Table 2). **A**: general cognitive factor association with the general factor of gray matter change. **B**: residualized HC/MTL change association with the residualized episodic memory change. General cognitive and gray matter changes are latent factor score estimates based on the SEM whereas the specific changes were estimated using the residuals adjusted for the corresponding general factors.

time, it also can be expected that the maintenance of a specific brain structure such as the hippocampus would be beneficial to cognitive domains that are closely linked to this structure [22]. This expectation was also borne out, as we identified several specific associations between cerebral and cognitive changes. Of particular importance, we found that changes in HC/MTL volume and changes in episodic memory establish a specific coupling beyond the most general levels of cognitive and cerebral aging. The delineation of a functionally specific link between cerebral and behavioral levels of analysis is a novel contribution to the study of normal human cognitive aging. Methodologically, it demonstrates the utility of a structural modeling approach to longitudinal data analysis [29].

Recent brain-cognition aging studies have stressed the importance of correlated change of *general* dimensions of brain atrophy and cognitive decline. Using longitudinal data of gray matter change in elderly, Cox and colleagues (2021) found low dimensionality of cortical change, which was related to cognitive change through a general factor of gray-matter atrophy, in line with Fletcher and colleagues (2018), yet they also found incremental effects of temporal lobe atrophy and baseline hippocampal volume to global cognitive change. The present findings speak for a co-existence of general and specific change-change associations in the aging of brain and behavior. Clearly, a strong g-like factor of cognitive change does not exclude the presence of reliable individual differences in change at the level of broad cognitive abilities. For instance, Tucker-Drob [38] found that 29% of the reliable variance of change in episodic memory is shared with a general factor of change [38], Fig. 1), but although the percentage might be higher at old ages [39], Fig. 6, 58%), there is still a large proportion of non-general variance. The present findings extend this observation to brain-behavior couplings.

Our observations support the assertion of a primary role of hippocampal/MTL maintenance in successful memory aging [22,24]. Longitudinal investigations of preserved episodic memory have found demographic, lifestyle, health-related, and genetic predictors of group differences among healthy older adults [13], as well as differences in cortical and hippocampal brain activity [27]. Longitudinal evidence further suggests that the number of apolipoprotein E (APOE) ε4-alleles modulates the change-change relationship between episodic memory and hippocampal atrophy [10]. Here, we found that the specific dimension of episodic memory change was associated with the specific dimension of hippocampal/MTL gray matter atrophy but not general brain or specific superior-PFC change. In other words, older adults who declined least in their episodic memory relative to other participants tended to either exhibit general brain maintenance and related preservation of cognition in general, or specific maintenance of the medial-temporal lobe structures, but not necessarily other structures of the brain. We further found that older adults who declined least in their composite cognitive score relative to other participants tended to show either less age-related decline in their composite brain score, or specifically in their HC/MTL or superior-PFC structures.

There are some limitations of the present study. Most importantly, the number of observations was relatively low in terms of the number of participants in the imaging part of the study (n = 262) and in terms of the follow-up time points, also with regard to the number of who that returned for follow-up imaging. At the same time, the imaging data were collected within a well-established lon-

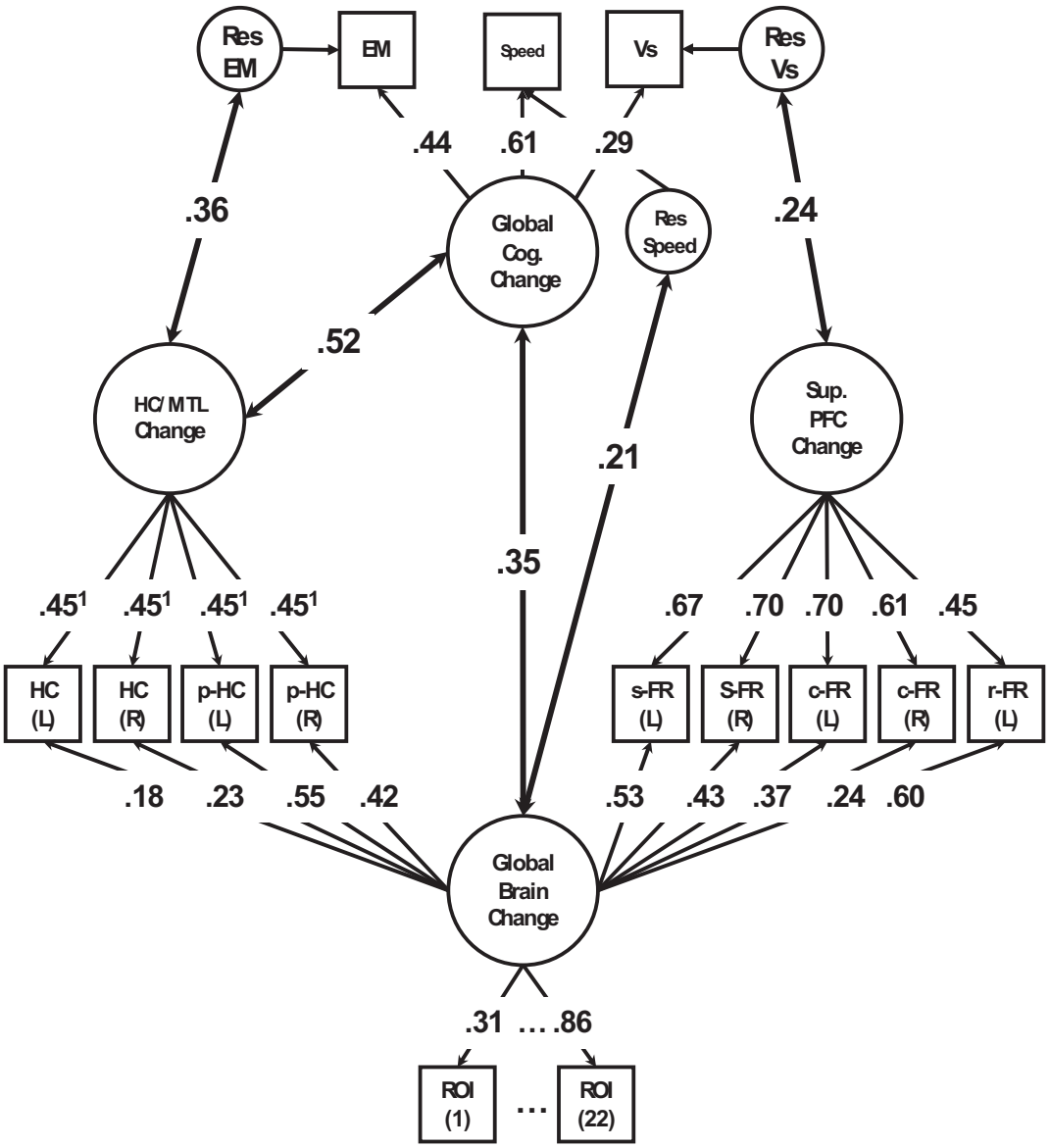

Fig. 3. Schematic representation of the standardized factor solution of the multivariate SEM for longitudinal change in brain and cognition. Indicators (squares) are the individual slopes from the LME model fit (see Materials and Methods). Thicker, bidirectional arrows represent statistically significant correlations between brain and cognition slopes, and all correlations are reported in Table 2. Abbreviations: L = left, R = right, HC = hippocampus, p-HC = parahippocampal gyrus, s-FR = superior fronta, c-FR = caudal middle frontal, r-FR = rostral middle frontal, Res = residual variance, EM = episodic memory, Vs = visuospatial ability.

gitudinal study of cognitive aging at a single research site [21], alleviating the typically encountered harmonization problems in multi-site studies with larger sample sizes. Furthermore, the analyses were cautiously designed to avoid the usage of raw change scores and deletion of incomplete cases, to maximize the ability to reliably detect change-change associations adjusted for the global effects.

Conclusion

We found evidence for region- and domain-specific longitudinal associations in normal human cognitive aging, together with a general association between gray-matter change and cognitive change. In particular, we found that relatively preserved episodic memory in aging was related to less medial temporal lobe and hippocampal gray matter atrophy. These results encourage future investigations of both domain-specific and domain-general brain-cognition associations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was supported by a scholar grant from the Knut and Alice Wallenberg's foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbas.2021.100027.

References

[1] Cox SR, Harris MA, Ritchie SJ, Buchanan CR, Valdés Hernández MC, Corley J, et al. Three major dimensions of human brain cortical ageing in relation to cognitive decline across the eighth decade of life. Mol Psychiatry 2021. doi: https://doi.org/10.1038/s41380-020-00975-1.

[2] Deary IJ, Penke L, Johnson W. The neuroscience of human intelligence differences. Nat Rev Neurosci 2010;11(3):201–11. doi: https://doi.org/10.1038/nrn2793.

[3] Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31(3):968–80. doi: https://doi.org/10.1016/j.neuroimage.2006.01.021.

[4] Fischl B. FreeSurfer Neuroimage 2012;62(2):774–81. doi: https://doi.org/10.1016/j.neuroimage.2012.01.021.

[5] Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. Wiley; 2011.

[6] Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB. Brain changes in older adults at very low risk for Alzheimer's disease. J Neurosci 2013;33(19):8237–42. doi: https://doi.org/10.1523/JNEUROSCI.5506-12.2013.

[7] Fjell AM, Westlye LT, Grydeland H, Amlien I, Espeseth T, Reinvang I, et al. Critical ages in the life course of the adult brain: Nonlinear subcortical aging. Neurobiol Aging 2013;34(10):2239–47. doi: https://doi.org/10.1016/j.neurobiolaging.2013.04.006.

[8] Fletcher E, Gavett B, Harvey D, Farias ST, Olichney J, Beckett L, et al. Brain volume change and cognitive trajectories in aging. Neuropsychology 2018;32(4):436–49. doi: https://doi.org/10.1037/neu0000447.

[9] Ghisletta P, Rabbitt P, Lunn M, Lindenberger U. Two thirds of the age-based changes in fluid and crystallized intelligence, perceptual speed, and memory in adulthood are shared. Intelligence 2012;40(3):260–8. doi: https://doi.org/10.1016/j.intell.2012.02.008.

[10] Gorbach T, Pudas S, Bartrés-Faz D, Brandmaier AM, Düzel S, Henson RN, et al. Longitudinal association between hippocampus atrophy and episodic-memory decline in non-demented APOE ε4 carriers. Alzheimer's Dement. Diagnosis. Assess Dis Monit 2020;12(1). doi: https://doi.org/10.1002/dad2.v12.110.1002/dad2.12110.

[11] Gorbach T, Pudas S, Lundquist A, Orädd G, Josefsson M, Salami A, et al. Longitudinal association between hippocampus atrophy and episodic-memory decline. Neurobiol Aging 2017;51:167–76. doi: https://doi.org/10.1016/j.neurobiolaging.2016.12.002.

[12] Johansson J, Salami A, Lundquist A, Wåhlin A, Andersson M, Nyberg L. Longitudinal evidence that reduced hemispheric encoding/retrieval asymmetry predicts episodic-memory impairment in aging. Neuropsychologia 2020;137:107329. doi: https://doi.org/10.1016/j.neuropsychologia.2019.107329.

[13] Josefsson M, de Luna X, Pudas S, Nilsson L-G, Nyberg L. Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. J Am Geriatr Soc 2012;60(12):2308–12. doi: https://doi.org/10.1111/jgs.12000.

[14] Karama S, Colom R, Johnson W, Deary IJ, Haier R, Waber DP, et al. Cortical thickness correlates of specific cognitive performance accounted for by the general factor of intelligence in healthy children aged 6 to 18. Neuroimage 2011;55(4):1443–53. doi: https://doi.org/10.1016/j.neuroimage.2011.01.016.

[15] Kievit RA, Brandmaier AM, Ziegler G, van Harmelen A-L, de Mooij SMM, Moutoussis M, et al. Developmental cognitive neuroscience using latent change score models: A tutorial and applications. Dev Cogn Neurosci 2018;33:99–117. doi: https://doi.org/10.1016/j.dcn.2017.11.007.

[16] Kramer JH, Mungas D, Reed BR, Wetzel ME, Burnett MM, Miller BL, et al. Longitudinal MRI and Cognitive Change in Healthy Elderly. Neuropsychology 2007;21(4):412–8. doi: https://doi.org/10.1037/0894-4105.21.4.412.

[17] Leong RLF, Lo JC, Sim SKY, Zheng H, Tandi J, Zhou J, et al. Longitudinal brain structure and cognitive changes over 8 years in an East Asian cohort. Neuroimage 2017;147:852–60. doi: https://doi.org/10.1016/j.neuroimage.2016.10.016.

[18] Menary K, Collins PF, Porter JN, Muetzel R, Olson EA, Kumar V, et al. Associations between cortical thickness and general intelligence in children, adolescents and young adults. Intelligence 2013;41(5):597–606. doi: https://doi.org/10.1016/j.intell.2013.07.010.

[19] Mungas D, Harvey D, Reed BR, Jagust WJ, DeCarli C, Beckett L, et al. Longitudinal volumetric MRI change and rate of cognitive decline. Neurology 2005;65(4):565–71. doi: https://doi.org/10.1212/01.wnl.0000172913.88973.0d.

[20] Nilsson L-G, BÄCkman L, Erngrund K, Nyberg L, Adolfsson R, Bucht GÖSta, et al. The betula prospective cohort study: Memory, health, and aging. Aging. Neuropsychol Cogn 1997;4(1):1–32. doi: https://doi.org/10.1080/13825589708256633.

[21] Nyberg L, Boraxbekk C-J, Sörman DE, Hansson P, Herlitz A, Kauppi K, et al. Biological and environmental predictors of heterogeneity in neurocognitive ageing: Evidence from Betula and other longitudinal studies. Ageing Res. Rev. 2020;64:101184. doi: https://doi.org/10.1016/j.arr.2020.101184.

[22] Nyberg, L., Lindenberger, U., 2020. Brain maintenance and cognition in old age, in: Poeppel, D., Mangun, G., Gazzaniga, M. (Eds.), The Cognitive Neurosciences. pp. 81–89.

[23] Nyberg L, Maitland SB, Rönnlund M, Bäckman L, Dixon RA, Wahlin Å, et al. Selective adult age differences in an age-invariant multifactor model of declarative memory. Psychol Aging 2003;18(1):149–60. doi: https://doi.org/10.1037/0882-7974.18.1.149.

[24] Nyberg L, Pudas S. Successful Memory Aging. Annu Rev Psychol 2019;70(1):219–43. doi: https://doi.org/10.1146/annurev-psych-010418-103052.

[25] Penke L, Maniega SM, Murray C, Gow AJ, Valdes Hernandez MC, Clayden JD, et al. A general factor of brain white matter integrity predicts information processing speed in healthy older people. J Neurosci 2010;30(22):7569–74. doi: https://doi.org/10.1523/JNEUROSCI.1553-10.2010.

[26] Persson J, Pudas S, Lind J, Kauppi K, Nilsson L-G, Nyberg L. Longitudinal structure-function correlates in elderly reveal MTL dysfunction with cognitive decline. Cereb Cortex 2012;22(10):2297–304. doi: https://doi.org/10.1093/cercor/bhr306.

[27] Pudas S, Persson J, Josefsson M, de Luna X, Nilsson L-G, Nyberg L. Brain characteristics of individuals resisting age-related cognitive decline over two decades. J Neurosci 2013;33(20):8668–77. doi: https://doi.org/10.1523/JNEUROSCI.2900-12.2013.

[28] Raz N, Daugherty AM. Pathways to brain aging and their modifiers: free-radical-induced energetic and neural decline in senescence (FRIENDS) model - a mini-review. Gerontology 2017;64:49–57. doi: https://doi.org/10.1159/000479508.

[29] Raz N, Lindenberger U. Only time will tell: Cross-sectional studies offer no solution to the age-brain-cognition triangle: Comment on salthouse (2011). Psychol Bull 2011;137:790–5. doi: https://doi.org/10.1037/a0024503.

[30] Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. Cereb. Cortex 15, 1676–1689. Doi: 10.1093/cercor/bhi044.

[31] Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 2012;61(4):1402–18. doi: https://doi.org/10.1016/j.neuroimage.2012.02.084.

[32] Rodrigue KM, Raz N. Shrinkage of the Entorhinal Cortex over Five Years Predicts Memory Performance in Healthy Adults. J Neurosci 2004;24:956–63. doi: https://doi.org/10.1523/JNEUROSCI.4166-03.2004.

[33] Rosseel Y. lavaan: An R Package for Structural Equation Modeling. J Stat Software Artic 2012;48:1–36. doi: https://doi.org/10.18637/jss.v048.i02.

[34] Salthouse TA, Habeck C, Razlighi Q, Barulli D, Gazes Y, Stern Y. Breadth and age-dependency of relations between cortical thickness and cognition. Neurobiol Aging 2015;36(11):3020–8. doi: https://doi.org/10.1016/j.neurobiolaging.2015.08.011.

[35] Schmid J, Leiman JM. The development of hierarchical factor solutions. Psychometrika 1957;22(1):53–61. doi: https://doi.org/10.1007/BF02289209.
[36] Schmidt P, Gaser C, Arsic M, Buck D, Förschler A, Berthele A, et al. An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. Neuroimage 2012;59(4):3774–83. doi: https://doi.org/10.1016/j.neuroimage.2011.11.032.
[37] Spearman C. The abilities of man., The abilities of man. Oxford, England: Macmillan; 1927.
[38] Tucker-Drob EM. Global and Domain-Specific Changes in Cognition Throughout Adulthood. Dev Psychol 2011;47:331–43. doi: https://doi.org/10.1037/a0021361.
[39] Tucker-Drob EM, Brandmaier AM, Lindenberger U. Coupled cognitive changes in adulthood: A meta-analysis. Psychol Bull 2019;145:273–301. doi: https://doi.org/10.1037/bul0000179.
[40] Tucker-Drob EM, Reynolds CA, Finkel D, Pedersen NL. Shared and unique genetic and environmental influences on aging-related changes in multiple cognitive abilities. Dev Psychol 2014;50:152–66. doi: https://doi.org/10.1037/a0032468.
[41] Wechsler D. Wechsler adult intelligence scale-revised (WAIS-R). Psychol Corporat 1981.