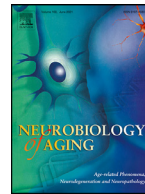




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# More flexible brain activation underlies cognitive reserve in older adults

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### ABSTRACT

The goal of this study was to identify the brain mechanisms underlying cognitive reserve using a parametric n-back working memory (WM) task in a sample of healthy older adults. We first identified the WM-related activations associated with years of education and then tested whether these activations mitigated the detrimental impact of age on cognition. Thirty-nine older adults received a magnetic resonance imaging examination while completing an n-back task with different levels of WM load (0-, 1- vs. 2-back). Results show that more education is associated with lower activation of the left medial superior frontal gyrus (BA8) in the 1-back condition and a greater activation of the right caudate nucleus in the 2-back condition. The caudate and frontal activations are task-positive and task-negative regions, respectively. Moderation analyses indicate that the effect of age on performance is less detrimental in participants with higher caudate activation in the 2-back condition. Overall, these results suggest that cognitive reserve is explained by a superior ability to flexibly engage greater or novel activation as cognitive demand increases.

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## 1. Introduction

The concept of cognitive reserve has been proposed to explain why some individuals better cope than others with the detrimental effects of aging or age-related neurodegenerative disorders on cognition. In this context, cognitive reserve refers to the notion that interindividual differences in brain function may cause some people to be less susceptible to the cognitive impact of age-related brain changes or neurodegenerative disease (Katzman, 1993; Stern, 2009; Stern et al., 2020). Arenaza-Urquijo and Vemuri (2018) have proposed the term resilience in the clinical context to capture the fact that some individuals can better cope with pathology and remain cognitively intact despite the presence of significant Alzheimer's disease pathology in their brain. Thus, both resilience and cognitive reserve seem to capture a broadly similar concept, but resilience has been proposed for clinical

populations. Here, we will use the term cognitive reserve as we are focusing on older adults without suspected pathologies.

One important question regarding cognitive reserve is that the functional mechanisms underlying it remain poorly understood (Cabeza et al., 2018; Stern et al., 2020). Given that working memory (WM) is a cognitive function that is highly sensitive to age (Reuter-Lorenz & Park, 2010; Belleville et al., 2015) and highly variable in older individuals (Sylvain-Roy & Belleville, 2015), exploring WM-related activation associated with cognitive reserve may contribute to understanding neural mechanisms behind cognitive reserve. Thus, this study aims to identify some of the brain processes underlying cognitive reserve by examining which functional activations are associated with education, a well-established reserve proxy (Stern et al., 2020), and assessing whether these activations counteract the detrimental effects of age on cognition.

Neural flexibility and neural efficiency were examined as 2 putative mechanisms underlying cognitive reserve. Neural flexibility refers to the capacity to engage greater activation of the task-related network (i.e. primary network) or to activate alternative brain regions when the task demand exceeds the capacity of the system (Cabeza et al., 2018; Stern, 2009; Stern et al., 2020). It is

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hypothesized that neural flexibility should be observed in people with larger scores on reserve proxies and result in a preserved level of performance. There is some evidence that increased neural flexibility is associated with more education or higher scores on reserve proxies, suggesting that flexibility may influence reserve effects. For example, Boller et al. (2017) found that higher education levels are associated with larger recruitment of the left prefrontal cortex during a WM task. Thus, individuals with a higher reserve may be protected against the effects of the aging brain or brain diseases, as they are able to recruit higher levels of the primary brain network and/or engage alternative brain regions to perform a task at more demanding levels.

Neural efficiency is defined as the capacity to complete a cognitive task with minimal cerebral activation (Cabeza et al., 2018; Stern, 2009; Stern et al., 2020). Thus, higher efficiency can be operationally defined as individuals with higher scores on reserve proxies and who show less activation than those with lower reserve proxy scores, while maintaining a similar performance level as individuals with higher activation. This should be found in brain regions that are typically recruited by the task. Lower levels of activation that suggest efficiency were reported in individuals with more education or higher scores on reserve proxy questionnaires (which combine education, occupational complexity, cognitively stimulating leisure activities, etc.) for WM (Bartres-Faz et al., 2009), episodic memory (Sole-Padullés et al., 2009) and verbal comprehension (Bosch et al., 2010) tasks. Thus, efficiency may be one possible mechanism underlying cognitive reserve, where individuals with higher reserve would require lower brain activation of the task-related network than those with a lower reserve to achieve a comparable level of performance.

In some cases, results interpreted to reflect neural efficiency may also indicate inter-individual differences in deactivation. N-back induced deactivations were found in the posterior cingulate cortex, as well as frontal and temporal regions (for a meta-analysis, see Mencarelli et al., 2019). This pattern of neural deactivations is consistent with those found using other cognitive paradigms (Anticevic et al., 2012; Binder, 2012) and overlaps with regions associated with the default mode network (DMN) (Schacter et al., 2008; Laird et al., 2009). Interestingly, greater DMN deactivations have been found to be associated with more efficient cognitive performance (Sinha et al., 2007; Binder et al., 2003), suggesting that the efficient deactivation of DMN may contribute to optimal cognitive performance. Cross-sectional and longitudinal studies have consistently reported lower task-induced deactivations in several regions of the DMN (Winocur et al., 2006; Lustig et al., 2003; Mak et al., 2017; Reuter-Lorenz et al., 2007; Nyberg et al., 2014; Sambataro et al., 2010) in older adults compared to younger adults engaged in a WM task (Eyler et al., 2014; Kramer et al., 2012). While very few studies have examined this pattern in relation to reserve proxies, at least one study reported that memory-impaired older adults with higher scores on reserve proxies showed increased deactivations within the DMN compared to those with lower scores (Bosch et al., 2010). Thus, it is important to examine differences in both activation and deactivation, which will be investigated in this present study.

Neural efficiency, and activation- and deactivation-related neural flexibility are not necessarily incompatible mechanisms. For instance, some models have proposed that efficiency and flexibility may operate preferentially at different levels of the difficulty spectrum (Boller et al., 2017; Reuter & Cappell, 2008; Steffener & Stern, 2012). Efficiency could occur at lower task demand, but as the primary network reaches its capacity, additional resources may be recruited. Evidence for co-occurrence has been reported either at the inter- or intra-individual levels. In some cases, this is apparent in different age groups but not within the same individuals.

For example, Boller et al. (2017) found larger activation associated with higher levels of education in a group of older adults (> 67 years of age), who were more likely to face difficulties with the task. However, they did not observe this effect in adults between the ages of 60–67. Thus, greater neural flexibility can allow older adults with a higher reserve to adapt their patterns of brain activation to cope with exceeding demand, whether this is due to increasing age or task-demand (Anthony & Lin, 2017; Boller et al., 2017; Steffener & Stern, 2012). In some conditions, neural efficiency and neural flexibility seem to co-occur in older adults with higher reserve (Haut et al., 2005; Scarmeas et al., 2003; Springer, McIntosh, Winocur, & Grady, 2005). Even if this might appear counterintuitive as efficiency and flexibility are conceptually conflicting mechanisms, both have been associated with higher scores on reserve proxies. Both are plausible reserve mechanisms, which may operate either concomitantly or at different levels of task demand. However, no study has assessed this hypothesis directly in older adults by manipulating task demand, and few studies have assessed the role of deactivation-related neural flexibility as a potential mechanism for reserve.

Furthermore, no study has analyzed whether these processes moderate the deleterious effect of age on cognition. If cognitive reserve is subtended at the neural level by higher neural efficiency at a low task load or higher flexibility at a high task load, the two mechanisms should moderate the deleterious effect of age on cognition (Stern et al., 2020). Identifying a moderation effect is critical because it would demonstrate that these activation differences are protective, which is the definition of a “true” reserve effect. Studies showing that individuals with more education are characterized by a higher level of brain activation are only reporting the association between a brain variable and a reserve proxy, rather than demonstrating what is actually underlying reserve. The hypothesis that an activation pattern reflects a reserve process can only be confirmed if it is shown to be protective. To provide stronger evidence that a brain variable plays the role of a reserve mechanism, moderation approaches can be used to assess if a higher expression of the brain variable is associated with reduced detrimental effects of age (Stern, 2017). Only a few recent studies have used moderation approaches in the cognitive reserve framework and their results indicate that the approach is valid and promising (Benson et al., 2018; Ewers et al., 2017; Habeck et al., 2018). These studies have identified that connectivity patterns, mainly in cognitive control networks (e.g. frontoparietal, salience, medial frontal cortex), moderate the relationship between cognition and neurodegeneration, white-matter changes or hypometabolism. While interesting, these studies focused on connectivity and did not assess efficiency and flexibility processes as reserve mechanisms.

The main objective of this study was to identify the functional mechanisms underlying cognitive reserve in older adults by determining whether reserve is associated with increased neural efficiency and/or improved activation- or deactivation-related flexibility. Based on recent findings, it was hypothesized that education-related activation patterns vary as a function of task-demand. We used an n-back WM task because it allows a parametric manipulation of the task load. Increasing from 1- to 2-back manipulates the difficulty level at a quantitative rather than qualitative level. The task also has the advantage that its pattern of activation is well established (see Bullmore et al., 2005 for a meta-analysis), thus allowing to compare these results to the abundant literature on this task. Imaging studies have shown that performing verbal n-back tasks is associated with activation in several frontoparietal regions bilaterally (Jonides et al., 1997; Ragland et al., 2002), and that increasing task load increases activation in these regions (Braver et al., 1997; Jonides et al., 1997).

If reserve is associated with efficiency, there should be an inverse relationship between education and activation in task-positive regions. Reduced activation should be found within or in the vicinity of the regions activated by the task. If reserve is subserved by more flexible activations, higher activations should be found in individuals with more education. These may be found either in the primary network or new alternative regions and at different levels of task demand.

To establish that these differences truly subserved reserve effects, a second objective was to assess if the activation differences associated with years of education moderate the deleterious effect of age on cognition. It was hypothesized that the negative effect of age on n-back performance would be attenuated in individuals showing the education-related activation pattern. Thus, for regions associated with efficiency or deactivation, we expected that individuals with a lower level of activation would perform better on tasks than those with higher activation with increased age. For flexibility, better performance is expected in individuals with higher activation than in those with lower activation as age increases. Determining that education-related activation differences reduce detrimental effects of age on cognition would strongly substantiate their role in supporting cognitive reserve. Thus, moderation analyses will assess whether the education-related differences in brain activation indicate a more positive outcome for cognition than what would normally be predicted with age.

For secondary analyses, we examined the correlation between activation and the volume of white matter lesions (WML) and whether the observed activations moderated the relationship between the volume of white matter lesions and WM performance.

## 2. Methods

### 2.1. Participants

Forty-one healthy older adults (24 women) age 65–88 were recruited through the *participants database* of the Research Center of the *Institut universitaire de gériatrie de Montréal* and through ads posted in the community. All participants were right-handed community-dwelling francophones and had normal or corrected-to-normal vision and hearing. Participants were excluded if they reported the presence or a history of a brain disease, alcoholism, substance abuse, severe psychiatric disorders, general anesthesia within the last 6 months, use of any medication that could impact cognitive or cerebral functioning, or if they scored below the education or age/education adjusted cut-off respectively on both the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) and the Mini-Mental State Examination (MMSE; McHugh et al., 1975).

Participants were further characterized by cognitive measures through the Free and Cued Recall Test (RL/RI; Van der Linden et al., 2004), the Victoria Stroop Test (Regard, 1981) and the Geriatric Depression Scale (GDS; Yesavage et al., 1982). The number of years of formal education completed without interruption was recorded and used as a reserve proxy.

This study was approved by the *Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec*. All participants provided informed written consent at the beginning of the study.

### 2.2. N-Back paradigm

A verbal n-back WM task was used to assess task-related functional magnetic resonance imaging (fMRI) activation (Braver et al., 1997). The task comprised a control (0-back) and two experimental conditions with a parametric difficulty gradient (1- and 2-back).

Participants were presented with a series of letters. Using a 2-button answer box (yes/no), they were asked to indicate whether the letter was an "X" (0-back condition), or if it was identical to the letter presented one (1-back condition) or 2 positions (2-back condition) earlier in the sequence. The task included 15 blocks alternating in a pseudo-random fashion between the 3 conditions (0-back, 1-back and 2-back). Each block was 32 seconds long and contained 16 letters (5 targets) presented at a rate of 500 ms per item. A 1500 ms crosshair interstimuli interval was presented between each stimulus. An additional 12-second rest period was inserted at the end of each block (see experimental paradigm in Figure S1). The task was projected on a screen visible through a mirror attached to the head coil. A brief reminder of the condition instructions was projected on the screen for 5 seconds at the beginning of each block. Task presentation and data collection were managed with E-Prime software (Psychology Software Tools, Inc.). MRI-compatible glasses were used for participants needing visual correction. Prior to the MRI session, all participants received a brief training session to ensure they understood instructions and were familiar with the task.

### 2.3. Neuroimaging data

#### 2.3.1. MRI and fMRI acquisition parameters

Participants underwent structural and fMRI examinations on a Siemens Magnetom TIM Trio 3T MRI system (Siemens Medical Solutions, Erlangen, Germany), using the Siemens 32-channel "receive only" head coil at the Functional Neuroimaging Unit of the Research Center of the *Institut universitaire de gériatrie de Montréal*.

A high resolution T1 weighted 3D-Multi-Echo MPRAGE (TR: 2530 ms; TE: 1.64 ms; flip angle: 7°; FoV: 256 mm; voxel size: 1.0 × 1.0 × 1.0 mm; 176 continuous slices) and FLAIR weighted sequence (*Fluid Attenuated Inversion Recovery*; TR: 9000 ms; TE: 90 ms; flip angle: 150°; FoV: 240 mm; voxel size: 0.9 × 0.9 × 4.0 mm with 4.0 mm distance gap factor; 44 slices) were acquired to obtain white matter lesion (WML) volume (white matter hypointensity volume from T1-weighted image and white matter hyperintensity volume from FLAIR). The task-related blood oxygen level dependent (BOLD) signal was acquired using a T2\* weighted gradient echo EPI sequence (TR: 2500 ms; TE: 30 ms; flip angle: 90°; FoV: 192 mm; voxel size 3.0 × 3.0 × 3.0 mm with 3.0 mm distance gap factor; 41 slices). Acquisition was in axial orientation coplanar with AC-PC whole brain coverage. The order of acquisition was descending. The functional images were acquired in one run, and the first 3 volumes were automatically discarded by the fMRI scanner.

#### 2.3.2. MRI image preprocessing

T1-weighted images were analyzed through FreeSurfer 5.3 automated software (<https://surfer.nmr.mgh.harvard.edu/>). White matter hypointensity volume was used after being proportioned according to the participant's estimated intracranial volume (ICV). WML obtained with FreeSurfer was further validated through a semi-automated technic developed by (Jagust et al., 2005) using FLAIR images (only available in 37 participants). There was a very high correlations between both measures.

#### 2.3.3. fMRI image preprocessing and first-level analyses

Functional data were analyzed with Statistical Parametric Mapping (SPM12; <http://www.fil.ion.ucl.ac.uk/spm>) and fine motion correction was applied through Functional Image Artifact Correction Heuristic (FIACH; Tierney et al., 2016), both implemented in MATLAB 8.3.0 software (<http://www.mathworks.com>).

First, the images were aligned to a mean functional image for head motion correction and were affined through FIACH, which uses a 2-step procedure to identify and correct physiological and

motion-generated noise in sensitive brain regions. Second, images were slice-time corrected to the middle slice using SPM12's Fourier phase shift interpolation. Third, images were co-registered with each subject's anatomical MRI image. Finally, images were spatially normalized to the Montreal Neurological Institute stereotaxic space, resliced to 3 mm<sup>3</sup> voxels, and smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM).

The first-level analyses were fixed effects based on the general linear model (GLM) with a box-car response. For each participant, GLM was set up by specifying the onsets and durations (32 seconds) of the task blocks for 0-, 1- and 2-back as separate regressors. The instructions were modeled as a condition of no-interest and the rest periods were modeled as an implicit baseline condition. The model function was convolved with a canonical haemodynamic response function (HRF) with the time derivative. Six motion parameters were included as covariates. A 128-second high-pass filter was also applied to remove low frequencies from the temporal series and a one-lag autoregression model was applied globally. Contrasts of interest were [1-back > 0-back] for 1-back activation, [2-back > 0-back] for 2-back activation, and [2-back > 1-back] for load-induced activation. The resulting set of images was used in a second level of analysis where subjects were treated as a random variable. The resulting images were visualized using either the BSPMVIEW (DOI: 10.5281/zenodo.168074) or the xjView (<http://www.alivelearn.net/xjview>) toolboxes implemented in SPM.

### 2.3.4. Neurofunctional analyses

**2.3.4.1. WM-Related activation.** Whole-brain one sample *t*-tests were used in SPM12 to identify task-related activation. Positive and negative contrasts were computed separately for the 1-back and 2-back conditions, using the 0-back condition as a baseline, and for the load-induced activation [2-back > 1-back]. In addition, a parametric analysis was conducted within a GLM. At the level of each participant, all block conditions (0-back, 1-back, 2back) were modeled together as a single regressor and weighted with individual N-back load demand as regressors of interest (value 0 for the blocks 0-back condition; value 1 for blocks 1-back condition and value 2 for blocks with a 2-back condition). Contrast images for parameters of load were used at the second level for random effects analyses (one-sample *t*-test). The significance threshold for each single contrast was set to  $p < 0.001$  uncorrected, at the voxel level, before a clusterwise or voxel wise FWE correction ( $p < 0.05$ ) was applied.

**2.3.4.2. Education-related activation.** A whole-brain multiple regression analysis was conducted in SPM12 to assess task-related brain activation associated with the number of years of education. Positive and negative regressions between fMRI images and years of education were conducted for the 3 contrasts of interest (1-back, 2-back, load-induced). As education-related activation is relatively unexplored and a weaker signal requiring more statistical power is expected relative to task-related activations, the significance threshold was set to  $p < 0.001$  uncorrected, at the voxel level, before a clusterwise FWE correction ( $p < 0.05$ ) was applied. Given our *a priori* hypotheses, the threshold to examine activation maps was set at  $p < 0.001$  uncorrected, and only clusters where a peak activation threshold of  $p < 0.05$  (FWE) was reached were considered for subsequent analyses. For validation, we also analyzed our data with a parametric procedure: The first level GLM included a regressor for the task block with a parametric modulator for WM load. The brain activation and deactivation, resulting from the voxel-wise multiple regressions between years of education and the parametric WM load regressor, was set to an uncorrected threshold of  $p < 0.005$  to increase power.

### 2.4. Behavioral and moderation analyses

All the statistical analyses were computed with the IBM Statistical Package for Social Science 19 (SPSS) and results were interpreted if they reached a threshold of  $p < 0.05$ . First, we used the hit rate and false alarm rate to calculate a discrimination index or corrected hit rate (*hit rate minus false alarm rate*; H-FA) (Snodgrass and Corwin 1988) for each condition of the n-back task. A repeated-measure ANOVA was computed with load (0-back, 1-back and 2-back) as a repeated factor and the discrimination index as the dependent variable. Pearson's correlations were calculated to assess the relationship between the discrimination index with age and education.

Moderation analyses were then used to assess whether the brain activation differences associated with years of education interacted with the effect of age to predict WM performance on the 1-back and the 2-back conditions (H-FA). Beta values from the clusters activated by education were first extracted with the Mars-Bar region of interest toolbox for SPM (Poline et al., 2002). The interaction terms for the low-load and the high-load conditions were created by multiplying the beta values with age (both centered). Separate hierarchical multiple regressions were then conducted through SPSS 19 using each interaction term to predict the participants' WM performance. When significant, the moderation effects were visualized and probed through the PROCESS macro for SPSS ([www.processmacro.org](http://www.processmacro.org)) following the procedure described in Hayes and Rockwood (2017). In sum, based on the regression equation, the macro automatically estimates several predicted values from different combinations (16th, 50th and 84th percentile) of the predictor and moderator variables, which can be plotted afterwards in a diagram. The macro further generates a simple slope analysis which provides the conditional effects of the predictor on the predicted variable and their significance level for different values of the moderator (16th, 50th and 84th percentile).

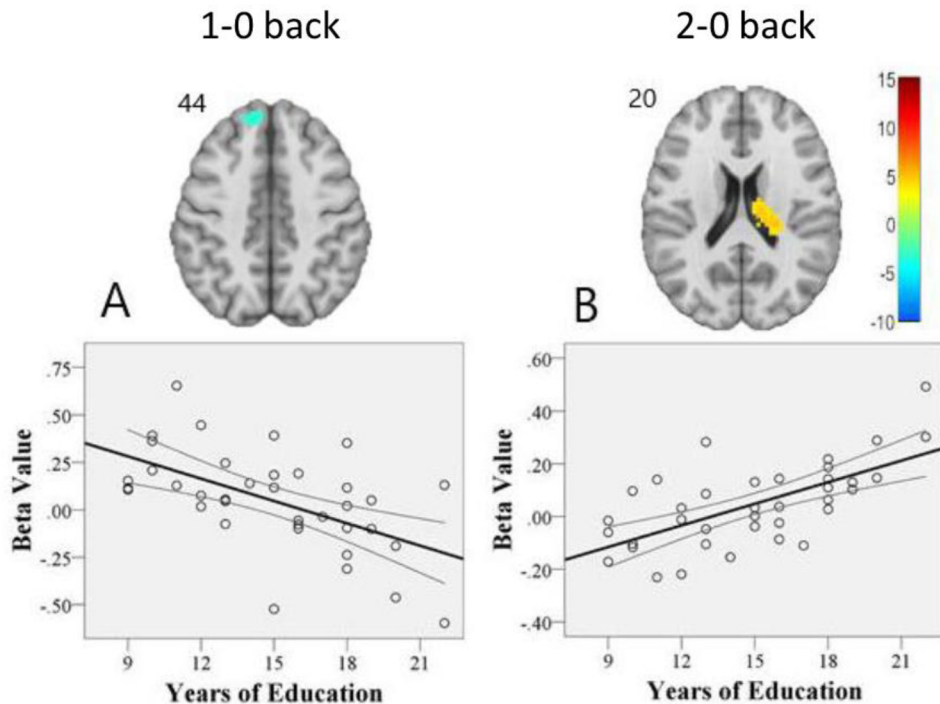
### 2.5. Confounding variables

Pearson's, Spearman's or point biserial correlations were computed between years of formal education and potential confounding demographic and cognitive variables. In order to assess a potential sex-specific influence on results, point biserial correlations were computed between sex and other variables, as well as 2-sample *t*-tests on WM-related activation maps resulting from the 2-back > 1-back, 2-back > 0-back and 1-back > 0-back contrasts with sex as a grouping variable. The significance threshold was set to  $p < 0.001$  uncorrected at the voxel level, before a clusterwise FWE correction ( $p < 0.05$ ) was applied.

## 3. Results

Of the 41 participants initially recruited, two withdrew consent following the clinical evaluation: one withdrew for health reasons and the other refused MRI scanning. Two other participants were excluded from the analyses because one fell asleep during the MRI examination and the other was unable to complete the task. The demographic, cognitive and clinical characteristics of the 37 participants (22 women) used in the analysis are presented in Table 1.

No significant association was found between the number of years of formal education and either age, sex, cognitive scores or GDS (in all cases,  $p > 1$ ). No association was found between sex and any of these variables (in all cases,  $p > 1$ ). Finally, there was no significant WM-related activation difference between men and women for any of the 3 contrasts of interest.



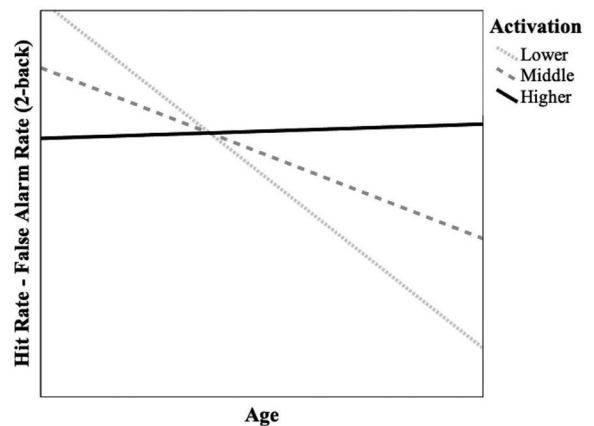
**Fig. 1.** Brain maps and associated scatterplots resulting from the voxel-wise multiple regressions between years of education and task-related activation. These depict (A) the negative relationship between the left medial frontal lobe and education in the 1-back > 0-back contrast ( $p < 0.001$  unc.;  $k > 20$  for visualization purposes); and (B) the positive relationship between the right caudate nucleus and education in the 2-back > 0-back contrast ( $p < 0.05$  clusterwise FWE). Color intensities reflect  $t$ -values.

**Table 1**  
Demographic and clinical characteristics of participants

	<i>M</i> ( <i>SD</i> )	Range
Age	73.11 (5.79)	65.00 – 88.00
Years of formal education	14.92 (3.73)	9.00 – 22.00
MoCA (max: 30)	28.54 (1.46)	24.00 – 30.00
MMSE (max: 30)	28.73 (1.20)	25.00 – 30.00
Stroop (plate 3; time)	26.18 (7.26)	15.30 – 47.81
RL/RI (total delayed recall; max: 16)	15.73 (0.56)	14.00 – 16.00
GDS (max: 15)	1.32 (1.60)	0.00 – 6.00
Accuracy (%)		
0-back	96.89 (3.80)	86.25 – 100.00
1-back	93.21 (8.00)	71.25 – 100.00
2-back	85.88 (6.57)	61.25 – 95.00
H-FA		
0-back	0.95 (0.07)	0.73 – 1.00
1-back	0.86 (0.16)	0.40 – 1.00
2-back	0.70 (0.13)	0.30 – 0.92

### 3.1. Education-related activation

In the 1-back condition, the regression analysis revealed no education-related suprathreshold activation after the clusterwise FWE correction for multiple comparisons ( $p < 0.05$ ). However, use of a more liberal threshold ( $p < 0.001$  uncorrected) indicated that more education was associated with lower activation in a cluster located in the left medial superior frontal gyrus (BA8;  $k = 37$  voxels; see Fig. 1A), where activation at peak coordinates [ $x: -9, y: 44, z: 50$ ] reached significance at the voxel level ( $t: 5.87, p < 0.05$  FWE). In the 2-back condition, the regression analysis indicated that more education was associated with a higher activation of the right caudate nucleus [ $x: 15, y: -13, z: 23$ ];  $t: 5.32, p < 0.05$  clusterwise FWE,  $k = 126$  voxels; see Fig. 1B). A parametric analysis



**Fig. 2.** Scatterplot displaying equation-based regressions between age and WM performance (Hit-FA for the 2-back condition) separately for higher, middle and lower ranges of activation in the right caudate nucleus. The conditional effect of age on WM performance is significant for older adults with lower and middle range of activation, but not for those with the higher range of activation.

with an uncorrected threshold led to the same activated and deactivated regions (see Figure S2).

### 3.2. Moderation analyses

Separate moderation analyses were computed to assess whether activation values in the two regions associated with years of education (left medial superior frontal gyrus and right caudate nucleus) moderated the detrimental effect of age on WM performance (H-FA).

A first moderation model included age and activation of the left medial superior frontal gyrus to predict WM performance

**Table 2**

Statistical model of moderation analysis predicting 1-back performance (*hit rate minus false alarm rate*; H-FA)

Full model		Predictors	Beta	p value
F value	p value			
6.70	0.001**	Age	-0.54	0.001**
		Left Superior Frontal Gyrus Activation ( $\beta$ -value)	-0.24	0.103
		Age* $\beta$ -value	-0.28	0.059

Note: \* significant at  $p < 0.05$ ; \*\* significant at  $p < 0.01$

**Table 3**

Statistical model of moderation analysis predicting 2-back performance (*hit rate minus false alarm rate*; H-FA)

Full model		Predictors	Beta	p value
F value	p value			
6.32	0.002**	Age	-0.33	0.024*
		Right Caudate nucleus Activation ( $\beta$ -value)	0.20	0.197
		Age* $\beta$ -value	0.37	0.019*

Note: \* significant at  $p < 0.05$ ; \*\* significant at  $p < 0.01$

(Table 2). The model was significant ( $F(3, 33) = 6.70, p = 0.001$ ) and indicated a meaningful contribution of age to WM performance ( $\beta = -0.54, p = 0.001; sr^2 = 0.27$ ). However, the “age by activation” interaction did not reach significance ( $\beta = -0.28, p = 0.059; sr^2 = 0.07$ ).

A second moderation model included age and activation of the right caudate nucleus to predict WM performance (Table 3). The model was significant ( $F(3, 33) = 6.32, p = 0.002$ ) and showed that the “age by activation” interaction ( $\beta = 0.37, p = 0.019; sr^2 = 0.12$ ) contributed the most to the prediction of performance, and that age was also significant ( $\beta = -0.33, p = 0.024; sr^2 = 0.11$ ) Fig. 2. shows that the negative relationship between age and WM performance is weaker for individuals demonstrating higher activation of the right caudate nucleus. The conditional effect of age on WM performance is significant for the lower ( $T = 3.32, p = 0.002$ ) and middle ( $T = 2.56, p = 0.015$ ) range of activation, but not for the higher range ( $T = 0.16, p = 0.878$ ).

### 3.3. Task-related activations/deactivations and performance

To determine whether education-related activation occurs in specialized alternative regions, task-related activation and deactivation were examined irrespective of education (see Supplemental Figure S2 for activation maps in low and high-education groups). The 1-0 back and 2-0 back contrasts both revealed a large and bilateral parieto-occipital cluster of activation consistent with literature (Fig. 3A and B, Supplemental Table S1). The cluster included the precuneus, the inferior and superior parietal lobules, the angular and supramarginal gyri, and the middle and superior occipital gyri. There was also a bilateral frontal cluster, which included the middle, inferior, superior, and medial frontal gyri, the insula, and the right middle cingulum. Other smaller clusters included a bilateral temporal cluster comprising the inferior and middle temporal gyri and a posterior cerebellum cluster. Overall, activations for the 1- and 2-back conditions took place in the same clusters. The load-induced contrast revealed higher activation in the left middle occipital and superior parietal gyri as load increased (Fig. 3C; see Supplemental Table S1). Deactivation occurred in bilateral middle orbital gyrus and right superior temporal gyrus for 1-back condition and in bilateral prefrontal cortex, bilateral superior temporal gyrus and right middle temporal for 2-back condition (see coordinates of clusters in Table S1). No significant deactivation was observed in load-induced contrast.

Table 1 shows hit rate and discrimination indexes (H-FA) for the 3 conditions of the n-back task. As expected, the ANOVA indicated a significant load effect ( $F(2, 72) = 59.09, p < 0.001$ ). Contrast analyses indicated that performance decreased from 0-back through 2-back. Significant negative correlations were found between age and the discrimination index for the 0-back ( $r(35) = -0.39, p = 0.019$ ), 1-back ( $r(35) = -0.53, p = 0.001$ ) and 2-back ( $r(35) = -0.36, p = 0.029$ ) conditions. Performance did not correlate with years of formal education (0-back: ( $r(35) = 0.17, p = 0.308$ ); 1-back: ( $r(35) = 0.31, p = 0.056$ ); 2-back: ( $r(35) = 0.09, p = 0.599$ )).

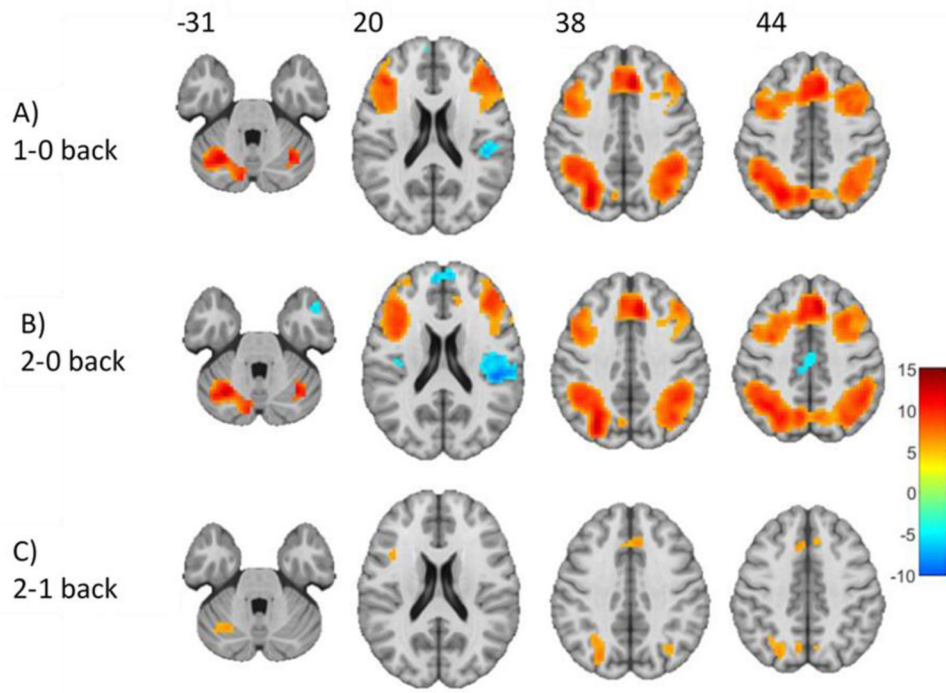
### 3.4. Impact of white matter changes

We completed two secondary analyses to assess the relationship between WML and activation. These analyses are reported in supplementary Tables S2 and S3. First, we determined that there was no correlation between the volume of white matter changes and the level of activation found in the two reported clusters. Second, we found that for both clusters, activation did not moderate the relationship between white matter volume and WM performance.

## 4. Discussion

The goal of this study was to identify the functional mechanisms underlying cognitive reserve in older adults. The first step was to identify brain activation regions associated with more years of formal education and determine if these activation differences vary as a function of the task load. Manipulating the load was used to examine whether the mechanisms proposed to be involved in cognitive reserve occur at different levels of task demand. A second step was to examine whether the activations associated with education buffer the detrimental effect of age on WM performance. This is a critical aspect of the study assessing whether the functional correlates of education are protective. In this case, it can be argued that these correlates may qualify as “true” reserve substrates.

As expected, differences in education were associated with differences in brain activation, and the pattern of education-related activations varied as a function of the task load. In the high WM load, more education was associated with higher activation in the right caudate nucleus, an effect that was resistant to the cluster-wise correction for multiple comparisons. In the low WM load



**Fig. 3.** Brain map of the task-related activation (warm colors) and deactivation (cool colors) resulting from the one sample *t*-test. (A) 1-back > 0-back contrast; (B) 2-back > 0-back contrast; and (C) 2-back > 1-back contrast.  $P < 0.05$  voxel-wise FWE for visualization purposes. Color intensities reflect *t*-value.

condition, more education was associated with *lower* activation in the left superior medial frontal gyrus (BA8). This effect was significant when using a more liberal threshold ( $p < 0.001$ ) but was no longer present when a clusterwise correction for multiple comparisons was applied. In addition, the activation in the left superior medial frontal gyrus did not significantly moderate the relation between age and WM. In contrast, the education-related activation found in the right caudate nucleus mitigated the age-related differences in WM performance. Overall, older age was associated with reduced WM performance. However, when examining how education relates to age for the prediction of WM performance, there was an age effect on the 2-back performance in the group of older adults showing *lower* activation of the right caudate nucleus but no age effect in participants with *higher* activation. The mechanisms reflected by this activation effect are discussed below.

More education was associated with a higher activation of the right caudate nucleus, but only in the high-load condition. This result is reliable as activation resisted correction and moderation was supported by a significant interaction. This activation is interpreted as reflecting neural flexibility, which refers to the capacity to engage greater activation of the task-related network (i.e. primary network) or an increased ability to recruit new regions, when the task demand exceeds the capacity of the specialized regions. One interpretation is that participants with more education activate a new brain region when the task demand exceeds the capacity of the system. There are arguments to support this interpretation: First, this region was not activated in individuals with lower education nor for the whole sample, at low or high load on the *n*-back task. Second, this is consistent with Owen *et al.*'s meta-analysis of the *n*-back-related activations, which did not report activation of the caudate nucleus (Owen *et al.*, 2005). Thus, as task demand increases, older adults with more education recruited the caudate nucleus, a region that is not typically activated by the task, while participants with lower education did not recruit

this brain region. Importantly, participants with higher activation in this region showed no age effect for memory performance. Thus, higher recruitment of this region by highly educated individuals is beneficial to their performance, buffering the effect of age on performance. The flexible recruitment of a “new” compensatory region in our sample is partly in line with the compensation-related utilization of neural circuits hypothesis (CRUNCH; Reuter & Cappell, 2008), which proposes that additional resources are needed to compensate for the reduced processing efficiency of the aging brain. The model hypothesizes that as the primary network reaches its capacity, the brain of an individual with higher education would recruit compensatory regions in an alternative network, which would maintain performance. Our results extend on this model by showing that intensive cognitively stimulating activities throughout one's life (i.e. through education) may increase this compensatory potential in older adults. The finding that this activation moderates the relationship between age and WM performance suggests that compensatory activation in alternative regions may attenuate the impact of age on WM performance when cognitive demand is high. This is congruent with a “true reserve effect” because the activation reduces the detrimental effect of age on cognition.

An alternative interpretation is that older adults with high education have more capacity to activate this area at a high cognitive load than those with lower education. Indeed, the interpretation that older adults with more education recruit a new region to buffer the effect of age on performance rests mostly on the observation that this area is not typically recruited as seen in Owen *et al.*'s meta-analysis. This may reflect the fact that the meta-analysis included a wide range of education and age levels as these are characteristics that will influence the level of activation in the caudate nucleus. Studies of task-activation maps probably combine different proportions of individuals with high and low education. This stresses the importance that future meta-analyses consider education, age, as well as other relevant socio-behavioral or de-

mographic variables in their analyses as these may be strong modifiers of activation effects. An implication is that caution should be exercised when interpreting whether an activation is inside or outside a typical positive or negative network, as we have observed that education modifies the pattern of activation. As more and more evidence indicate that activation varies with individual characteristics, the inclusion of these factors in meta-analyses will provide a more realistic and perhaps more complex picture of what is “typical” recruitment.

Lower activation of the left superior medial frontal gyrus (BA8) in individuals with more education could be interpreted as an increased efficiency in individuals with less education. The interpretation that lower activation of the left superior medial frontal gyrus (BA8) reflects greater neural efficiency may be supported by the fact that it took place during the low-demand condition, where performance is high in both groups. Note that prior results have also reported that higher scores on a composite reserve factor are associated with lower activation in the left prefrontal region during an n-back task (Bartres-Faz et al., 2009). However, BA8 was not found to moderate the relationship between age and performance.

There have been some propositions regarding the location of the cognitive reserve mechanisms in the brain. The implication of the caudate nucleus is interesting as it is part of the fronto-striatal network, which is believed to mediate load-dependent prefrontal cortex activation and is associated with higher WM capacity and maintenance (Jagust et al., 2009). Moreover, this region has been shown to contribute to higher-order executive functions, particularly when there is a high degree of uncertainty and/or when complex information is manipulated (see Monchi et al., 2015 for a review). In turn, some studies have proposed that reserve may be subserved by a generic or task-invariant network (Stern, 2009, 2017). For instance, a vast network of activations comprising frontal, parietal, temporal and cerebellar regions (Stern et al., 2018), and global functional connectivity of the left frontal cortex (Franzmeier et al., 2017), are potential candidates for such a generic substrate of cognitive reserve. In the present study, it was hypothesized that the regions where these mechanisms occur depend on the nature of the task. Here, the caudate is a region that is part of the fronto-striatal network and involved in WM. We propose that the regions found to underlie reserve are involved or highly connected with the task for which compensation is required. Interestingly however, there is an extensive overlap between the WM network and those indicated by Benson et al. (2018), Franzmeier et al. (2017) and Stern et al. (2018), suggesting that these may correspond. It remains to be determined whether this is because we have used a task that elicits a putative “generic” network.

Our goal was to assess whether activation moderates the relationship between age and WM performance. The use of age as an indicator of the neurobiological changes accompanying WM decline is pragmatic in that identification of the unique neuropathological features associated with WM decline requires a robust and accurate model of what underlies this change. However, this choice has limitations: One limitation is that it is not possible to identify the exact brain change or pathology that is protected by caudate activation. One candidate we have considered is white matter changes, which has been associated with WM decline in older adults. However, we did not find that caudate nucleus activation moderated the association between white matter changes and WM. Another limitation with our design is that individuals with high education might have better brain maintenance, that is a more preserved brain, which would explain the differential task-related activation patterns. For example, we recently reported that individuals with higher levels of education had a lower volume of white matter lesions than individuals with lower levels of educa-

tion (Ducharme-Laliberté et al., 2022). Again, and consistent with the lack of moderation, we did not observe a correlation between white matter change and activation. In any case, the presence and nature of the links between activation and maintenance should be explored in future studies.

This study has many important and novel components. A critical strength was the use of moderation models to test whether activation differences associated with years of education buffer the impact of age on performance. This test has rarely been performed in prior studies. We argue that only the finding that these activations are protective would confirm their interpretation as plausible cognitive reserve mechanisms. Another strength of this study was the manipulation of task load to elicit different processes. Further studies should include a gradient of task demand to capture the full extent of reserve processes across the task load. Another key element is that we reported both task-negative and task-positive activation maps, which also allows to assess the role of deactivation.

In addition to what was described above, the study also has the following limitations: First, even though task load was manipulated, the inclusion of only 2 levels of task demand limited our ability to determine the full range of effects that increasing demand may have on brain activation, and assess the possibility of non-linear or inverse u-shape functions (Reuter & Cappell, 2008). Sample size was relatively small and insufficient power may explain that the superior medial frontal gyrus activation did not resist the correction for multiple comparison. Notably also, the age effect on WM performance in participants with high activation of the frontal lobe was marginally significant, which could be explained by our small sample size. This suggests that caution should be exercised when interpreting the null results for the low load condition. Furthermore, the relationship between education and differences in activation must also be interpreted with caution given that it relies on a cross-sectional design, thus limiting inference on causality. Additionally, we cannot rule out the contribution of other factors associated with education including genotype, socioeconomic status or lifestyle (e.g. nutrition, physical activity). Finally, we must acknowledge that there is inconsistency in the field regarding the terminology associated with age-related interindividual differences, although recent attempts have been made to propose a consensus definition (Cabeza et al., 2018; Stern et al., 2020). For example, neural flexibility as defined here is sometimes considered neural compensation or neural dedifferentiation by others (Cabeza et al., 2018; Li & Lindenberger, 1999; Sikström et al., 2001; Park et al., 2004). When attempting to differentiate these different concepts, it may be useful to consider them in relation to performance. For example, although both dedifferentiation and flexibility lead to greater activation, greater dedifferentiation should be associated with poorer performance, whereas greater flexibility should be associated with better performance. The difference between neural flexibility and neural compensation is probably more subtle, as both are associated with better performance. One difference might be that in the case of compensation, the difference occurs within a group, whereas flexibility most often reflects differences between two groups of individuals with varying reserve proxies. Compensation may also depend on reserve to the extent that individuals with more reserve may be better able to engage compensation. Thus, the effect found here with a larger cognitive load could reflect greater compensation in individuals with more reserve.

In conclusion, this study indicates that cognitive reserve is sub-tended by a greater ability to flexibly engage brain regions as task demand exceeds capacity. This process is protective and allows individuals to maintain cognitive performance against the effects of age. However, future studies are needed to replicate these results



with a broader task demand range and larger sample sizes. Also, the present results suggest that imaging studies investigating functional recruitment associated with cognitive processes or future meta-analyses should take into account the potential effects of factors, such as education or other reserve proxies on activation differences, since these appear to moderate the effect of activation. Finally, our results may be relevant to developing interventions to increase cognitive reserve in older adults (Belleville et al., 2011; Bier et al., 2014; Willis & Belleville, 2016), particularly as some intervention studies were found to induce either improved efficiency or greater flexibility depending on their content (Belleville et al., 2014). Thus, another avenue for future research, which we are currently undertaking, is to examine if engagement in cognitively stimulating activities later in life fosters similar functional brain processes and promotes reserve against the effects of age in individuals with lower levels of education or less cognitively stimulating engagement early in life.

### Credit author statement

*Gabriel Ducharme-Laliberté*: Conceptualization; Methodology; Data collection; Formal analysis; Writing of original draft. *Samira Mellah*: Methodology; Software; Data collection; Data curation; Formal analysis; Revision of draft and final version; Project administration; Supervision. *Benjamin Boller*: Revision of draft and final version. *Sylvie Belleville*: Conceptualization; Methodology; Data curation; Writing of original draft and final version; Supervision; Funding acquisition.

### Disclosure statement

The authors have no conflicts of interest to disclose.

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### Supplementary materials

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### References

- Anthony, M., Lin, F., 2017. A systematic review for functional neuroimaging studies of cognitive reserve across the cognitive aging spectrum. *Arch Clin Neuropsychol* 33 (8), 937–948.
- Anticevic, A., Cole, M.W., Murray, J.D., Corlett, P.R., Wang, X.J., Krystal, J.H., 2012. The role of default network deactivation in cognition and disease. *Trends Cognit Sci* 16 (12), 584–592.
- Arenaza-Urquijo, E.M., Vemuri, P., 2018. Resistance vs. resilience to Alzheimer disease: clarifying terminology for preclinical studies. *Neurology* 90 (15), 695–703.
- Bartres-Faz, D., Sole-Padullés, C., Junque, C., Rami, L., Bosch, B., Bargallo, N., Falcon, C., Sanchez-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 (2), 256–259.
- Belleville, S., Clement, 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 (Pt 6), 1623–1634.
- Belleville, S., Mellah, S., de Boisson, 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 (8), e102710.
- Benson, G., Hildebrandt, A., Lange, C., Schwarz, C., Kobe, T., Sommer, W., Floel, A., Wirth, M., 2018. Functional connectivity in cognitive control networks mitigates the impact of white matter lesions in the elderly. *Alzheimers Res Ther* 10 (1), 109.
- Binder, J.R., 2012. Task-induced deactivation and the "resting" state. *Neuroimage* 62 (2), 1086–1091.
- Boller, B., Mellah, S., Ducharme-Laliberte, 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 (2), 304–317.
- Bosch, B., Bartres-Faz, D., Rami, L., Arenaza-Urquijo, E.M., Fernández-Espejo, D., Junqué, C., Solé-Padullés, C., Sánchez-Valle, R., Bargallo, N., Falcón, C., Molinuevo, J.L., 2010. Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnesic mild cognitive impairment and mild Alzheimer's disease. *Cortex* 46 (4), 451–461.
- Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., Noll, D.C., 1997. A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage* 5 (1), 49–62.
- Brett, M., Anton, J.L., Valabregue, R., Poline, J.B., 2002. Region of interest analysis using the MarsBar toolbox for SPM 99. *NeuroImage* 16 (2), S497.
- Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: Anatomy, function, and relevance to disease. *Ann New York Acad Sci* 1124, 1–38.
- 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 (11), 701–710.
- DeCarli, C., Fletcher, E., Ramey, V., Harvey, D., Jagust, W.J., 2005. Anatomical mapping of white matter hyperintensities (WMH): Exploring the relationships between periventricular WMH, deep WMH, and total WMH burden. *Stroke* 36 (1), 50–55.
- Ducharme-Laliberté, G., Mellah, S., Belleville, S., 2022. Having a stimulating lifestyle is associated with maintenance of white matter integrity with age. *J Brain Imaging Behavior* 1–8 Epub Ahead of Print.
- Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12 (3), 189–198.
- Franzmeier, N., Duering, M., Weiner, M., Dichgans, M., Ewers, M., Alzheimer's Disease Neuroimaging, I., 2017. Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease. *Neurology* 88 (11), 1054–1061.
- Grady, C.L., Springer, M.V., Hongwanishkul, D., McIntosh, A.R., Winocur, G., 2006. Age-related changes in brain activity across the adult lifespan. *J Cognit Neurosci* 18 (2), 227–241.
- Haut, M.W., Kuwabara, H., Moran, M.T., Leach, S., Arias, R., Knight, D., 2005. The effect of education on age-related functional activation during working memory. *Aging, Neuropsychol, Cognit* 12 (2), 216–229.
- Hayes, A.F., Rockwood, N.J., 2017. Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation. *Behav Res Ther* 98, 39–57.
- Jonides, J., Schumacher, E.H., Smith, E.E., Lauber, E.J., Awh, E., Minoshima, S., Koeppel, R.A., 1997. Verbal working memory load affects regional brain activation as measured by PET. *J Cogn Neurosci* 9 (4), 462–475.
- Katzman, R., 1993. Education and the prevalence of dementia and Alzheimer's disease. *Neurology* 43 (1), 13–20.
- Kaup, A.R., Drummond, S.P., Eyler, L.T., 2014. Brain functional correlates of working memory: Reduced load-modulated activation and deactivation in aging without hyperactivation or functional reorganization. *J Int Neuropsychol Soc* 20 (9), 945–950.
- Laird, A.R., Eickhoff, S.B., Li, K., Robin, D.A., Glahn, D.C., Fox, P.T., 2009. Investigating the functional heterogeneity of the default mode network using coordinate-based meta-analytic modeling. *J Neurosci* 29 (46), 14496–14505.
- Landau, S.M., Lal, R., O'Neil, J.P., Baker, S., Jagust, W.J., 2009. Striatal dopamine and working memory. *Cereb Cortex* 19 (2), 445–454.
- Li, C.S., Yan, P., Bergquist, K.L., Sinha, R., 2007. Greater activation of the "default" brain regions predicts stop signal errors. *Neuroimage* 38 (3), 640–648.
- Li, S.-C., Lindenberger, U., 1999. Cross-level unification: A computational exploration of the link between deterioration of neurotransmitter systems and dedifferentiation of cognitive abilities in old age. In: Nilsson, L.-G., Markowitsch, H.J. (Eds.), *Cognitive neuroscience of memory*. Hogrefe & Huber Publishers, pp. 103–146.
- Li, S.C., Lindenberger, U., Sikström, S., 2001. Aging cognition: From neuromodulation to representation. *Trends Cogn Sci* 5 (11), 479–486.
- Lustig, C., Snyder, A.Z., Bhakta, M., O'Brien, K.C., McAvoy, M., Raichle, M.E., Morris, J.C., Buckner, R.L., 2003. Functional deactivations: change with age and dementia of the Alzheimer type. *Proceed Nat Acad Sci* 100 (24), 14504–14509.
- Mak, L.E., Minuzzi, L., MacQueen, G., Hall, G., Kennedy, S.H., Milev, R., 2017. The default mode network in healthy individuals: a systematic review and meta-analysis. *Brain Connect* 7 (1), 25–33.
- McKiernan, K.A., Kaufman, J.N., Kucera-Thompson, J., Binder, J.R., 2003. A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J Cognit Neurosci* 15 (3), 394–408.

- Mencarelli, L., Neri, F., Momi, D., Menardi, A., Rossi, S., Rossi, A., Santarnecchi, E., 2019. Stimuli, presentation modality, and load-specific brain activity patterns during n-back task. *Human Brain Mapping* 40 (13), 3810–3831.
- Nasreddine, Z.S., Phillips, N.A., Bedirian, 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* 53 (4), 695–699.
- Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp* 25 (1), 46–59.
- Park, D.C., Polk, T.A., Park, R., Minear, M., Savage, A., Smith, M.R., 2004. Aging reduces neural specialization in ventral visual cortex. *Proc Natl Acad Sci U S A* 101 (35), 13091–13095.
- Persson, J., Lustig, C., Nelson, J.K., Reuter-Lorenz, P.A., 2007. Age differences in deactivation: a link to cognitive control? *J Cognit Neurosci* 19 (6), 1021–1032.
- Persson, J., Pudas, S., Nilsson, L.G., Nyberg, L., 2014. Longitudinal assessment of default-mode brain function in aging. *Neurobiol Aging* 35 (9), 2107–2117.
- Prakash, R.S., Heo, S., Voss, M.W., Patterson, B., Kramer, A.F., 2012. Age-related differences in cortical recruitment and suppression: Implications for cognitive performance. *Behav Brain Res* 230 (1), 192–200.
- Provost, J.S., Hanganu, A., Monchi, O., 2015. Neuroimaging studies of the striatum in cognition Part I: Healthy individuals. *Front Syst Neurosci* 9, 140.
- Ragland, J.D., Turetsky, B.I., Gur, R.C., Gunning-Dixon, F., Turner, T., Schroeder, L., Chan, R., Gur, R.E., 2002. Working memory for complex figures: An fMRI comparison of letter and fractal n-back tasks. *Neuropsychology* 16 (3), 370–379.
- Regard, M., 1981. Cognitive rigidity and flexibility: A neuropsychological study. University of Victoria, Canada.
- Reuter-Lorenz, P.A., Park, D.C., 2010. Human neuroscience and the aging mind: A new look at old problems. *The journals of gerontology. Series B, Psychol sci social sci* 65 (4), 405–415.
- Reuter, P.A., Cappell, K.A., 2008. Neurocognitive Aging and the Compensation Hypothesis. *Current Directions Psychol Sci* 17 (3), 177–182.
- Sambataro, F., Murty, V.P., Callicott, J.H., Tan, H.Y., Das, S., Weinberger, D.R., Mattay, V.S., 2010. Age-related alterations in default mode network: Impact on working memory performance. *Neurobiol Aging* 31 (5), 839–852.
- Scarmeas, N., Zarahn, E., Anderson, K.E., Hilton, J., Flynn, J., Van Heertum, R.L., Sackeim, H.A., Stern, Y., 2003. Cognitive reserve modulates functional brain responses during memory tasks: A PET study in healthy young and elderly subjects. *Neuroimage* 19 (3), 1215–1227.
- Sole-Padullés, C., Bartres-Faz, D., Junque, C., Vendrell, P., Rami, L., Clemente, I.C., Bosch, B., Villar, A., Bargallo, N., Jurado, M.A., Barrios, M., Molinuevo, J.L., 2009. Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 30 (7), 1114–1124.
- Springer, M.V., McIntosh, A.R., Winocur, G., Grady, C.L., 2005. The relation between brain activity during memory tasks and years of education in young and older adults. *Neuropsychology* 19 (2), 181–192.
- Steffener, J., Stern, Y., 2012. Exploring the neural basis of cognitive reserve in aging. *Biochim Biophys Acta* 1822 (3), 467–473.
- Stern, Y., 2009. Cognitive reserve. *Neuropsychologia* 47 (10), 2015–2028.
- Stern, Y., 2017. An approach to studying the neural correlates of reserve. *Brain Imaging Behav* 11 (2), 410–416.
- 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. *Alzheimers Dement* 16 (9), 1305–1311.
- Stern, Y., Gazes, Y., Razlighi, Q., Steffener, J., Habeck, C., 2018. A task-invariant cognitive reserve network. *Neuroimage* 178, 36–45.
- Sylvain-Roy, S., Belleville, S., 2015. Interindividual differences in attentional control profiles among younger and older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 22 (3), 259–279.
- Sylvain-Roy, S., Lungu, O., Belleville, S., 2015. Normal aging of the attentional control functions that underlie working memory. *J Gerontol B Psychol Sci Soc Sci* 70 (5), 698–708.
- Tierney, T.M., Weiss-Croft, L.J., Centeno, M., Shamshiri, E.A., Perani, S., Baldeweg, T., Clark, C.A., Carmichael, D.W., 2016. FIACH: A biophysical model for automatic retrospective noise control in fMRI. *Neuroimage* 124 (Pt A), 1009–1020.
- Van der Linden, M., Adam, S., Agniel, A., Baisset-Mouly, C., Bardet, F., Coyette, F., Desgranges, B., Deweer, B., Ergis, A.M., Gély-Nargeot, M.C., Grimompres, L., Juillerat, A.C., Kalafat, M., Poitrenaud, J., Sellal, F., Thomas-Antérion, C., 2004. L'évaluation de troubles de la mémoire: Présentation de quatre tests de mémoire épisodique (avec étalonnage). Solal, Marseille.
- Willis, S.L., Belleville, S., 2016. Cognitive Training in Later Adulthood. In: Schaie, K.W., Willis, S.L. (Eds.), *Handbook of the Psychology of Aging*. Academic Press, pp. 219–243.
- 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* 17 (1), 37–49.