Neurobiology of Aging 121 (2023) 107–118

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Activation changes induced by cognitive training are consistent with improved cognitive reserve in older adults with subjective cognitive decline

Sylvie Belleville[a,b,*], Samira Mellah[a], Benjamin Boller[a,c], Émilie Ouellet[a]

[a] Research Center, Institut universitaire de gériatrie de Montréal, Montreal, Quebec, Canada
[b] Université de Montréal, Montreal, Quebec, Canada
[c] Université du Québec à Trois-Rivières, Quebec, Canada

ARTICLE INFO

Article history:
Received 14 October 2021
Revised 5 May 2022
Accepted 19 October 2022
Available online 23 October 2022

Keywords:
Cognitive training
fMRI
Cognitive reserve
Subjective cognitive decline
Aging
Education

ABSTRACT

Functional magnetic resonance imaging (fMRI) was used to assess the effect of cognitive training on brain activation as a function of the learning phase and level of education. Forty older adults with subjective cognitive decline (SCD) received 6 1-hour memory training sessions with the method of loci. Brain imaging (N = 29) was measured during word list encoding and retrieval before training (PRE), after 3 training sessions (POST3), and after 6 training sessions (POST6). Participants showed increased activation of the left inferior pre-frontal gyrus from PRE to POST6 during encoding and reduced bilateral frontostriatal activation from PRE to POST3 during retrieval, regardless of education. Activation changes from PRE to POST3 varied as a function of education in 2 regions of the right temporal lobe: participants with lower education showed increased activation, while those with higher education showed decreased activation. These regions were initially less active in people with lower education. Results suggest a strategic shift in people with lower education and expertise building in those with higher education, along with a restoration of initial education-related differences.

1. Introduction

The cognitive reserve model has been proposed to account for inter-individual variability in cognitive decline observed in older age (Cabeza et al., 2018; Stern et al., 2020). Cognitive reserve is defined as a property of the brain, which would explain why cognition may be better than expected given the amount of age or disease-related changes present in a person's brain (https://reserveandresilience.com/framework/). Cognitive reserve is thought to operate through neural enhancement processes that mitigate the impact of age-related decline or disease on cognition. Formal education and cognitively engaging activities were identified as some of the factors that could promote cognitive reserve (Fratiglioni et al., 2004; Kramer et al., 2004).

As the brain is potentially malleable in adulthood, cognitive training – defined as a set of behavioral approaches aimed at increasing cognition – may provide a unique contribution to understanding the neuroplastic processes underlying cognitive reserve. Cognitive training can be used to experimentally study the impact of late-life cognitive stimulation on the brain and determine the effect of different parameters on neuroplastic mechanisms. Such studies have the additional benefit of identifying ways to potentiate neuroprotective mechanisms, which could have major implications for older adults interested in maintaining brain and cognitive health. Hence, cognitive interventions could be designed to reproduce or amplify the effect of formal education on the brain. In the following section, we will briefly describe studies that have used brain imaging to assess the effect of education or other reserve proxies on brain function. We will then discuss the effect of cognitive training on the brain in relation to models of learning that highlight the importance of the learning phase as a factor that may modify the brain's response to training.

This manuscript is part of the Virtual Special Issue titled "*COGNITIVE NEUROSCIENCE OF HEALTHY AND PATHOLOGICAL* ", edited by Drs. M. N. Rajah, S. Belleville, and R. Cabeza.

* Corresponding author at: Research Center, Institut universitaire de gériatrie de Montréal, 4565 Queen Mary Rd, Montreal, Quebec, Canada, H3W 1W5. (S. Belleville), Tel.:15143403540, Fax:15143403548.
E-mail address: sylvie.belleville@umontreal.ca (S. Belleville).

0197-4580/$ – see front matter
https://doi.org/10.1016/j.neurobiolaging.2022.10.010

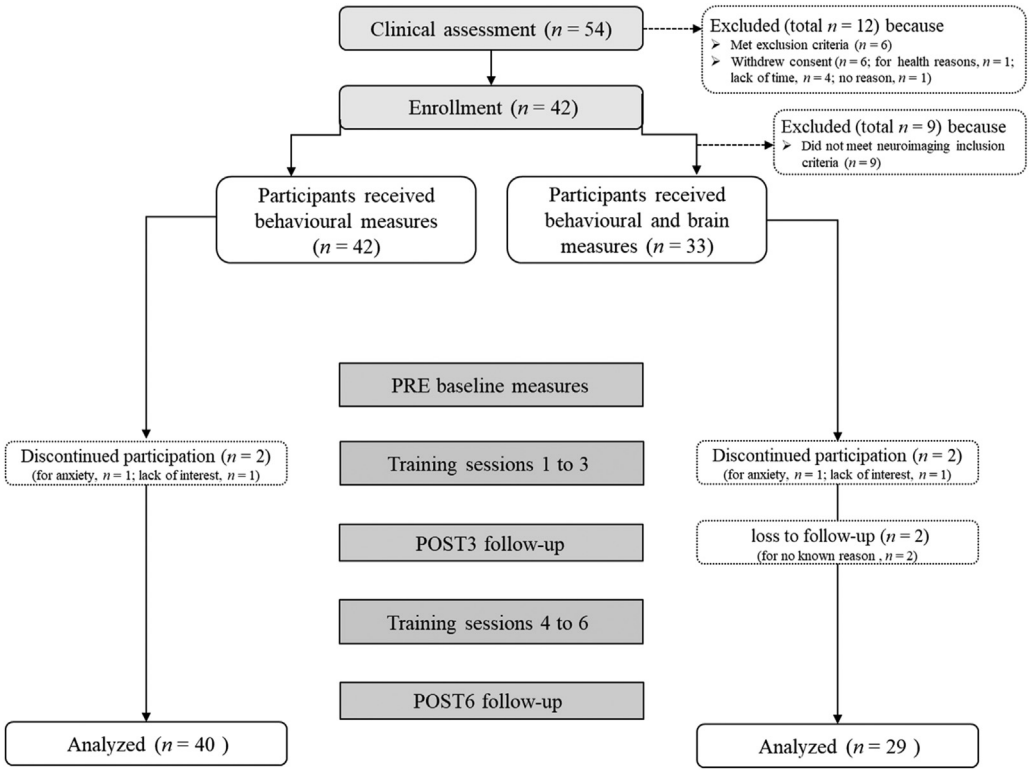


Fig. 1. Design and participant flow.

1.1. The role of education on brain activation

Results from studies examining the association between education or other reserve proxies and brain activation have identified 3 patterns that may reflect differences in adaptability, defined as the ability to adjust brain processes to age-related brain changes (Steffener and Stern, 2012; Stern et al., 2018b). First, some studies have reported a negative correlation between reserve proxies and brain response (Bartrés-Faz et al., 2009; Boller et al., 2017), a pattern that could reflect a more efficient use of neural resources. Second, studies have observed increased activation in individuals with higher reserve proxies when conditions are more difficult, which reflects higher neural capacity (Steffener and Stern, 2012; Stern et al., 2018a). Finally, other studies report greater recruitment of brain regions other than those typically activated by a task, suggesting that cognitive reserve may allow more flexible compensation (Colangeli et al., 2016; Steffener and Stern, 2012; Stern, 2009; Tucker and Stern, 2011). In a recent study (Belleville et al., 2021), we found that higher scores on reserve proxies were associated with greater activation of the right inferior temporal gyrus during an episodic memory task. Furthermore, we observed a moderation effect as older adults with a reduced hippocampal volume showed preserved memory if they had increased activation in that region. Thus, higher recruitment of the right inferior temporal lobe may provide neural adaptability to hippocampal volume loss (Belleville et al., 2021).

1.2. The role of training on brain activation and differences related to the training phase

Studies that have used fMRI to assess the effect of cognitive training on the brain often reported brain changes in the frontoparietal network (Belleville et al., 2014, 2011; (Belleville and Bherer, 2012; Duda and Sweet, 2020; Simon et al., 2020; van Balkom et al., 2020) with additional increased activation often reported in temporal regions following memory training (e.g., Belleville et al., 2011; Hampstead et al., 2012; Simon et al., 2020). However, changes in activation may depend on the training phase. According to the triarchic theory of learning (Chein and Schneider, 2012), the metacognitive system, which is located mostly in the anterior portion of the frontal lobe, would be recruited when participants engage in a new task. With learning, the metacognitive recruitment would no longer be necessary and would give way to greater involvement of the cognitive control network, which is involved in guiding processing to the most relevant components of the task. This network is located in the dorsolateral prefrontal, anterior cingulate, and parietal cortices. As learners increase their expertise with practice, cognitive control processes would no longer be required, and activation would reflect engagement of more automatic routines located in widely distributed cortical modules. Our prior work on attentional training is broadly consistent with the triarchic model as we found evidence that variable priority training that involved metacognitive strategies, results in increased activation of the anterior portion of the prefrontal cortex (Belleville et al., 2014). However, activation changes probably vary as a function of individual characteristics at baseline.

1.3. Interaction between training and education

The INTERACTIVE model was proposed to predict differences in activation as a function of individual and training characteristics. The model proposes that the training phase should interact with the level of education or prior expertise with the task (Belleville et al., 2014). People with different levels of education may stand at different phases of a continuum when they initiate cognitive training: People with lower education may require a larger dose of training to reach automaticity or to develop sufficient “expertise”, so that metacognitive or attentional controlled processes are no longer required. This means that the shift from anterior to more posterior recruitment should occur later in people

with lower levels of education. However, to our knowledge, the effect of the training phase on activation change has not been tested with cognitive training in older adults with different levels of education in previous studies.

In summary, our prior study has found that lower education is related to lower activation of the temporal lobe. Cognitive training could be considered as a form of "late-life education" that may provide neuroprotection later in life. It is therefore critical to better understand the brain changes induced by cognitive training, whether they differ in people with higher or lower education, and whether the effect of training on the brain is comparable to the education difference examined at baseline. This should also contribute to a better understanding of inter-individual age differences on the brain.

Thus, this study has 3 objectives: (1) Examine activation changes related to training as a function of the intervention phase; (2) Assess whether people with lower levels of formal education have different initial brain activation patterns compared to those with higher levels of education; (3) Determine whether changes related to training and intervention phase differ as a function of education and whether training changes are similar to the education difference at baseline. Previous empirical work and models of learning-dependent neuroplasticity offer critical predictions. (1) According to the triarchic model of learning, activation of the anterior portion of the prefrontal cortex was expected to be present prior to training, but to gradually decrease as participants learn and practice the memory strategy, along with an increase in dorsolateral prefrontal activation. Therefore, we expect a decrease activation of the anterior prefrontal cortex with an increase in dorsolateral prefrontal activation when comparing activation for the different training phases. (2) Based on our prior work (Belleville et al., 2021), brain activation is expected to differ at baseline as a function of education level, with people with lower levels of education expected to show less temporal activation than those with higher levels of education. (3) If cognitive training involves mechanisms similar to those of early education, activation of the temporal region is expected to increase following memory training, and this increase should be more pronounced in older adults with lower levels of education.

Here, cognitive training involved teaching the method of loci, a well-known mnemonic method that provides rich and elaborate encoding to facilitate subsequent retrieval of material. Training was provided over 6 1-hour sessions and brain activation was measured prior to training, after 3 and 6 training sessions. This was assessed in older adults with subjective cognitive decline (SCD), who have a higher risk of progressing to dementia (Jessen et al., 2020, 2014). These participants were not impaired on objective cognitive measures but report that their memory is not as good as it used to be, and it worries them. Our primary goal was to identify activation changes measured during encoding and retrieval of word lists. However, recognition was used at retrieval to reduce the in-scan motion artifacts found from the verbal response in free recall. Thus, off-scan free recall measurement was the primary behavioral outcome, as this is a more sensitive task related to the technique taught to participants during training.

2. Material and methods

2.1. Study design

This was a mixed factorial design with training stage as a within-subject factor and education as a between group factor[1]. Participants received memory training with the method of loci for 6 1-hour sessions provided every other weekday over 2 weeks (1 session per day, 3 sessions per week). MRI and behavioral measures were taken no more than 1 week prior to the first training session (PRE), after the third training session (POST3) and no more than 1 week following the last training session (POST6). The design and participant flow are illustrated in Fig. 1. The staff involved in the assessment were different from those involved in the intervention and they were unaware of the participants' clinical status.

2.2. Participants

Participants were recruited from the community through advertisements in community centers, public conferences, and magazines for seniors. To be included, participants were required to be over age 50, francophone, have normal or corrected-to-normal hearing and vision, and meet research criteria for SCD (Belleville et al., 2019; Jessen et al., 2014). SCD criteria included presence of a memory complaint with worries and absence of objective cognitive impairment. To assess the presence of a complaint with worries, participants were asked: "Do you feel that your memory is not as good as it used to be?" and "Does it worry you?". Absence of cognitive impairment was determined based on the Montreal Cognitive Assessment (MoCA; score $\geq$ 26 (Nasreddine et al., 2005)) and clinical tests of episodic memory (RL/RI-16; (Van der Linden et al., 2004); Logical Memory I subtest, LM I [French version]; from Wechsler Memory Scale III, 1997)), language (Boston Naming Test, BNT; (Kaplan et al., 1983)), and executive function (Stroop-Victoria; (Troyer et al., 2006); French adaptation from (Moroni and Bayard, 2009); Norms from (Tremblay et al., 2016)). Cognition was considered normal if performance was no more than 1.5 standard deviations below the mean of age- and education-matched normative samples or based on education-adjusted cut-off scores used in the Alzheimer's Disease Neuroimaging Initiative study for the LM1 Subtest (Belleville et al., 2019).

Participants also completed the Geriatric Depression Scale to assess depressive symptoms (GDS- 15); (Yesavage et al., 1982), the Hachinski Scale (Hachinski et al., 1975) to assess vascular health, the Charlson Comorbidity Index (Charlson et al., 1987) to assess general health, and the Activities of Daily Living-Prevention Instrument (ADL-PI, from ADCS; (Galasko et al., 2006) to measure functional independence. The number of completed years of formal education was used as a proxy for cognitive reserve for the purposes of this study.

The study was approved by the Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie Québec (CMER-RNQ) and all participants completed a written informed consent form prior to study participation.

2.3. Training

The method of loci was used as a memory training program (Lea, 1975). Using this technique, participants first learned a fixed set of locations from their home. The selected locations were positioned along an orderly and stable route that the participant could follow to recover their associations. Participants then learned to create interactive image-based associations between locations and item lists by matching the order of the locations on the route with the order of the items in the list. For example, the first item in a list was associated with the first location, the second item with the second location, and so on. At retrieval, participants simply walked their route to retrieve the association made between the location and the items on the list (Verhaeghen and Marcoen, 1996). The technique and materials were adapted from the MEMO+ program, which has been shown to be effective in healthy older adults

[1] The data presented here is part of a larger project. Transfer and behavioral results were presented in Boller et al 2021.

and people with mild cognitive impairment (Belleville et al., 2018, 2006). The mnemonic leads to the creation of rich and elaborate encoding and retrieval cues.

There were 6 1-hour sessions: Session 1 consisted of exercises to improve mental imagery and teach participants to create interactive mental images, as this is a key part of successful use of the method. Participants also selected and learned their route as well as 12 familiar locations along the route. In Session 2, the principles behind the method were learned. This was followed by a guided practice using short lists of visually presented concrete words on a PC computer run by E-prime 2 (Psychology Software Tools, Sharpsburg, PA, USA). Participants were invited to practice the method and received feedback and tips for creating vivid images. In Sessions 3, additional exercises were provided with different lists, and the level of difficulty was gradually increased by reducing the time allocated to create the interactive images and by reducing feedback and advice. This was continued over sessions 4–6. Each session lasted approximately 50 minutes and was delivered face-to-face in small groups of 2 – 4 participants. Half of the participants received a brief training with virtual reality, but this was not included as a factor because it did not modify functional brain outcomes or performance (see (Boller et al., 2021).

2.4. Brain imaging measurement

Scanning was performed using a SIEMENS 3T Magnetom TRIO Tim System (Erlangen, Germany) at the Unité de Neuroimagerie Fonctionnelle (UNF) of the Institut universitaire de gériatrie de Montréal. Whole brain structural scans were obtained with a 3-dimensional ME-MPRage anatomical sequence with TR = 2530 ms (multiple TE: 1.64 ms, 3.5 ms, 5.36 ms, 7.22 ms; TI = 1200 ms, flip angle = 7°, FOV = 256 mm, 256 × 256 matrix, 176 slices, voxel size = 1 × 1 × 1 mm^3). Whole brain fMRI data were obtained during 1 run of functional imaging data using an EPI T2* pulse sequence, in an axial plane (50 slices of 3mm thickness with no gap; TR/TE = 2500/20 ms, flip angle = 90 °; voxel size = 3 × 3 × 3 mm^3, FOV = 220 mm, 74 × 74 matrix, descending acquisition). A total of 380 images were acquired.

During the scan, participants performed the encoding and retrieval of word lists. Participants were asked to memorize 4 lists of 12 visually and semantically unrelated concrete words, which were each presented for 4 seconds. Each list was followed by a recognition phase where all the items from the previous list were presented in a different order, in addition to 6 distractors. For each item presented, participants were asked to determine if the word was part of the learning list (Yes/No response). In the reference condition, participants were asked to silently read 4 9-word lists of weekdays presented in random order. One reference list was presented before each encoding list. Different versions of the lists with new stimuli were presented at the different scan sessions and counterbalanced across participants.

For the in-scan task, the number of old correctly recognized words (Hit) and the number of new falsely recognized words (False Alarm, FA) were recorded to determine recognition accuracy based on a discrimination index (d-prime; d'), which was adapted from signal detection theory (Macmillan, 1993; Snodgrass and Corwin, 1988; Stanislaw and Todorov, 1999).

2.5. Off-scan behavioral measure

Memory was also measured off-scan using a free recall procedure, which is more comparable to the training protocol than recognition. Participants were asked to memorize 2 lists of 12 visually-presented words and 2 lists of 12 auditorily-presented words. Each item was presented at a rate of 1 item every 5 seconds. Recall of each list was done in writing, immediately after the end of its presentation, and participants were asked to report the items in the order they came to mind. The mean number of correctly recalled words pooled over the 4 lists was used as the dependent variable.

2.6. Statistical analyses

Functional brain imaging data were preprocessed with Statistical Parametric Mapping 12 (SPM12) (http://www.fil.ion.ucl.ac.uk/spm) in Matlab v9.4.0 using the following steps: (1) realigning the images to the first volume; (2) slice timing; (3) co-registering the structural image to the mean functional image; (4) segmenting the structural image into its constituent tissue classes; (5) applying the estimated transformations to Montreal Neurological Institute (MNI) space derived from the segmentation to the functional scans; (6) smoothing the functional scans using a Gaussian kernel with a Full Width at Half Maximum (FWHM) of 8 × 8 × 8 mm. At the first level of analysis, a fixed effect general linear model at the single subject level was conducted to obtain the task activation contrasts of interest. The models were fit using the hemodynamic response function (HRF) and time derivative basis set with the addition of 6 movement regressors. Low frequency variation was eliminated using a 128-second high pass filter, and a one-lag autoregression model was applied globally. As the in-scan memory task was a block design, we modelled the 3 conditions of the task (weekday reading, encoding and recognition), leaving the rest periods as an implicit baseline. Instructions were modelled as no-interest regressors. All correct and incorrect trials were included within the same regressor. At the second level of analysis, one-sample t-tests were first conducted to obtain areas activated and deactivated during the task. The interaction between education and the training phase was investigated with the Sandwich Estimator (SwE) Toolbox for the Analysis of Longitudinal and Repeated Measures Neuroimaging Data v2.1.0, implementing for SPM12 (Guillaume et al., 2014). The SwE method, which uses the marginal model, has several advantages, including that no random effects need to be specified, it can handle missing data (unbalanced design), and the setup of the design matrix and specifying the contrasts are also simpler. We fitted the model with a simplified approach: 3 columns for the factorial effect of training phase as repeated factors (PRE, POST3 and POST6), a column for education (lower vs. higher), and another column to test their linear interaction. The covariates included are age (i.e., cross-sectional age (baseline age) and centred within-subject age of participant) and sex. We used the modified SwE to estimate our model (which can handle small groups) and false discovery rate (FDR) voxel-wise, with a level of $p < 0.05$ inference, as usual for the parametric mode.

Using MARSBAR, we then extracted (Brett et al., 2002) the average parameter estimates (beta weight), which provided information on the effect size and direction of activation (BOLD response of fMRI signal) in the education by training clusters. This allowed interpretation of the pattern related to the training phases as a function of education. The activation data was analyzed with mixed ANOVAs using education (lower vs. higher) as a between-subject factor and training phase (PRE, POST3 POST6) as a within-subject factor. When required, the Greenhouse-Geisser correction was used to correct for lack of sphericity. Since we were interested in how education modifies activation at each training phase, presence of an interaction was followed with education x training phase ANOVAs, that use PRE and POST3 as a repeated factor and education (lower vs. higher) as a between-subject factor. ANOVAs were also conducted for POST3 to POST6 as a repeated factor and

Table 1
Characteristics of the participants at baseline.

a) Participants with full neuroimaging and behavioral assessment	Whole group N = 29	Lower education N = 14	Higher education N= 15	Group difference *p* value
Age (y)	67 ± 8.44	69.4 ± 7.26	64.7 ± 9.09	.141
Sex; number of females (%)	24 (83%)	12 (86%)	12 (80%)	1
Education (y)[a]	15.10 ± 3.06	12.78 ± 2.39	17.27 ± 1.75	< .000
MOCA (/30)	27.52 ± 1.66	27.5 ± 1.79	27.53 ± 1.60	.958
RL/RI (total delayed recall /16)	12.21 ± 1.7	11.86 ± 1.75	12.53 ± 1.64	.293
WMS logical memory II subtest (delayed recall)	14.5 ± 3.74	13.46 ± 4.11	15.4 ± 3.24	.184
Stroop (time on third plate)	28.11 ± 1.37	28.37 ± 5.44	27.86 ± 9.05	.856
Boston naming test (/15)	13.9 ± 1.26	13.57 ± 1.50	14.2 ± .94	.195
Vocabulary (/19)	13.66 ± 2.72	13.21 ± 2.63	14.06 ± 1.87	.118
GDS (/15)	1.83 ± .54	1.5 ± 2.62	2.13 ± 3.25	.567
Charlson comorbidity index (/41)	.59 ± .73	.64 ± .84	.53 ± .64	.698
Hachinski score (/18)	.72 ± .88	.93 ± .92	.53 ± .83	.236

b) Participants with behavioral assessment	Whole group N = 40	Lower education N = 20	Higher education N= 20	Group difference *p* value
Age (y)	67 ± 7.49	68.7 ± 6.38	65.9 ± 8.39	.243
Sex; number of females (%)	33 (82.5%)	18 (90%)	15 (75%)	.407
Education (y)[a]	15 ± 2.97	12.65 ± 2.13	17.25 ± 1.55	< .000
MOCA (/30)	27.65 ± 1.62	27.7 ± 1.84	27.6 ± 1.43	.849
RL/RI (total delayed recall /16)	12.05 ± 1.7	11.9 ± 1.77	12.2 ± 1.7	.589
WMS logical memory II subtest (delayed recall)	14.5 ± 3.64	13.84 ± 4.17	15.2 ± 3.02	.254
Stroop (time on third plate)	28.55 ± 7.3	29.05 ± 6.27	28.04 ± 8.36	.668
Boston naming test (/15)	13.8 ± 1.21	13.7 ± 1.42	14 ± .97	.441
Vocabulary (/19)	13.8 ± 2.22	13.55 ± 2.7	14.05 ± 1.64	.16
GDS (/15)	1.9 ± 2.95	1.55 ± 2.23	2.25 ± 3.55	.461
Charlson comorbidity index (/41)	.55 ± .78	.50 ± .76	.60 ± .82	.692
Hachinski score (/18)	.80 ± 1.02	.85 ± .99	.75 ± 1.07	.760

NOTE. Values are means ± SD. Analysis of t-test was performed for group difference. A Chi-Square test of independence was performed for sex.
Abbreviations: MoCA = Montreal Cognitive Assessment (Nasreddine et al., 2005); RL/RI = Free and Cued Recall Test (Van der Linden et al., 2004); Stroop : Stroop-Victoria (Regard, 1981); Geriatric Depression Scale; GDS = Geriatric Depression Scale (Yesavage et al., 1982); Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987); Hachinski = Hachinski's Ischemic Score (Hachinski et al., 1975).
[a] Significant group effect

Table 2
Performance for the off-scan (mean number of correct recall) and in-scan (discrimination index score d') memory tasks at pretest (PRE) and after 3 (POST3) and 6 (POST6) training sessions in older adults with higher educationand lower education.

a) off-scan task	PRE	POST3	POST6
Participants who completed only behavioral assessment (N = 40)			
ALL	6.14 (.19)	7.83 (.31)	8.04 (.30)
Lower education	6.26 (.27)	7.21 (.44)	7.59 (.43)
Higher education	6.02 (.27)	8.44 (.44)	8.50 (.43)
Participants who completed behavioral and neuroimaging assessments (N = 29)			
ALL	6.11 (.24)	7.84 (.35)	8.03 (.36)
Lowe education	6.14 (.34)	6.93 (.51)	7.25 (.25)
Higher education	6.07 (.33)	8.75 (.49)	8.80 (.49)
b) in-scan task	PRE	POST3	POST6
ALL	2.65 (.15)	2.84(.12)	2.84 (.15)
Lower education	2.92 (.22)	2.91 (.17)	2.60(.21)
Higher education	2.43 (.22)	2.78 (.17)	3.08 (.21)

Note. Values are means (SE)

education (lower vs. higher) as a between-subject factor. We also performed an ANOVA with PRE and POST6 as a repeated factor and education (lower vs. higher) as the between-subject factor, as this analysis is consistent with what is typically done in PRE-POST intervention studies. This analysis can thus be used to compare our findings to those of prior studies and is likely to increase power. In all cases, interactions were followed by paired comparisons.

To analyze off-scan behavioral data, we used mixed ANOVAs on correct recall as the dependent variable with training phase (PRE, POST3 and POST6) as a within-subject factor and education (lower vs. higher) as a between-subject factor. When required, the Greenhouse-Geisser correction was used to correct for lack of sphericity. Post-hoc comparisons were 2-sided, with an alpha level of 0.05, where the Bonferroni–Holm multiple test adjustment was applied. To analyze the in-scan memory data, we used a repeated-factor ANOVA on d-prime as the dependant variable with training phase (PRE, POST3 and POST6) as the repeated factor.

The statistical analyses of behavioral data and extracted activation were performed using SPSS, version 25 (IBM Corp) software package for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Demographic and behavioral data

Participant flow is shown in Fig. 1. Fifty-four participants were assessed for eligibility (see Fig. 1). Of these, 42 met inclusion criteria and 33 met neuroimaging inclusion criteria. Of the 33 meeting neuroimaging criteria, four withdrew consent before follow-up. Thus, 29 participants completed training and the data from 3 MRI sessions was used for the neuroimaging analyses. Eleven additional participants received training and behavioral assessments but did not complete the full MRI procedure. These participants were not included in the neuroimaging analysis, but to increase power, their data was used to analyze off-scan behavior. Note that similar results were obtained overall with the smaller and larger data set (see Table S1 and S1 Text in supplementary material). Table 1a presents the demographic and clinical data for the 29 participants who completed the full protocol, separated by level of education. Table 1b presents the demographic and clinical data for the 40 participants who did not complete fMRI examination but completed the training and behavioral assessment. The lower and higher edu-

Table 3
Brain regions associated with the encoding and retrieval tasks at pretraining.

a) Encoding task > reading			MNI coordinates		
Anatomical labeling	Extent	t-value	X	y	z
R superior temporal gyrus	1067	6.913	66	-13	2
R postcentral gyrus		6.476	63	-1	20
R Putamen		5.870	24	5	17
R insula lobe		5.234	45	11	2
L insula lobe	715	6.020	-39	14	-4
L inferior frontal gyrus (p. orbitalis)		5.780	-33	32	2
L middle frontal gyrus		4.019	-39	50	14
L Hippocampus	216	5.434	-33	-37	2
L Thalamus		4.565	-15	-34	5
L precentral gyrus	218	4.904	-54	-4	23
L rolandic operculum		4.665	-45	-7	14
R superior temporal gyrus	1067	6.913	66	-13	2
R postcentral gyrus		6.476	63	-1	20
R putamen		5.870	24	5	17
b) Retrieval task > reading			MNI coordinates		
Anatomical labeling	Extent	t-value	X	y	z
R caudate nucleus	4140	10.769	12	14	8
L caudate nucleus		9.320	-9	14	8
R rolandic operculum		9.302	63	-4	11
R inferior frontal gyrus (p. opercularis)		9.148	45	14	11
L insula lobe		9.012	-33	20	5
R IFG (p. triangularis)		8.998	42	17	14
L middle temporal gyrus	205	8.715	-60	-25	-1
L cerebelum (VI)	118	7.758	-30	-58	-28
L inferior temporal gyrus		6.051	-45	-49	-13
L fusiform gyrus		5.710	-42	-58	-19
R cerebelum (VI)	34	7.063	24	-61	-25
R posterior-medial frontal	21	6.513	9	14	65

FWE p < 0.05 voxelwise inference

cation groups did not differ on demographic or neuropsychological measures, except for level of education, which differed by design.

Analysis of the off-scan performance data (see Table 2a) indicated an education by training phase interaction (F(2,76)= 5.571, p = 0.008, eta-square = 0.128) and a training phase effect (F(2,76) = 40.598, p < 0.001, eta-square = 0.517), but no education effect (F(1,38) = 1.766, p = 0.192, eta-square = 0.044). A closer examination of the interaction revealed an education x training phase interaction in the PRE-POST6 comparison (F(1,38)=5,135, p = 0.029, eta-square = 0.119), a main effect of training phase (F(1, 38) = 56.063, p < 0.001, eta-square = 0.596) but no main effect of education (F(1,38) = 0.60, p = 0.443, eta-square = 0.016). When analyzing the PRE-POST3 comparison, there was an education x training phase interaction (F(1, 38) = 8,637, p = 0.006, eta-square = 0.185), a main effect of training phase (F(1, 38) = 45.63, p < 0.001, eta-square = 0.546) but no main effect of education (F(1,38) = 1,196, p = 0.281, eta-square = 0.031). When analyzing the POST3-POST6 comparison, there was no main effect of training phase (F(1,38) = 1.432, p = 0.239, eta-square = 0.036, education F(1,27) = 3.34, p = 0.075, eta-square = 0.081) or education x training phase interaction (F(1, 38) = 0.731, p = 0.398, eta-square = 0.019). Mean comparisons for the higher education group indicated an improvement in performance from PRE to POST3 (p < 0.001) with no further improvement from POST3 to POST6. Mean comparisons for the lower education group also indicated an improvement in performance from PRE to POST3 (p = 0.001) with no further improvement from POST3 to POST6. The magnitude of the effect from PRE to POST3 was larger in the higher education group (mean difference = 2.412, SE = 0.352) than lower education group (Mean difference= 0.950, SE = 0.352). There were no significant group differences at any of the time points.

Analysis of the in-scan recognition (Table 2b) data[2] indicated no education x training phase interaction (F(2,52) = 3.304 p = 0.058, eta-square = 0.113, training phase (F(2,52) = 0.511, p = 0.575, eta-square = 0.019) or education effect (F(1,26) = 0.063, p = 0.804, eta-square = 0.002).

3.2. Brain imaging data

3.2.1. Baseline data (PRE)

3.2.1.1. Task-related activation at PRE. Table 3 and Fig. 2 show the regions associated with the encoding and retrieval task at pretraining. Encoding activated 2 large fronto-temporal clusters, which included the hippocampus in both hemispheres, as well as smaller left occipital and fronto-striatal clusters. Retrieval activated a large fronto-temporal cluster comprising the right superior and middle temporal gyrus, the right superior, middle and medial frontal gyrus as well striatal regions. Activation was also found in the left temporal gyrus and left cerebellum. There was no negative activation associated with the task.

3.2.1.2. Education-related activation at PRE. There was no education-related activation for encoding. For retrieval, one cluster encompassing the right middle and inferior temporal gyri (BA20, 21, 37) was positively associated with education (Table 4, Fig. 3). There was no region negatively associated with education.

3.2.2. Training-related activations

3.2.2.1. Main effects for training-related activations. Fig. 4a shows the main effect of training, that is, the training-related activation

[2] Note that one participant was excluded from the behavioural analyses of in-scan recognition because his/her performance data was missing at postintervention.

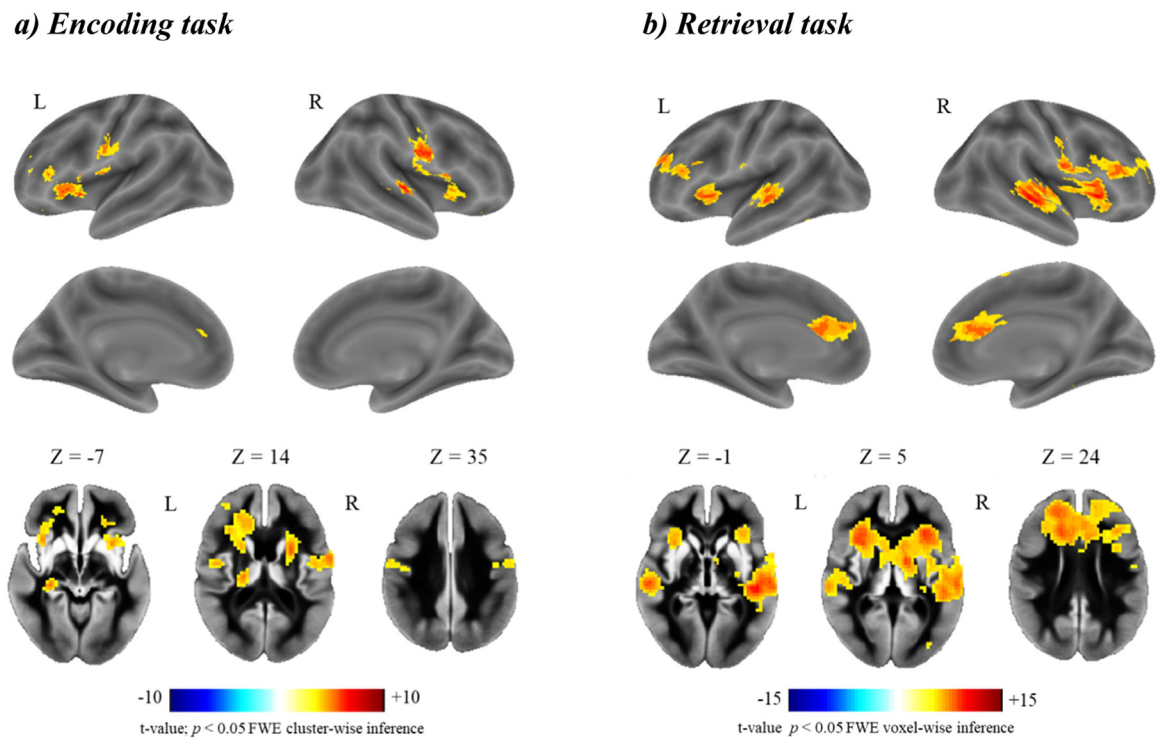


Fig. 2. Brain regions associated with the encoding and retrieval tasks at pretraining.

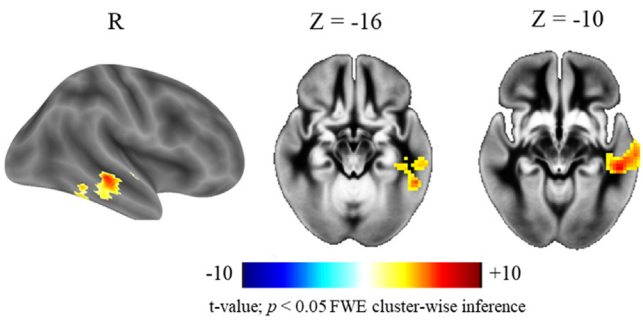


Fig. 3. Brain regions associated with level of education at pretraining for the retrieval task.

Table 4
Brain regions associated with level of education at pretraining.

Anatomical labeling	Extent	t-value	MNI coordinates x	y	z
Encoding task					
None					
Retrieval task					
R inferior temporal gyrus (BA37)	234	5.729	54	-46	-16
R middle temporal gyrus (BA21)		5.471	66	-22	-10

FWE p < 0.05 clusterwise inference

changes observed in both groups. At encoding, training resulted in increased prefrontal activation in the left inferior frontal gyrus (BA9), which is part of the dorsolateral prefrontal cortex from PRE to POST6. At retrieval, there was decreased activation from PRE to POST3 in a cluster comprising the left and right inferior and anterior portion of the middle frontal gyrus, left anterior cingulate and basal ganglia. There were no further changes when comparing POST3 to POST6.

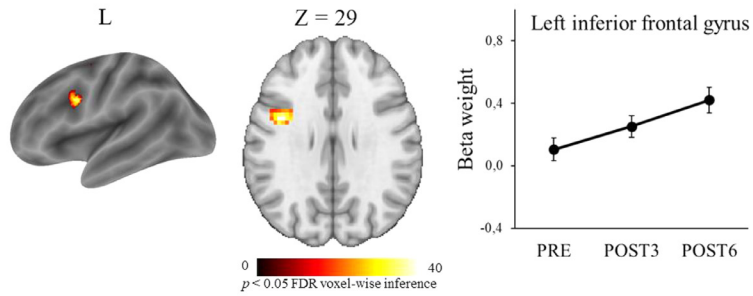
3.2.2.2. Education by training phase interactions. There was no education by training phase interaction for encoding-related activation. There was an education by training phase interaction for activation during retrieval in 2 regions of the right temporal lobe: the right middle temporal gyrus (BA21) and the right inferior temporal gyrus (BA37). These interactions are illustrated in Fig. 4b and detailed in Table 5.

When analyzing activation in the right middle temporal gyrus (BA21) with ANOVA, we observed an education x training phase interaction, ($F(2,54) = 12.082$, $p < 0.001$, eta-square = 0.309, with no main effect of training phase, $F(2,54) = 2.551$, $p = 0.088$, eta-square = 0.86, or education, $F(1,27) = 0.182$, $p = 0.67$, eta-square = 0.007). To understand the source of the interaction, we compared the different training phases. On the PRE-POST3 comparison for the right middle temporal lobe, there was an education x training phase interaction ($F(1, 27) = 13.296$, $p = 0.001$, eta-square = 0.33) with no main effect of training phase ($F(1, 27) = 3.469$, $p = 0.073$, eta-square= 0.114) or education ($F(1,27) = 4.092$, p =0.053, eta-square = 0.132). Mean comparisons indicated a decreased activation in the higher education group ($p = 0.001$; mean difference= -0.585, SE = 0.148) but no change in the lower education group ($p = 0.226$; mean difference= 0.189, SE = 0.153). When analyzing the POST3-POST6 comparison, there was a main effect of the training phase ($F(1, 27)=4.389$, $p = 0.046$, eta-square = 0.14) with no main effect of education, ($F(1,27) = 2.457$, $p = 0.129$, eta-square = 0.08), or education x training phase interaction ($F(1, 27)=0.779$, $p = 0.385$, eta-square = 0.028)

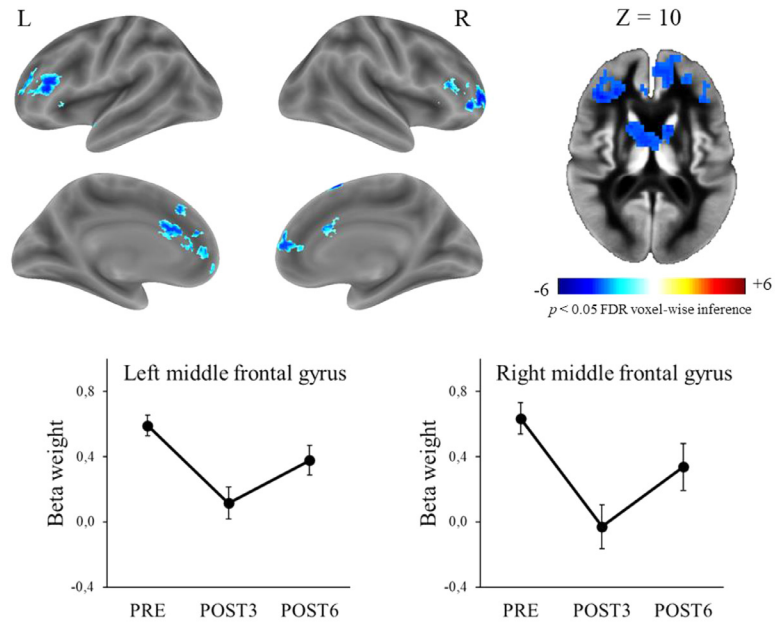
When analyzing the PRE-POST6, there was no main effect of the training phase ($F(1, 27)=0.003$, $p = 0.96$, eta-square = 0), and no main effect of education ($F(1,27) = 1.450$, eta-square = 0.05). However, there was an education x training phase interaction ($F(1,$

a) Main effects for training-related activations

Encoding task



Retrieval task



b) Education by training phase interactions

Retrieval task

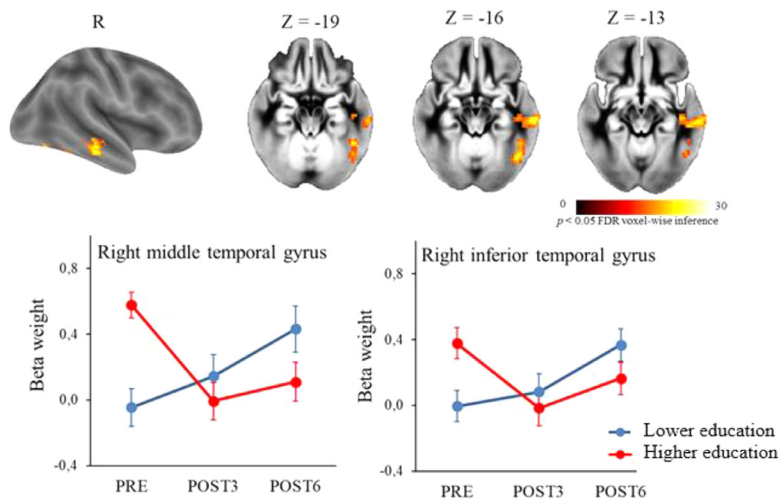


Fig. 4. Brain region activation associated with training.

Table 5
Brain regions associated with training.

a) Main effects for the training-related activations

Anatomical labeling	Extent	z-value	MNI coordinates x	y	z
Encoding task					
L inferior frontal gyrus (BA9)	120	26.98	-42	-2	29
Retrieval task					
L temporal pole (BA38)	30	-4.729	-54	11	-10
R temporal pole (BA38)	42	-4.272	51	17	-10
L inferior frontal gyrus (p. triangularis) (BA32)	382	-3.830	-42	32	11
L ACC (BA32)		-3.550	-6	26	23
L superior medial gyrus (BA10)		-3.544	-15	47	5
R middle orbital gyrus	259	-4.046	42	56	2
R middle frontal gyrus (BA9,10)		-3.993	27	50	5
R superior medial gyrus		-3.518	12	53	11
R posterior-medial frontal	37	-4.033	9	17	65
L Pallidum	262	-3.987	-9	2	2
L Putamen		-3.436	-18	8	11
L rectal gyrus		-3.375	-18	11	-10
L mid orbital gyrus	20	-3.658	-3	53	-4
R inferior frontal gyrus (p. triangularis)	33	-3.635	42	29	14
R middle frontal gyrus		-3.358	45	41	8

$p < 0.05$ FWE voxel-wise inference

b) Education by training phase interactions

Anatomical labeling	Extent	x-value	MNI coordinates x	y	z
Encoding task					
None					
Retrieval task					
R middle temporal gyrus	120	24.51	63	-25	-16
R fusiform gyrus	66	23.12	45	-64	-16
R inferior gyrus		22	48	-49	-19

$p < 0.05$ FDR voxel-wise inference

27)=20.620, $p < 0.001$, eta-square = 0.43). Mean comparisons indicated an increased activation in the lower education group from PRE to POST6 ($p = 0.048$; Mean difference= 0.289, SE = 0.139). There was a significant group difference at PRE ($p = 0.001$) with the higher education group activating more than the lower education group (mean difference = 0.624, SE = 0.139) but the group difference was no longer found at POST3 ($p = 0.396$) and POST6 ($p = 0.091$).

The education x training phase ANOVA for activation in the right inferior temporal lobe (BA37) indicated an education x training phase interaction ($F(2,54) = 11.714$, $p < 0.001$, eta-square=0.303) and a main effect of training phase ($F(2,54) = 3.757$, $p = 0.031$, eta-square = 0.122) but no effect of education ($F(1,27) = 0.007$, $p = 0.935$, eta-square= 0.00). When analyzing the PRE-POST3 comparison for the right inferior temporal lobe (BA37), there was an education x training phase interaction ($F(1, 27)=14.616$, $p < 0.001$, eta-square = 0.351), but no main effect of training phase ($F(1, 27) = 1.824$, $p = 0.188$, eta-square = 0.063), or education ($F(1,27) = 1.229$, $p = 0.277$, eta-square = 0.044). Mean comparisons indicate a decreased activation in the higher education group ($p = 0.001$; Mean difference= -0.503, SE = 0.135) but no change in the lower education group ($p = 0.097$; Mean difference= 0.24, SE = 0.14). When analyzing the POST3-POST6 comparison, there was a main effect of phase ($F(1, 27) = 9.29$, $p = 0.005$, eta-square = 0.256), but no main effect of education ($F(1,27) = 3.415$, $p = 0.076$, eta-square = 0.112), and no education x training phase interaction ($F(1, 27) = 0.12$, $p = 0.732$, eta-square = 0.004). Mean comparisons indicate increased activation in the lower education group ($p = 0.026$; Mean difference= 0.281, SE = 0.119).

When analyzing the PRE-POST6 comparison for the right inferior temporal lobe (BA37), there was no main effect of training phase ($F(1, 27)=1.604$, $p = 0.216$, eta-square = 0.056), or education ($F(1,27) = 0.595$, $p = 0.447$, eta-square = 0.022), but an education x training phase interaction ($F(1, 27)=14.616$, $p < 0.001$, eta-square = 0.392). Mean comparisons indicate an increased activation in the lower education group from PRE to POST6 ($p = 0.048$; Mean difference = 0.289, SE = 0.139). There were significant group differences at PRE ($p = 0.003$) with the higher education group activating more than the lower education group (mean difference = 0.504, SE = 0.153), but the group differences were no longer found at POST3 ($p = 0.136$) and POST6 ($p = 0.107$).

4. Discussion

Our goal was to assess how cognitive stimulation provided by formal education and cognitive training interface at the brain level in older adults with subjective cognitive decline. This study addressed the activation changes induced by cognitive training at different training phases, and whether they varied in older adults with lower vs. higher levels of education. The study also assessed whether the changes related to training were similar to those associated with education differences. Based on the triarchic model of learning, activation changes were expected to be observed in the prefrontal regions as learners increased their expertise. However, our critical hypothesis was that lower education would be associated with lower levels of temporal activation at baseline, as found in prior work, and that cognitive training would modify these brain activations. Some of the training changes were expected to promote similar brain processes as those associated with formal education as proposed by the INTERACTIVE model.

4.1. Training effect on brain activation

When examining the baseline activation irrespective of education, we found initial activation of the anterior frontal gyrus, anterior cingulate and basal ganglia at retrieval. Activation in that cluster decreased from PRE to POST3 while activation of the dorsolateral prefrontal cortex (BA 9) increased from PRE to POST6 at encoding. Initial activation of the anterior part of the frontal lobe seems to reflect initial reliance on metacognitive processes, which is required when people need to carry on an unfamiliar or demanding task followed by a reduction of that activation along with increased engagement of the cognitive control network, which guides attention to the most relevant aspects of information processing. Thus, as predicted by the triarchic model, we found a reversed learning phase effect when comparing the activation change pattern of the 2 brain regions: As the cognitive control network increases its engagement, the metacognitive region decreases its involvement. Again, this is consistent with the triarchic learning theory, which postulates that the involvement of the two networks varies in the opposite direction as the learners move through the different phases of learning. Thus, both the location and pattern of change support the triarchic theory of learning. The observation of an activation increase at encoding and activation reduction at retrieval is consistent with how training is provided as proposed by the INTERACTIVE model. The gradual increase in activation of the dorsolateral cortex at encoding is consistent with the fact that the method of loci is applied at that stage and involves that participants pay attention to the content of the material which is relevant to the learned mnemonic. Reduction at retrieval is also consistent with the format of the memory training used here. As learners become more competent in increasing the quality of their memory trace at encoding, retrieval is expected to require reduced reliance on active retrieval search. Thus, participants seem to reduce their recruitment of regions involved in metacognitive processes during retrieval because encoding is more active and better supports learning.

4.2. Effect of education at baseline

The observation that higher levels of education are associated with higher recruitment of the inferior temporal lobe is interesting and consistent with our second hypothesis based on prior findings (Belleville et al., 2021). In a prior work, we found that higher engagement of the right inferior temporal lobe was associated with higher reserve proxy and that it protected against hippocampal atrophy in older adults. The current findings confirm this earlier result in a slightly different population and using a different episodic memory task. It is important to recognize that the cognitive engagement activation reported in our previous work was found during encoding as retrieval was not tested. In this current study, only retrieval showed a significant education effect. This difference between the 2 studies may be due to differences in methods, population or power

4.3. Interaction between training and education

When examining whether the right temporal lobe activation changes with training phase and if this differs as a function of the level of education, we observed a cross-over interaction between training phase and education. The interaction is explained by the fact that before training, temporal activation (both in the right middle temporal gyrus (BA21) and right inferior temporal (BA37)) was lower at retrieval in the lower education compared to the higher education group as mentioned above. Then, activation increased during training in the lower education group, while it remained similar or decreased in the higher education group. As a result, the 2 groups no longer differed at POST3 and later. This confirms our third hypothesis that training has an effect comparable to that of formal education. In terms of mechanism involved, this pattern of brain changes may reflect a better engagement of the memory-related network at retrieval in people with lower education and the development of automaticity in those with higher education. When combined with the changes observed in the prefrontal regions, memory training seems to involve an increased engagement of the cognitive controlled processes at encoding. During retrieval, there is a lesser need to recruit metacognitive processes as temporal regions that are part of the episodic memory network become more involved during training, and this is particularly the case in those people with lower education. The differences observed in the temporal lobe activation changes when comparing participants with higher and lower education are consistent with a strategic shift in less educated people and increased expertise in highly educated participants.

A major goal here was to use a training protocol to examine the neural implementation of cognitive reserve and determine if it was potentially useful as a means of increasing reserve. Our results are consistent with an increase in cognitive reserve in individuals with lower education levels. However, they do not provide definitive evidence that these individuals have indeed increased reserve, and we must be wary of a phenomenological similarity. Additional criteria must be met to conclude that there is an increase in cognitive reserve in these individuals, including evidence that participants show reduced cognitive decline over time and/or that these activation changes moderate the relationship between cognition and their brain status, such as hippocampal atrophy.

While the focus of this study was on brain changes, it is relevant to discuss the behavioural results and implications for our activation findings. Because free recall is more amenable to the method of loci, we will focus here on the off-scan free recall data. Results indicate that both groups increased from PRE to POST3 with no further change afterward. This can be related to our finding that the anterior frontal gyrus, anterior cingulate, and basal ganglia reduced their activation from PRE to POST3 at retrieval, with no further change. We also note that most of the temporal activation change occurred between PRE and POST3. Therefore, the first few training sessions appear to be key in developing brain processes that lead to behavioral changes. One possible explanation for the lack of improvement after POST3 is accumulated interference from the repeated use of the same locations over many lists, which may have limited the training effect from sessions 3 to 6. However, this is unlikely as most studies that have examined proactive interference with the method of loci, compared to other methods, actually report better recall and less interference, even under conditions with high levels of interference (Bass and Oswald, 2014; De Beni and Cornoldi, 1988; Massen and Vaterrodt-Plünnecke, 2006). These studies conclude that using the method of loci actually reduces proactive interference by increasing distinctive encoding. Interestingly, analysis of the off-scan behavioural data showed an interaction effect where older adults with higher education benefitted more from PRE to POST3 than those with lower education. This is an interesting observation that may be related to the activation findings and supports the notion that the two groups were at different levels of their learning phase and those with higher education had started to develop expertise earlier.

There are several limitations to this study. First, the sample size is relatively small and replication with larger samples is required. Second, the cognitive training method was limited to the method of loci, which was considered a methodological strength because it allows a more fine-grained evaluation of the brain mechanisms

involved in task-relation activation. However, this approach limits the generalizability of the results. Third, we could have used a more comprehensive measure of reserve, such as reserve proxy questionnaires that rely on broader characteristics rather than only education. However, education has the advantage of being a well-recognized predictor of dementia that is easy to quantify and does not rely on subjective assessment. We compared the performance of 2 educational subgroups separated by a median and, therefore, some of the results could be interpreted as reflecting regression to the mean. However, we take comfort in the fact that the results are consistent with independent theories of training-related brain changes. Regardless, these limitations suggest that the outcome model should be tested with different samples and procedures. Another limitation is that recognition was used to assess retrieval in-scan to reduce motion artifacts. Because recognition is not perfectly adapted to the method of loci, free-recall was used off-scan to assess training efficacy. Finally, we did not ask participants to report the strategy they used in-scan. Since our program included one session on interactive imagery, and since there is substantial literature on the effectiveness of interactive imagery (Dunlosky and Hertzog, 1998; Smith et al., 1998), it is possible that our participants used it as an encoding strategy in alternance with the method of loci.

5. Conclusions

This study reported a number of critical findings in relation to neural-based models of cognitive intervention and reserve. First, it shows that the type of functional neural changes induced by cognitive training differ as a function of the training phase, similar to what is found in more traditional learning experiences. Brain regions associated with metacognitive processes are initially engaged during encoding, but gradually recede as participants move through the learning phases, giving way to the cognitive control network during retrieval. Our results also show different activation changes in the temporal lobe in those with lower vs. higher levels of education, and that the temporal activation changes following training were similar to those associated with education. This study contributes to the important question of whether reserve depends only on cognitive experience accumulated over the course of life or whether it can be promoted later in life. The results support the hypothesis that cognitive reserve can be promoted by cognitive training later in life.

Author contributions

Conceptualization: SB; First full version of the manuscript: SB; Revision: SM and BB; Final revision: SB, SM, and BB; Approval of final revision: SB, SM, BB and EO. Data analysis: SM and SB; Study design: SB, BB, EO. E-prime task preparation: SM. Data collection: EO, BB and SM. Supervision and study funding: SB.

Disclosure statement

There are no actual or potential conflicts of interest.
SB is a consultant on dementia prevention for Lucilab Inc.

Acknowledgements

This work was supported by Grants to SB from the [Canadian Institutes of Health Research (CIHR)] [number MOP81302], National Science and Engineering Research Council (NSERC) [number RGPIN-2016-06132), [Canada foundation for innovation (CFI)] [number FCI-30063] and Canada Research Chair on Cognitive Neuroscience of Aging and Brain Plasticity. EO received a [Fonds de recherche du Québec - Santé (FRQS) Master's training scholarship] [number 26074], [CIHR Master's award] [number RN109554 - 246831] and a [CIHR doctoral research award] [number RN205414 - 315174]. B.B. was supported by postdoctoral fellowships from the Fondation Institut de gériatrie de Montréal and the Fondation Famille Lemaire.

We would like to thank Nadia Jaffer for her help with recruitment through the CRIUGM participants' registry, Émilie Lepage, Christel Cornelis, for their help in testing participants and Annie Webb for English editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2022.10.010.

References

Bartrés-Faz, D., Solé-Padullés, C., Junqué, C., Rami, L., Bosch, B., Bargalló, N., Falcón, C., Sánchez-Valle, R., Molinuevo, J.L., 2009. Interactions of cognitive reserve with regional brain anatomy and brain function during a working memory task in healthy elders. Biol. Psychol. 80, 256–259. doi:10.1016/j.biopsycho.2008.10.005.

Bass, W.S., Oswald, K.M., 2014. Proactive control of proactive interference using the method of loci. Adv. Cogn. Psychol. 10, 49.

Belleville, S., Bherer, L., 2012. Biomarkers of cognitive training effects in aging. Curr. Transl. Geriatr. Exp. Gerontol. Rep. 1, 104–110. doi:10.1007/s13670-012-0014-5.

Belleville, S., Clément, F., Mellah, S., Gilbert, B., Fontaine, F., Gauthier, S., 2011. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. Brain 134, 1623–1634. doi:10.1093/brain/awr037.

Belleville, S., Gilbert, B., Fontaine, F., Gagnon, L., Ménard, E., Gauthier, S., 2006. Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: evidence from a cognitive intervention program. Dement. Geriatr. Cogn. Disord. 22, 486–499. doi:10.1159/000096316.

Belleville, S., Hudon, C., Bier, N., Brodeur, C., Gilbert, B., Grenier, S., Ouellet, M.C., Viscogliosi, C., Gauthier, S., 2018. MEMO+: efficacy, durability and effect of cognitive training and psychosocial intervention in individuals with mild cognitive impairment. J. Am. Geriatr. Soc. doi:10.1111/jgs.15192.

Belleville, S., LeBlanc, A.C., Kergoat, M., Calon, F., Gaudreau, P., Hébert, S.S., Hudon, C., Leclerc, N., Mechawar, N., Duchesne, S., Gauthier, S., Bellec, P., Belleville, S., Bocti, C., Calon, F., Chertkow, H., Collins, L., Cunnane, S., Duchesne, S., Gaudreau, P., Gauthier, S., Hébert, S.S., Marie-Jeanne-Kergoat, C.H., LeBlanc, A.C., Leclerc, N., Mechawar, N., Philips, N., Soucy, J., Dang Vu, T.T., Verret, L., Villalpando, J.M., 2019. The Consortium for the early identification of Alzheimer's disease–Quebec (CIMA-Q). Alzheimer's Dement. Diagnosis, Assess. Dis. Monit. 11, 787–796. doi:10.1016/j.dadm.2019.07.003.

Belleville, S., Mellah, S., Cloutier, S., Dang-Vu, T.T., Duchesne, S., Maltezos, S., Phillips, N., Hudon, C., 2021. Neural correlates of resilience to the effects of hippocampal atrophy on memory. NeuroImage. Clin. 29, 102526. doi:10.1016/j.nicl.2020.102526.

Belleville, S., Mellah, S., de Boysson, C., Demonet, J.-F., Bier, B., 2014. The pattern and loci of training-induced brain changes in healthy older adults are predicted by the nature of the intervention. PLoS One 9, e102710. doi:10.1371/journal.pone.0102710.

Boller, B., Mellah, S., Ducharme-Laliberté, G., Belleville, S., 2017. Relationships between years of education, regional grey matter volumes, and working memory-related brain activity in healthy older adults. Brain Imaging Behav 11, 304–317. doi:10.1007/s11682-016-9621-7.

Boller, B., Ouellet, É., Belleville, S., 2021. Using virtual reality to assess and promote transfer of memory training in older adults with memory complaints: a randomized controlled trial. Front. Psychol. 12, 627242. doi:10.3389/fpsyg.2021.627242.

Brett, M., Anton, J.-L., Valabregue, R., Poline, J.-B., 2002. Region of interest analysis using an SPM toolbox. [abstract] Present. 8th Int. Conf. Funct. Mapp. Hum. Brain, June 2-6, Sendai, Japan, 16 Available CD-ROM NeuroImage.

Cabeza, R., Albert, M., Belleville, S., Craik, F.I.M., Duarte, A., Grady, C.L., Lindenberger, U., Nyberg, L., Park, D.C., Reuter-Lorenz, P.A., Rugg, M.D., Steffener, J., Rajah, M.N., 2018. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nat. Rev. Neurosci. 19, 701–710. doi:10.1038/s41583-018-0068-2.

Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R., 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chronic Dis. 40, 373–383. doi:10.1016/0021-9681(87)90171-8.

Chein, J.M., Schneider, W., 2012. The brain's learning and control architecture. Curr. Dir. Psychol. Sci. 21, 78–84. doi:10.1177/0963721411434977.

Colangeli, S., Boccia, M., Verde, P., Guariglia, P., Bianchini, F., Piccardi, L., 2016. Cognitive reserve in healthy aging and alzheimer's disease: a meta-analysis of

fMRI studies. Am. J. Alzheimers. Dis. Other Demen. 31, 443–449. doi:10.1177/1533317516653826.
De Beni, R., Cornoldi, C., 1988. Does the repeated use of loci create interference? Percept. Mot. Skills 67, 415–418.
Duda, B.M., Sweet, L.H., 2020. Functional brain changes associated with cognitive training in healthy older adults: a preliminary ALE meta-analysis. Brain Imaging Behav 14, 1247–1262. doi:10.1007/s11682-019-00080-0.
Dunlosky, J., Hertzog, C., 1998. Aging and deficits in associative memory: what is the role of strategy production? Psychol. Aging 13, 597.
Fratiglioni, L., Paillard-Borg, S., Winblad, B., 2004. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol doi:10.1016/S1474-4422(04)00767-7.
Galasko, D., Bennett, D.A., Sano, M., Marson, D., Kaye, J., Edland, S.D., 2006. ADCS prevention instrument project: assessment of instrumental activities of daily living for community-dwelling elderly individuals in dementia prevention clinical trials. Alzheimer Dis. Assoc. Disord. 20, S152–S169. doi:10.1097/01.wad.0000213873.25053.2b.
Guillaume, B., Hua, X., Thompson, P.M., Waldorp, L., Nichols, T.E., 2014. Fast and accurate modelling of longitudinal and repeated measures neuroimaging data. Neuroimage 94, 287–302. doi:10.1016/j.neuroimage.2014.03.029.
Hachinski, V.C., Iliff, L.D., Zilhka, E., Boulay, G.H., McAllister, V.L., Marshall, J., Russell, R.W.R., Symon, L., 1975. Cerebral blood flow in dementia. Arch. Neurol. doi:10.1001/archneur.1975.00490510088009.
Hampstead, B.M., Stringer, A.Y., Stilla, R.F., Giddens, M., Sathian, K., 2012. Mnemonic strategy training partially restores hippocampal activity in patients with mild cognitive impairment. Hippocampus 22, 1652–1658. doi:10.1002/hipo.22006.
Jessen, F., Amariglio, R.E., Buckley, R.F., van der Flier, W.M., Han, Y., Molinuevo, J.L., Rabin, L., Rentz, D.M., Rodriguez-Gomez, O., Saykin, A.J., Sikkes, S.A.M., Smart, C.M., Wolfsgruber, S., Wagner, M., 2020. The characterisation of subjective cognitive decline. Lancet. Neurol. 19, 271–278. doi:10.1016/S1474-4422(19)30368-0.
Jessen, F., Amariglio, R.E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K.A., van der Flier, W.M., Glodzik, L., van Harten, A.C., de Leon, M.J., McHugh, P., Mielke, M.M., Molinuevo, J.L., Mosconi, L., Osorio, R.S., Perrotin, A., Petersen, R.C., Rabin, L.A., Rami, L., Reisberg, B., Rentz, D.M., Sachdev, P.S., de la Sayette, V., Saykin, A.J., Scheltens, P., Shulman, M.B., Slavin, M.J., Sperling, R.A., Stewart, R., Uspenskaya, O., Vellas, B., Visser, P.J., Wagner, M., 2014. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers. Dement. 10, 844–852. doi:10.1016/j.jalz.2014.01.001.
Kaplan, E., Googlass, H., Weintraub, S., 1983. Boston Naming Test. Philadelphia: Lea & Febiger, 2nd edit.
Kramer, A.F., Bherer, L., Colcombe, S.J., Dong, W., Greenough, W.T., 2004. Environmental influences on cognitive and brain plasticity during aging. J. Gerontol. A. Biol. Sci. Med. Sci. 59, M940–M957. doi:10.1093/gerona/59.9.m940.
Lea, G., 1975. Chronometric analysis of the method of loci. J. Exp. Psychol. Hum. Percept. Perform. 1, 95–104. doi:10.1037/0096-1523.1.2.95.
Macmillan, N., 1993. Signal detection theory as data analysis method and psychological decision model.
Massen, C., Vaterrodt-Plünnecke, B., 2006. The role of proactive interference in mnemonic techniques. Memory 14, 189–196.
Moroni, C., Bayard, S., 2009. [Inhibitory process: what evolution after the age of 50?]. Psychol. Neuropsychiatr. Vieil. 7, 121–129. doi:10.1684/pnv.2009.0155.
Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. doi:10.1111/j.1532-5415.2005.53221.x.
Simon, S.S., Hampstead, B.M., Nucci, M.P., Duran, F.L.S., Fonseca, L.M., Martin, M., da, G.M., Ávila, R., Porto, F.H.G., Brucki, S.M.D., Martins, C.B., Tascone, L.S., Amaro, E.J., Busatto, G.F., Bottino, C.M.C., 2020. Training gains and transfer effects after mnemonic strategy training in mild cognitive impairment: a fMRI study. Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 154, 15–26. doi:10.1016/j.ijpsycho.2019.03.014.
Smith, A.D., Park, D.C., Earles, J.L.K., Shaw, R.J., Whiting IV, W.L., 1998. Age differences in context integration in memory. Psychol. Aging 13, 21.
Snodgrass, J.G., Corwin, J., 1988. Pragmatics of measuring recognition memory: applications to dementia and amnesia. J. Exp. Psychol. Gen. 117, 34–50. doi:10.1037//0096-3445.117.1.34.
Stanislaw, H., Todorov, N., 1999. Calculation of signal detection theory measures. Behav. Res. Methods, Instruments, Comput. 31, 137–149. doi:10.3758/BF03207704.
Steffener, J., Stern, Y., 2012. Exploring the neural basis of cognitive reserve in aging. Biochim. Biophys. Acta 1822, 467–473. doi:10.1016/j.bbadis.2011.09.012.
Stern, Y., 2009. Cognitive reserve. Neuropsychologia doi:10.1016/j.neuropsychologia.2009.03.004.
Stern, Y., Arenaza-Urquijo, E.M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W.S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., Arenaza Urquiljo, E.M., Bartrés-Faz, D., Belleville, S., Cantillon, M., Chetelat, G., Clouston, S.A.P., Estanga, A., Ewers, M., Franzmeier, N., Gold, B., Habeck, C., Jones, R., Kempermann, G., Kochhann, R., Kremen, W., Lim, Y.Y., Martínez-Lage, P., Morbelli, S., Okonkwo, O., Ossenkoppele, R., Pettigrew, C., Rosen, A.C., Scarmeas, N., Soldan, A., Song, X., Udeh-Momoh, C., Stern, Y., Valenzuela, M., Van Loenhoud, A.C., Vemuri, P., Vuoksimaa, E., 2018a. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimer's Dement doi:10.1016/j.jalz.2018.07.219.
Stern, Y., Arenaza-Urquijo, E.M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W.S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., 2020. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimer's Dement 16, 1305–1311. doi:10.1016/j.jalz.2018.07.219.
Stern, Y., Gazes, Y., Razlighi, Q., Steffener, J., Habeck, C., 2018b. A task-invariant cognitive reserve network. Neuroimage 178, 36–45. doi:10.1016/j.neuroimage.2018.05.033.
Tremblay, M.-P., Potvin, O., Belleville, S., Bier, N., Gagnon, L., Blanchet, S., Domingues, N.-S., Gaudreau, G., Macoir, J., Hudon, C., 2016. The victoria stroop test: normative data in Quebec-French adults and elderly. Arch. Clin. Neuropsychol. acw029. doi:10.1093/arclin/acw029.
Troyer, A.K., Leach, L., Strauss, E., 2006. Aging and response inhibition: normative data for the victoria stroop test. Neuropsychol. Dev. Cogn. Sect. B, Aging, Neuropsychol. Cogn. 13, 20–35. doi:10.1080/138255890968187.
Tucker, A.M., Stern, Y., 2011. Cognitive reserve in aging. Curr. Alzheimer Res. 8, 354–360. doi:10.2174/156720511795745320.
van Balkom, T.D., van den Heuvel, O.A., Berendse, H.W., van der Werf, Y.D., Vriend, C., 2020. The effects of cognitive training on brain network activity and connectivity in aging and neurodegenerative diseases: a systematic review. Neuropsychol. Rev. 30, 267–286. doi:10.1007/s11065-020-09440-w.
Van der Linden, M., Coyette, F., Poitrenaud, J., Kalafat, M., Calicis, F., Wyns, C., Adam, S., 2004. II. L'épreuve de rappel libre/rappel indicé à 16 items (RL/RI-16).
Verhaeghen, P., Marcoen, A., 1996. On the mechanisms of plasticity in young and older adults after instruction in the method of loci: evidence for an amplification model. Psychol. Aging 11, 164–178. doi:10.1037//0882-7974.11.1.164.
Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., Leirer, V.O., 1982. Development and validation of a geriatric depression screening scale: a preliminary report. J. Psychiatr. Res. doi:10.1016/0022-3956(82)90033-4.