



## Age-related differences in the structural and effective connectivity of cognitive control: a combined fMRI and DTI study of mental arithmetic



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### ABSTRACT

Cognitive changes with aging are highly variable across individuals. This study investigated whether cognitive control performance might depend on preservation of structural and effective connectivity in older individuals. Specifically, we tested inhibition following working memory (WM) updating and maintenance. We analyzed diffusion tensor imaging and functional magnetic resonance imaging data in thirty-four young adults and thirty-four older adults, who performed an arithmetic verification task during functional magnetic resonance imaging. Results revealed larger arithmetic interference in older adults relative to young adults after WM updating, whereas both groups showed similar interference after WM maintenance. In both groups, arithmetic interference was associated with larger activations and stronger effective connectivity among bilateral anterior cingulate, bilateral inferior frontal gyrus, and left angular gyrus, with larger activations of frontal regions in older adults than in younger adults. In older adults, preservation of frontoparietal structural microstructure, especially involving the inferior frontooccipital fasciculus, was associated with reduced interference, and stronger task-related effective connectivity. These results highlight how both structural and functional changes in the cognitive control network contribute to individual variability in performance during aging.

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### 1. Introduction

Some older individuals exhibit similar cognitive performance to young adults while others are significantly impaired (e.g., Hinault et al., 2016; Lemaire and Hinault, 2014). The alteration or preservation of cognitive control processes is a crucial factor in understanding general age-related cognitive changes (e.g., Reuter-Lorenz and Park, 2014). Cognitive control refers to a set of processes needed to adjust behavior to internal goals in changing environments (Luna et al., 2015) and includes the active maintenance or updating of goal-relevant information (working memory [WM]),

and the suppression of competing goal-irrelevant information (inhibition). Neuroimaging studies have shed light on the neural correlates of these processes and age-related differences (e.g., Cabeza and Dennis, 2013; Zanto and Gazzaley, 2016), and have shown preservation of performance to be associated with either activations similar to those of younger participants or with additional frontal and bilateral recruitments (e.g., Reuter-Lorenz and Park, 2014). Age-related changes in WM ability appear to depend most strongly on the executive processes of updating and inhibition (Zuber et al., 2018). These two processes appear to interact, with increased efficiency of inhibition following WM updating (Scharinger et al., 2015). We hypothesized that this facilitated inhibition might crucially depend on frequent, precise communication among distant brain regions, as observed for other high-order cognitive activities (e.g., Bettcher et al., 2016). We further hypothesized that impairment in these communications might underlie

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age-related changes in WM. Specifically, our goal was to determine whether individual differences in structural connectivity in older individuals could account for preserved cognitive function and differences in the engagement of cognitive control networks on a task involving both updating and inhibition.

Structural and functional/effective connectivity analyses of neuroimaging data allow us to evaluate how neural networks interact during cognitive tasks. A study in older adults revealed an association between frontoparietal white matter microstructure and cognitive control abilities (Bettcher et al., 2016). Previous work using functional MRI revealed that WM updating is associated with connectivity between dorsolateral prefrontal cortex (DLPFC) and parietal regions, depending on the source of the newly relevant information (e.g., Roth and Courtney, 2007), whereas interference detection and resolution for nonsensory information has been related to a more intrafrontal network, including insula, anterior cingulate cortex (ACC), inferior frontal gyrus (IFG), and DLPFC (e.g., Sheu and Courtney, 2016). With aging, the altered microstructure of frontoposterior tracts has been associated with lower sensorimotor inhibitory performance (e.g., Li et al., 2018). Age-related reductions in frontoparietal functional connectivity have also been observed (e.g., Fjell et al., 2017; see Sala-Llanch et al., 2015, for a review). Recent work revealed that resting-state functional networks were modulated by white matter microstructural measures (e.g., Madden et al., 2017). Understanding how individual variability of white matter microstructure influences the implementation of the functional network associated with facilitated inhibition may improve our understanding of the mechanisms and cognitive processes underlying individual differences with aging.

Cognitive control processes are involved during numerical and arithmetic processing (see Hinault and Lemaire, 2016a, b, for reviews). Arithmetic tasks offer situations close to daily life, with relatively preserved performance (e.g., Allen et al., 1997), while inducing little stereotype threat in older participants (e.g., Abrams et al., 2008). Arithmetic verification tasks can be designed to bring out interference effects (De Visscher et al., 2018, 2015; Grabner et al., 2013; Lemaire et al., 1996, 1994; Megias et al., 2014; Megias and Macizo, 2015). For example, participants demonstrate lower accuracy and longer response times to correctly reject a false equation when the proposed product is the correct product of another operation type (e.g.,  $8 \times 4 = 12$ ), compared with when the proposed product is incorrect in any operation (e.g.,  $8 \times 4 = 16$ ). The higher difficulty of these false-related problems has been attributed to the coactivation of arithmetic representations for multiple operation types and the need to inhibit the irrelevant operation (e.g., Megias et al., 2014; Megias and Mecizo, 2015). Previous neuroimaging work revealed that false-related arithmetic problems elicit increased activation of the angular gyrus (AG), ACC, and DLPFC (e.g., De Visscher et al., 2015, 2018; Grabner et al., 2013), the activation of AG being interpreted as reflecting the activation of arithmetic representations. Moreover, cueing participants to update arithmetic representations immediately before problem verification might be associated with reduced arithmetic interference, as it could improve the suppression of the related arithmetic representations. However, age-related differences in arithmetic interference and the modulation of its efficiency after WM updating have not been investigated (but see Archambeau et al., 2018).

So far, no studies have been conducted to investigate the specific contribution of individual changes in white matter structure to functional networks associated with WM and inhibitory processes. Here, we combined functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) to investigate (1) the structural and effective connectivity associated with arithmetic interference and its reduction after WM updating, (2) age-related differences in this effect and the associated brain connectivity, and (3) how

individual differences in structural connectivity are associated with age-related differences in the functional implementation of the network and behavioral performance. We hypothesized a larger arithmetic interference effect in older adults, and a reduction of facilitated inhibition. We also predicted that individual differences in microstructural properties of frontoposterior tracts would be associated with reduced effective connectivity between relevant frontal and parietal regions and greater behavioral interference. The results demonstrated an age-related decline of facilitated inhibition that was partially related to the structural and effective connectivity in specific frontal tracts. The results illustrate how the multimodal investigation of structural and effective connectivity contributes to our understanding of cognitive variability during healthy aging.

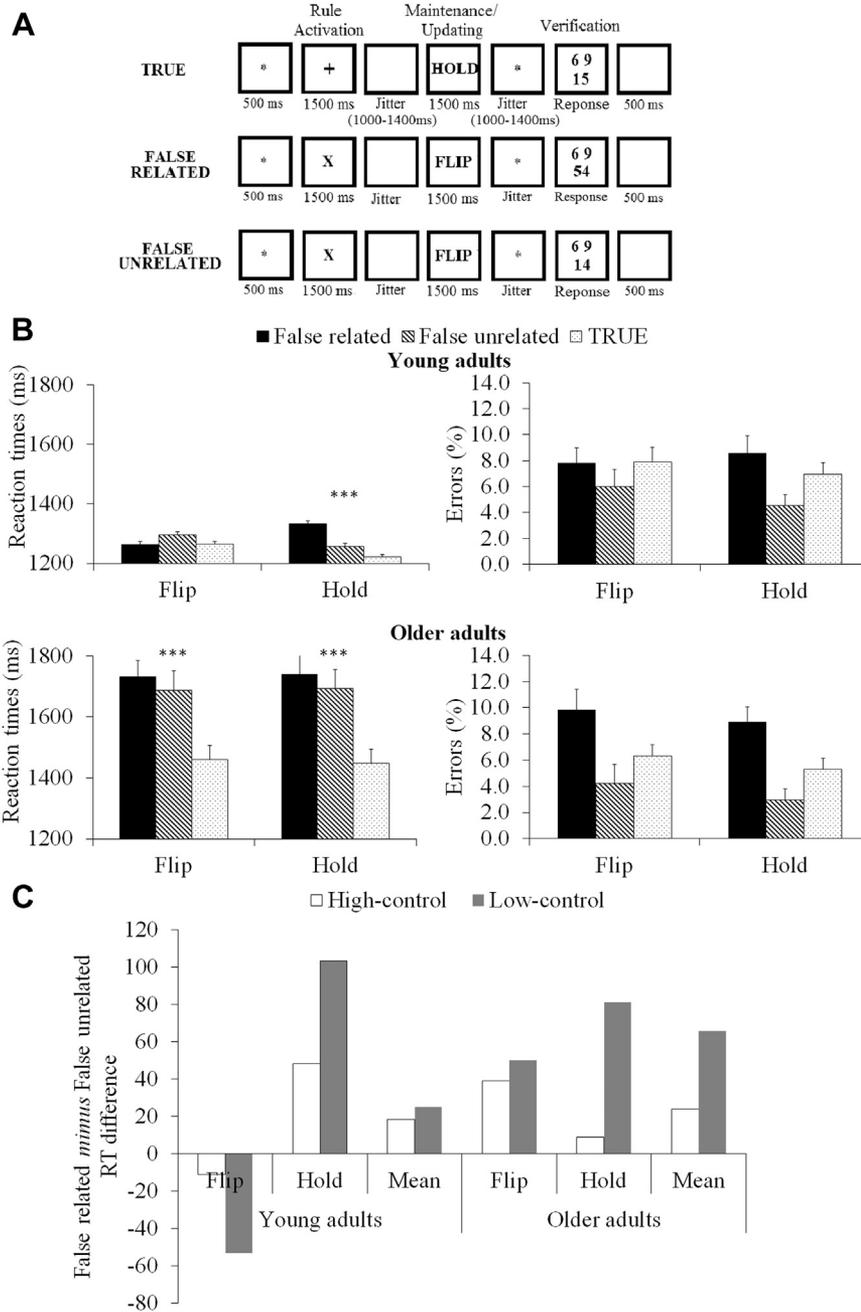
## 2. Materials and methods

### 2.1. Participants

Data were analyzed from 34 young adults (18–34, mean age 23) and 34 older adults (65–85, mean age 71; see participants' characteristics in supplementary material, Table 1). All participants were right-handed and reported normal or corrected-to-normal vision. Standard MRI exclusion criteria included claustrophobia and the presence of metal in body. All older adults performed within normal range (i.e., score >26) on the Montreal Cognitive Assessment (Nasreddine et al., 2005). No participant had a history of neurological or cognitive disorders, or traumatic brain injury, and no history of major psychiatric disorders within the last 12 months. They were not on any neurologically/psychiatrically active medication at the time of testing (with the exception of a stable antidepressant regimen). The study was approved by the Montreal Neurological Institute Research Ethics Board. Participants were paid \$50 for their participation. Thirty-six older adults were recruited, but two participants were excluded from the analyses because of accuracy below 50% in several experimental blocks. Forty young adults were recruited, but six young participants were excluded from the analyses because of accuracy below 50% in several experimental blocks or excessive head motion in the scanner (>0.4 mm). Recruitment of young adults continued until the sample size matched the older adult group.

### 2.2. Experimental paradigm

An arithmetic verification task (see Fig. 1A) was implemented in OpenSesame software (Mathôt et al., 2012). Addition or multiplication problems consisted of equations presented in "a b c" form, where "a" and "b" are the operands and "c" is the sum or product of the operands. The operator to be used was cued at the beginning of each trial and was not displayed with the numbers. Problem selection followed the procedure described in previous work (e.g., Grabner et al., 2013; Lemaire et al., 1996; Megias and Mecizo, 2015, 2016; see supplementary material, Table 6). There were a total of 252 trials divided into 4 blocks of 63 trials (see supplementary material for a list of the stimuli used in the task). Half the presented problems (126) were multiplications and half were additions. Half the presented problems had the correct solution to the equation (i.e., according to the rule cued to be held or updated in WM) whereas, within the other half, 63 problems were false-related problems (i.e., the proposed solution corresponds to the rule that was not currently relevant; e.g., "9 6 15" when the current rule is multiplication) and 63 were false-unrelated problems (i.e., the proposed solution does not correspond to a correct answer for either addition or multiplication; e.g., "9 6 14"). Half the presented problems were "maintenance" problems, in which the cued arithmetic rule did not change within the trial (indicated by a "HOLD"



**Fig. 1.** Experimental procedure and behavioral results. (A), Sequence of events within a trial. (B), Mean solution times and percentages of errors for false-unrelated problems, false-related problems, and True problems as a function of whether a Flip or Hold cue was displayed, in young and older adults. Errors bars represent the standard error of the mean (S.E.M). (C), Modulation of the false-related minus false-unrelated difference as a function of age.  $***p < 0.001$ .

cue between the operator cue and the problem presentation), and half were “updating” problems, in which the cued arithmetic rule had to be updated to the other operator (“FLIP” cue) before the presentation of the operands and proposed solution. The order of the problems was pseudorandomized to ensure that there was half repetition and half switching of rule (i.e., Hold, Flip), problem type (i.e., addition, multiplication), and condition (i.e., true and false problems) throughout the session.

Each trial began with a fixation dot presented for 500 ms in the center of the screen (Fig. 1A). The rule cue (i.e., a “+” sign for addition problems and a “X” sign for multiplication problems) was then displayed on the computer screen for 1500 ms. After this rule

activation phase, a fixation dot was presented with a pseudo-random jitter between 1000 ms and 1400 ms. Then, the WM instruction (“HOLD”, or “FLIP”) was presented for 1500 ms. The “HOLD” cue indicated that participants should use the cued rule. The “FLIP” cue instructed a change to the alternate, noncued rule. Following the WM instruction, a fixation dot was presented with a pseudo-random jitter between 1000 ms and 1400 ms. Both operands and a proposed answer were then displayed simultaneously on the screen. The proposed answer appeared below the operands. Both operands and the proposed answer remained on the screen until participants’ response, or for a maximum duration of 4000 ms. After the verification phase, a 500 ms blank screen was displayed

before the next trial started. Participants indicated via an MRI-compatible two-button box whether the “c” term was the correct result of the equation given the currently relevant rule, or if the equation was incorrect. All participants completed a short training session of 20 problems, different from the experimental stimuli, outside the scanner. Instructions emphasized both accuracy and speed. Participants were reminded to keep their eyes fixed on the white fixation cross and to try to lie as still as possible. There was a pause of approximately 30 seconds after each block. All participants underwent several neuropsychological tests (see [supplementary material](#)) outside the MRI scanner.

### 2.3. Behavioral analysis

The first trial of each block and trials with no response or an erroneous response were not included in the analyses. Mean reaction times and percentages of errors were analyzed using 2 (age: young adults, older adults)  $\times$  3 (item: true, false-related, false-unrelated)  $\times$  2 (WM cue: Hold, Flip) mixed-design ANOVA. To correct for multiple comparisons in ANOVA analyses, Šidák correction (Šidák, 1967) was applied, and Šidák-adjusted *p*-values are reported. Bootstrapping was used for correlations.

### 2.4. MRI acquisition and preprocessing

Individuals were scanned with a 3T Siemens PRISMA MRI scanner with a 32-channel head coil. Total scanning time was 45–60 minutes, because participants had up to four seconds to provide their answer in each trial. Extra padding was placed around the head to minimize head motion (e.g., [Fellner et al., 2016](#)). After localizer scans, T1-weighted images were recorded with a 3D MP-RAGE sequence (field of view: 256  $\times$  256  $\times$  176 mm, sagittal orientation, 1  $\times$  1  $\times$  1 mm voxel size, repetition time: 2300 ms, echo time: 2.98 ms, flip angle: 9°). fMRI data were then acquired while participants performed the task, using a whole brain gradient echo planar imaging sequence sensitive to BOLD contrast in 54 slices, with a multiband acceleration factor of 6 [TR = 621 ms, TE = 30 ms, 3.0 mm slice thickness, voxel sizes = 3  $\times$  3  $\times$  3 mm, FA = 56°, FOV = 240  $\times$  240  $\times$  162 mm]. Diffusion whole brain images were acquired with the following parameters: 78 axial slices, slice thickness = 2.0 mm, voxel size = 2  $\times$  2  $\times$  2 mm, TR = 4000 ms, TE = 55.60 ms, FOV = 256  $\times$  256  $\times$  156 mm. Diffusion gradients were applied along 64 noncollinear directions ( $b = 1000$  s/mm<sup>2</sup>).

### 2.5. fMRI preprocessing

We detected and removed voxelwise spikes through despiking, and then performed slice timing correction. Functional images were realigned to correct for head motion, and high-pass filtered (0.01 Hz) to remove signal drift. Functional echo planar imaging data were phase-shifted to correct for slice acquisition time and aligned to the second image of the run to correct for motion. Head motion corrections did not differ significantly between young and older adults ( $F_s < 0.7$ ). Age-related brain atrophy can introduce artificial differences in the BOLD response in the regions adjacent to the ventricles, such as the ACC, when directly projecting to a standard space (e.g., [Liu et al., 2017](#)). Therefore, population specific T1-weighted templates were created based on the averaged anatomical scans of each age group (i.e., one template per group, following the study by [Yoon et al., 2009](#)). Linear registration of the functional image to T1-weighted, and nonlinear registration to the template were completed using FLIRT ([Jenkinson et al., 2002](#)) and FNIRT ([Andersson et al., 2007](#)), respectively, before normalization into the Montreal Neurological Institute (MNI) stereotaxic space with trilinear interpolation. The normalized functional images were

convolved spatially with a 3D isotropic Gaussian kernel (8 mm FWHM) to improve signal-to-noise ratio.

### 2.6. fMRI analyses

fMRI data were analyzed using Statistical Parametric Mapping 12 (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>). First-level statistical analyses were carried out using a general linear model (GLM) with the following regressors of interest: Hold and Flip cue (see [supplementary material](#)), and false-related and false-unrelated problems during the verification phase, as a function of the Hold or Flip cue for that trial. Error trials and true problems were also modeled. The head realignment parameters were included in the GLM as variables of no interest. For the problem verification phase, each event was modeled as boxcar function starting at the onset of the problem presentation with a duration of the corresponding reaction time for each trial. These boxcar functions were then convolved with a canonical hemodynamic response basis function to create regressors for the GLM, from which beta estimates were calculated. Data were combined across blocks using a fixed-effect model and across participants using a mixed-effects linear model. For the first-level analyses, we applied a voxelwise *t*-test to compare False-related\_Hold versus False-unrelated\_Hold, and False-related\_Flip versus False-unrelated\_Flip problems. Individual contrast images were entered into a one-sample *t*-test at the second (group) level to test between-condition differences. Clusters were regarded as significant when falling below an initial uncorrected voxel threshold of  $p < 0.001$  and an FWE-corrected cluster threshold of  $p < 0.05$ . The average variance inflation factor was 3.3, estimated with a script from the Cognitive and Affective Neuroscience Laboratory (<https://github.com/canlab/CanlabCore>). A variance inflation factor indicates a problematic amount of collinearity when greater than 5 ([James et al., 2013](#)).

### 2.7. DTI analyses

Preprocessing of the raw diffusion data was performed using ExploreDTI ([Leemans et al., 2009](#)) and contained the following steps: (1) images were corrected for eddy current distortion and participants motion; (2) a nonlinear least square method was applied for diffusion tensor estimation, and (3) a whole brain DTI deterministic tractography was estimated using the following parameters, for each participant: uniform 2 mm resolution, FA (i.e., fractional anisotropy) threshold of 0.2 (limit: 1), angle threshold of 45°, and fiber length range of 50–500 mm. White matter tracts were delineated for each participant in native space. Following previous work (e.g., [Mori et al., 2008, 2009](#)), the following tracts were manually delineated in the native space based on the same anatomical ROIs (i.e., anterior and posterior parts of the corpus callosum): left and right inferior frontal-occipital fasciculus (IFO), left and right superior longitudinal fasciculus (SLF), and left and right cingulum bundle (CB). The FA values of each tract were extracted for each participant, and fiber bundles were then resampled and normalized at the group level based on the group average. Following the study by [Walsh et al. \(2011\)](#), an FA profile for each tract and each participant was calculated as the average FA of all the voxels within each slice, positioned anteriorly to posteriorly along the tract. A normal FA profile for each tract was calculated by combining the FA profiles of the young adults. To specify white matter changes to each tract during aging, each older adult's FA was compared with the younger control mean profile. In young adults, normal interindividual variations in the FA profile were examined by comparing each participant to the FA profile averaged across the profiles of all the other young participants. To quantify an individual

participant's tract microstructure, we performed a least-square linear regression for each individual's profile against the control mean profile. This analysis yielded a residual ( $1-R^2$ ) value for the fit of each participant's curve for each tract, which reflects how well the shape of the individual's tract profile matches or deviates from the mean FA profile for that tract. This method was used as a more sensitive measure of the microstructural integrity of the entire tract than average FA value. As an example, a lesion resulting in a localized dip in FA in the portion of the tract could result in an overall normal average FA if FA in other parts of the tract were relatively high, but such a dip would result in a high deviation from the profile (see also the study by Walsh et al., 2011).

## 2.8. Dynamic causal modeling (DCM)

ROIs were selected based on group-level task-related brain activations from fMRI results (FDR-corrected) obtained in the present study (following the study by Hinault et al., 2019). From these activations, a subset of regions was selected based on previous meta-analyses on cognitive control processes (e.g., Nee et al., 2013; Niendam et al., 2012) and previous DCM work (e.g., Bönstrup et al., 2016). While the maximum number of eight ROIs was used in young adults, reduced bilateral activations in older adults led to a model with seven ROIs. BOLD time courses were extracted as the first eigenvariate from 6 mm diameter spheres centered on the maximum BOLD signal change for each condition. We investigated the interactions among the following ROIs (MNI coordinates): left ventral ACC ( $x = -9, y = 36, z = -6$ ), right dorsal ACC ( $x = 6, y = 18, z = 33$ ), left orbitofrontal cortex (OFC;  $x = -13, y = 45, z = -6$ ), left IFG ( $x = -54, y = 30, z = -9$ ), left AG ( $x = -60, y = -54, z = 12$ ), right AG ( $x = 54, y = -39, z = 27$ ), left occipital lobe ( $x = -39, y = -81, z = -6$ ), and right occipital lobe ( $x = 42, y = -75, z = 0$ ). Similar to previous DCM experiments (e.g., Bönstrup et al., 2016; see supplementary material), the endogenous network (i.e., Matrix A) was formulated as unrestricted and fully connected. The resulting model was inverted separately for False-related\_Hold, and False-related\_Flip problems, in each participant. DCM12, as implemented in SPM, was used for effective connectivity analyses. The group-level optimal sparse model was found using Bayesian estimation of parameters, integrated in the `spm_dcm_post_hoc` routine (e.g., Ma et al., 2015) and by comparisons of coupling strengths between conditions (e.g., Rowe et al., 2010). Gray matter volumes were extracted from the FreeSurfer segmentation (i.e., following the "recon-all" pipeline) and included, together with participants'

age, as a covariate in the comparison of coupling strengths between conditions and age groups.

## 3. Results

### 3.1. Behavioral results

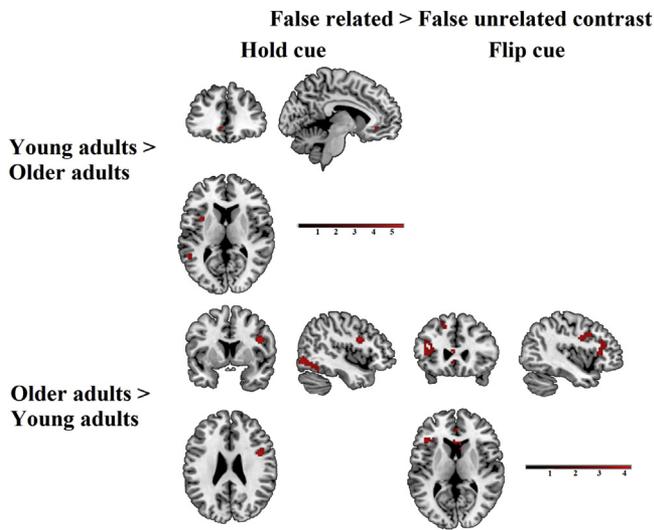
Overall, there was evidence of arithmetic interference, as shown by a main effect of item,  $F(2,132) = 44.79, p < 0.001, MSe = 16,297.33, np^2 = 0.40$ . Planned comparisons showed that participants were slower to solve false-related problems (1517 ms) than either false-unrelated problems (1483 ms;  $F(1,66) = 13.16, p < 0.001, MSe = 2291.83, np^2 = 0.17$ ), or true problems (1349 ms;  $F(1,66) = 61.98, p < 0.001, MSe = 58,143.81, np^2 = 0.48$ ). In addition, participants took more time to solve false-unrelated problems than true problems ( $F(1,66) = 34.88, p < 0.001, MSe = 37,348.35, np^2 = 0.35$ ). A similar effect of item was observed with percentages of errors ( $F(2,132) = 21.59, p < 0.001, MSe = 9.82, np^2 = 0.25$ ). Larger error rates were observed for false-related problems (8.8%) than false-unrelated problems (4.4%,  $F(1,67) = 33.27, p < 0.001, MSe = 19.35, np^2 = 0.33$ ), or true problems (6.6%,  $F(1,67) = 8.07, p = 0.006, MSe = 4.79, np^2 = 0.11$ ), and false-unrelated problems yielded smaller error rates than true problems,  $F(1,67) = 23.18, p < 0.001, MSe = 4.88, np^2 = 0.26$ . Similar error rates were observed between age groups ( $F < 1.0$ ).

Young adults were faster than older adults ( $F(1,66) = 22.99, p < 0.001, MSe = 194151.74, np^2 = 0.26$ ; Fig. 1B; average response times of 1272 ms and 1627 ms, respectively). Most importantly, older adults failed to benefit from WM updating, as shown by a significant Age  $\times$  Item  $\times$  WM interaction ( $F(2,132) = 3.56, p = 0.03, MSe = 637.08, np^2 = 0.05$ ). Planned comparisons revealed that the difference between false-related and false-unrelated problems was significant for both Hold and Flip trials in older adults (45 ms and 44 ms, respectively,  $F(2,33) = 29.21, p < 0.001, MSe = 23.01, np^2 = 0.64$ ), whereas in young adults the difference was only significant for Hold trials (76 ms,  $F(2,33) = 15.34, p < 0.001, MSe = 16.06, np^2 = 0.05$ ). To control for an alternative interpretation of the results in terms of general aging or processing speed, participants' ages and the digit coding scores were used as a covariate in separated ANOVAs (i.e., one ANOVA per covariate, and an additional ANOVA combining these factors). No significant interaction involving age or processing speed was observed ( $F_s < 2.0$ ). Data were also log-transformed to control for general slowing in baseline

**Table 1**  
Significant activation clusters (FWE-corrected) for age-related differences in the false-related versus false-unrelated contrasts, including regions (Brodmann area), cluster size (number of k voxels), t-values, and MNI coordinates

Contrasts	Age	Regions (BA)	k	T	Coordinates (MNI)		
					X	Y	Z
False-related versus false-unrelated (Hold cue)	Young > Old	Right STG (22)	39	4.53	51	-21	-6
		Left AG (39)	47	4.00	-60	-51	15
		Right IPL (40)	29	3.84	60	-42	30
	Old > Young	Left occipital lobe (19)	58	4.28	-45	-75	-15
		Right IFG (44)	21	3.73	42	6	24
		Right occipital lobe (19/37)	92	3.94	45	-75	-6
False-related versus false-unrelated (Flip cue)	Old > Young			3.40	33	-81	0
				3.39	48	-54	-18
		Left DLPFC (8/9)	362	4.71	-3	54	30
				3.59	-18	30	48
		Right ACC (32)	139	4.07	9	33	-6
				3.60	-3	42	0
Left IFG (45/46)		71	3.86	-45	30	15	
			3.43	-33	30	12	

Key: ACC, anterior cingulate cortex; AG, angular gyrus; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; STG, superior temporal gyrus.



**Fig. 2.** Analyses of BOLD activity difference between young adults and older adults in the false-related problems versus false-unrelated contrast, following the Flip or Hold working memory cue.

performance among older adults (see also Goffaux et al., 2008), but similar results were observed.

To summarize, behavioral results showed arithmetic interference, which differed between age groups. In young adults, this effect was reduced when the activated rule was updated within the trial (Flip trials), compared with when the rule was actively maintained (Hold trials), suggesting that inhibition of the previously activated rule facilitated inhibition of the irrelevant arithmetic knowledge. In older adults, greater interference was observed and the interference was not modulated by rule updating.

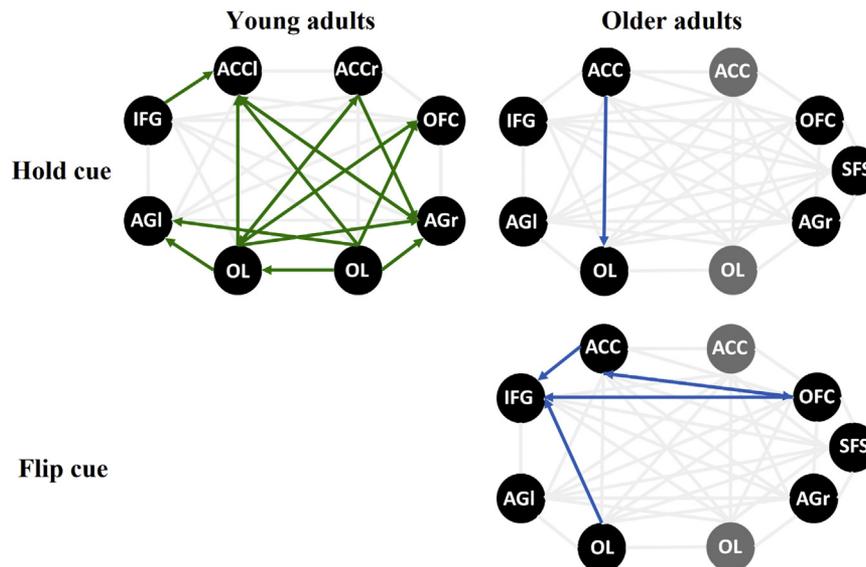
**3.2. fMRI results**

We investigated the effect of WM updating on arithmetic interference by contrasting the difference between false-related and false-unrelated problems during the problem verification

phase as a function of the WM cue (Table 1, Fig. 2; see supplementary materials for results of the WM phase, and within-group contrasts during the problem verification phase). Group comparison revealed a greater interference effect (i.e., false-related versus false-unrelated activation) in the right superior temporal gyrus, right AG, and right inferior parietal lobule in young adults than in older adults for Hold trials. During Hold trials, older adults showed more false-related versus false-unrelated activations than young adults in bilateral occipital lobes and right IFG. Following the Flip cue, larger false-related versus false-unrelated activations of the left DLPFC, the right ACC and the left IFG were observed in older adults than in young adults. Young adults did not show any regions of greater activation in this same contrast. Therefore, consistent with the behavioral results, older adults showed larger frontal activations than young adults during arithmetic interference (i.e., false-related versus false-unrelated contrasts), suggesting less efficient inhibition of the related interfering information and a need for frontal compensatory activation. This result was found following both Hold and Flip cues, but the difference was larger after WM updating (i.e., Flip cue).

**3.3. Dynamic causal modeling**

DCM effective connectivity analyses at the group level revealed differences in significant couplings on false-related problems as a function of the WM cue (Fig. 3). In young adults, following the Hold cue, significant couplings mainly involved right ACC, IFG, OFC, and bilateral occipital lobes. Following the Flip cue, no significant coupling was observed. In older adults, similar patterns of significant couplings were observed, but the modulation by the WM cue was different than in young adults. Following the Hold cue, only the ACC to occipital lobe coupling was significant, whereas significant couplings involving the IFG and OFC were also observed after the Flip cue. Thus, while young adults showed fewer couplings following the Flip cue than the Hold cue, older adults showed the opposite, with an increased engagement of frontal regions of the network. In older adults, the left AG to left IFG coupling was correlated with performance on false-related problems following the Hold cue ( $r = -0.480, p = 0.004$ ), with stronger couplings being



**Fig. 3.** DCM network of false-related problems for young and older adults, as a function of the Hold or Flip WM cue. Only couplings that reached the defined threshold are displayed in the DCM networks. Abbreviations: DCM, dynamic causal modeling; WM, working memory.

associated with faster correct rejection (i.e., better inhibition of the irrelevant information).

Important modulations of the significant couplings were also observed between age groups. A mixed-design ANOVA on the DCM couplings revealed a significant Age  $\times$  WM  $\times$  Coupling interaction ( $F(20,47) = 3.70, p = 0.007, MSe = 9.82, \eta^2 = 0.50$ ). Planned comparisons revealed that coupling strengths were overall lower in older adults than in young adults. This difference between age groups was larger following the Flip than the Hold cue, and mainly involved the left IFG, left OFC, right OL, and the right AG (see [supplementary material, Table 5](#)). Mean gray matter volumes and participants' ages were included as covariates in the analyses. No significant interaction involving these factors and the factors of interest was observed ( $F_s < 1.5$ ). However, a main effect of age ( $F(1,64) = 19.66, p < 0.001, MSe = 0.011, \eta^2 = 0.50$ ), was observed on gray matter volume, with lower overall gray matter volume in older adults than in young adults.

### 3.4. DTI results

Older adults showed overall smaller FA values than young adults ( $F(1,66) = 15.72, p = 0.001, MSe = 0.99, \eta^2 = 0.19$ ). This difference in FA values between age groups was similar across tracts ( $F < 1.0$ ), but across-individual white matter microstructure measures (residual for FA tract profile fit, see Methods) were not correlated between tracts. Only correlations between significant DCM couplings (i.e., on false-related problems as a function of the WM cue) and white matter microstructure (i.e., low deviation from the young adults' profile) that were related to the SLF, IFO, and CB tracts were investigated. Correlation with significant couplings was observed on false-related models following the Hold cue. In young adults, correlations involved the dorsal pathways, as the right ACC-AG coupling was positively correlated with CB white matter microstructure ( $r = 0.388, p = 0.023$ ), and the left and right occipital lobe-AG couplings were positively correlated with the microstructure of the respective SLF ( $r = 0.442, p = 0.009$ , and  $r = 0.425, p = 0.012$ ). In older adults, on the other hand, a correlation with the ventral pathway was observed, as the right ACC-occipital lobe coupling strength was positively correlated with the IFO microstructure ( $r = 0.351, p = 0.042$ ). An ANOVA of the DCM-DTI correlations revealed a significant Age  $\times$  Coupling interaction following the Flip cue ( $F(29,1682) = 41.44, p < 0.001, MSe = 0.01, \eta^2 = 0.98$ ) although this difference did not survive FDR correction for multiple comparisons. The Age  $\times$  Coupling interaction was not significant following the

Hold cue ( $F < 1.5$ ). As with the DTI-behavior correlations, white matter microstructure appears to be important for functional/effective network connectivity, but the dependencies appear to be somewhat different for older versus younger adults.

### 3.5. Regression analyses

To better understand the relationship between structural and effective connectivity, simultaneous least-square linear regressions were performed on each DCM coupling with individual levels of frontoposterior white matter microstructure as predictors. In separated analyses, each DCM coupling was entered as the dependent variable, whereas the IFO, CB, and SLF individual microstructure levels were entered in a single regression step as three independent variables (i.e., nonhierarchical model). The analyses were performed separately for young and older adults and yielded a  $R^2$  value for the fit of each participant's white matter microstructure for each coupling within the DCM model of the Flip and Hold conditions. Higher values reflect how well levels of white matter microstructure of frontoposterior tracts account for the variance across individuals regarding each effective connectivity coupling.  $R^2$  values of the correlation of microstructure with each coupling for each WM condition (Flip/Hold) and age group were then used as a dependent variable in an Age  $\times$  WM mixed-design ANOVA. Results showed a main effect of WM condition ( $F(1,58) = 44.64, p < 0.001, MSe = 0.01, \eta^2 = 0.44$ ), as the proportion of variance explained by the regression models was higher for DCM coupling in the Flip relative to the Hold condition. This factor also significantly interacted with Age ( $F(1,58) = 16.69, p < 0.001, MSe = 0.01, \eta^2 = 0.22$ ). Planned comparisons revealed that the difference in dependence on white matter microstructure between Flip and Hold was significant for older adults ( $F(1,58) = 57.96, p < 0.001, MSe = 0.01, \eta^2 = 0.50$ ) but not for young adults ( $F < 3.5$ ). Within the older adults' group, after FDR correction for multiple comparisons, the regression models accounted for a significant amount of the variance of couplings involving left ACC, left AG, left IFG, and left OFC following the Flip cue (see [Table 2](#)), whereas no significant coupling survived FDR correction for multiple comparisons following the Hold cue. Comparisons of standardized beta of each regression revealed a significant contribution of the microstructural properties of cingulum and IFO tracts in the explained variance of the related DCM couplings. These results indicate that individual differences in age-related degradation of structural connectivity in specific frontal-posterior white matter tracts relates to individual

**Table 2**  
Output of the regression models of tract integrity that accounted for a significant amount of the variance of the DCM couplings, in older adults, following the Flip cue

Coupling	R-2	p value	CB (beta)	CB (p value)	IFO (beta)	IFO (p value)	SLF (beta)	SLF (p value)
ACC-AGI	0.428	0.001	0.121	0.002	0.083	0.019	0.063	0.041
ACC-OL	0.359	0.004	0.171	0.001	0.019	0.623	0.021	0.537
ACC-SPFC	0.361	0.003	0.162	0.001	0.049	0.211	0.023	0.507
AGI-ACC	0.340	0.005	0.206	0.004	0.118	0.067	0.100	0.078
AGI-AGr	0.339	0.006	0.240	0.001	0.091	0.146	0.039	0.477
AGI-IFG	0.374	0.003	0.176	0.001	0.036	0.386	0.052	0.156
AGI-OFCI	0.300	0.013	0.129	0.003	0.011	0.771	0.052	0.111
AGI-SPFC	0.361	0.003	0.185	0.003	0.128	0.023	0.066	0.171
AGI-OL	0.335	0.006	0.239	0.001	0.018	0.755	0.010	0.837
IFG-ACC	0.297	0.013	0.135	0.039	0.131	0.032	0.097	0.066
IFG-AGI	0.395	0.002	0.150	0.001	0.069	0.084	0.073	0.039
IFG-OFC	0.319	0.008	0.103	0.002	0.025	0.394	0.044	0.092
IFG-SPFC	0.294	0.014	0.118	0.067	0.152	0.013	0.080	0.125
OFC-ACC	0.280	0.019	0.108	0.006	0.038	0.279	0.048	0.121
SPFC-ACC	0.378	0.002	0.162	0.001	0.077	0.079	0.068	0.077
SPFC-AGr	0.274	0.021	0.042	0.550	0.185	0.008	0.091	0.123

Only models that survived FDR corrections for multiple comparisons are reported.

Key: CB, cingulum bundle; IFO, inferior frontal-occipital fasciculus; SLF, superior longitudinal fasciculus; DCM, dynamic causal modeling.

differences in the ability to establish effective functional engagement of the network when representation updating in WM is required. Older individuals with higher white matter microstructure levels (i.e., closer to the young adults' profile) showed stronger functional couplings following the Flip cue.

#### 4. Discussion

We investigated the arithmetic interference effect, interpreted as reflecting the need to inhibit irrelevant arithmetic facts when the proposed answer is the correct product of the noncued operation (e.g.,  $8 + 4 = 32$ ). We combined this task with the requirement to maintain or update the cued arithmetic rule before resolving the interference. Young and older adults showed comparable inhibition performance following WM maintenance. After WM updating, however, inhibition performance was facilitated in young adults, but not in older adults, leading to larger arithmetic interference. These results indicate that there is not a general loss of interference resolution ability with age (i.e., no Age  $\times$  Item interaction), but rather a lack of normal facilitation of this ability after the initiation of similar cognitive control processes, such as WM updating. In addition, fMRI results showed larger prefrontal activations in older adults than in young adults during arithmetic interference following WM updating, suggesting a greater residual need for cognitive control, and thus activation of the prefrontal cortex, in the older adults. We also tested how individual variability of white matter microstructure with age may be related to the coordinated engagement of updating- and inhibition-related functional networks and behavioral performance. Analyses of effective and structural connectivity revealed (1) engagement of frontoposterior connectivity during resolution of arithmetic interference, and (2) associations between white matter microstructure, functional couplings, and cognitive control performance in both young and older adults, but with apparent differences between the age groups regarding which tracts had the greatest influence on effective connectivity and behavioral performance. We also observed that relatively preserved white matter microstructure in older adults was associated with higher levels of activation of frontoposterior couplings and reduced interference effects.

Previous studies investigated age-related changes in brain connectivity associated with cognitive control. For both structural (e.g., De Lange et al., 2016) and functional (e.g., Cabral et al., 2017b; Daselaar et al., 2015) connectivity, these studies found age-related alterations in the cognitive control network (see Hedden et al., 2016, for a review). However, these studies did not examine the potential relationship between age-related individual differences in the microstructure of particular white matter tracts and the effective connectivity of functional networks associated with WM and inhibitory processes (but see Cabral et al., 2017a, in a young population). Based on previous work conducted in the laboratory (e.g., Walsh et al., 2011), we hypothesized that low white matter microstructure levels of relevant connections within the network could impair task-related functional couplings and underlie age-related changes in cognitive control processes. Conversely, a relative preservation of white matter microstructure could be associated with increased network functional connectivity and better inhibitory and WM behavioral performance.

The integrities of the CB, IFO, and SLF were investigated, as they have previously been associated with the efficiency of WM and inhibitory processes and the preservation of these processes during aging (e.g., Bettcher et al., 2016). Following the study by Walsh et al. (2011), we defined a profile based on white matter microstructure measures in young adults along each tract, and then quantified the deviation from the shape of this profile in each group. This method is sensitive to small deflection in FA anywhere

along the length of the tract while being relatively insensitive to overall reductions in FA that are uniform across the tract and which may reflect overall changes in tissue density or other age-related changes unrelated to localized tract damage. In young adults, higher microstructural integrity of the dorsal pathways, involving the SLF and CB, was associated with greater frontoposterior effective connectivity. In older adults, frontoposterior connectivity differences involved a more ventral pathway and were associated with IFO microstructure. The greater reliance on this pathway is in line with a larger engagement of inhibitory processes to solve the interference, as inferior frontal cortex and its connectivity to posterior areas via the IFO are both associated with inhibitory control (Forstmann et al., 2008). These results suggest that the microstructure of these tracts plays a role in the preservation of cognitive control with age. The finding that deviations from the average tract FA profile also correlated with effective connectivity and performance in young adults suggests that factors other than aging also play a role, such as past traumatic injury or variability in myelination of these long prefrontal to posterior tracts.

DCM modeling was based on fMRI results and highlighted (1) age-related differences in the brain network engaged by arithmetic interference, (2) modulations of the activated couplings as a function of the WM cue, and (3) how this network differs between young and older adults. In young adults, following the Hold cue, significant couplings mainly involved the bilateral occipital lobes, ACC, IFG, and OFC. In older adults, for both Flip and Hold cues, similar regions were engaged but the number of significant couplings was lower. Results within the older adult group showed larger coupling with prefrontal regions, including the ACC, IFG, and OFC, following the Flip cue, compared with after the Hold cue, in contrast to the results in the young adults. Compared with young adults, results suggest a decrease of the frontoposterior connectivity with age and a larger engagement of the cinguloopercular network (see also Jordan et al., 2018). Increased recruitment of the right superior frontal cortex was not associated with better behavioral performance, indicating that this activation is not compensatory (e.g., Cabeza et al., 2018). Results suggest that inefficient additional frontal recruitment could be the result of decreased frontoposterior connections. The correlation between white matter microstructure of the IFO tract and the ACC-occipital lobe coupling strength highlights the relationship between effective and structural brain connectivity. Regression analyses revealed differences between age groups and the significant association between individual levels of white matter microstructure and effective connectivity couplings, as older individuals with greater white matter microstructure integrity were able to establish effective functional engagement of the network when representation updating in WM is required.

The results also highlight the complexity of age-related changes in cognition because of changes in the interactions among distinct but related cognitive processes. We documented the facilitated inhibition on the resolution of arithmetic interference, and age-related differences in this effect. In young adults, when the operation rule was updated immediately before the problem verification phase, the difference between false-related and false-unrelated problems was no longer significant. Results support the interpretation that the suppression of the no-longer-relevant rule during WM updating involves similar inhibitory processes as those needed to suppress irrelevant arithmetic knowledge activated by the information presented during the problem verification phase of the false-related trials. In contrast with young adults, the interference in older adults was not modulated by the WM cue, indicating that while updating the rule in WM facilitated inhibition of irrelevant

arithmetic facts in young adults, it did not do so in the older adults. As young and older adults did not differ in arithmetic abilities, and differences in processing speed (as indicated by digit coding performance) were controlled, results cannot be interpreted as reflecting differences in arithmetic skills or processing speed between age groups.

## 5. Conclusions

Results have implications for our understanding of how functional and structural alterations of the cognitive control network underlie individual differences in cognitive functioning during aging. The results here are consistent with the STAC-r and CRUNCH models (i.e., Scaffolding Theory of Cognitive Aging: Reuter-Lorenz and Park, 2014; Compensation-Related Utilization of Neural Circuits Hypothesis: Reuter-Lorenz and Cappell, 2008; see also GOLDEN, Growth of Lifelong Differences Explains Normal Aging: Fabiani, 2012) but provide greater specificity regarding the role of individual variability of white matter microstructure in the ability to engage dynamic networks and in cognitive performance. Older individuals with a relative preservation of frontoposterior white matter tracts, especially involving the inferior frontaloccipital fasciculus, showed stronger functional coupling strengths among bilateral anterior cingulate, bilateral inferior frontal gyrus, and left angular gyrus and reduced behavioral interference. Conversely, alterations of the microstructure of these tracts were associated with reduced effective connectivity in the engaged functional network and less facilitated inhibition. This association between white matter microstructure, activation, effective connectivity, and performance suggests a potential way to measure the brain basis of cognitive reserve and a way to predict an individual's future age-related cognitive trajectory. The present results highlight the importance of considering network characteristics, and dynamic interactions between networks and cognitive control processes, to further our understanding of the preservation or alteration of cognitive functioning during aging.

## Disclosure

The authors disclose any potential sources of conflict of interest.

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## Appendix A. Supplementary data

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