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Aging modulates fronto-temporal cortical interactions during lexical production. A dynamic causal modeling study

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ABSTRACT

In this dynamic causal modeling (DCM) study, we evaluated the effect of age on the effective connectivity of a cerebral network involved in lexical production. Younger and older adults performed an object naming task during fMRI. The DCM was used to explore the interactions between four regions of interest: the occipital cortex, OC; the lateral temporal cortex, LTC; the medial temporal cortex, MTC; and the inferior frontal cortex, IFC. We mainly focused on the modulation of the fronto-temporal interaction, according to the hypothesis that aging requires strategies that modulate the access to the semantic knowledge, either through a neural reserve mechanism (increased MTC-LTC connectivity) or through a neural compensation mechanism (supplementary IFC-MTC connectivity). For younger adults, our results indicated a bi-directional interaction between the left IFC and LTC suggesting a typical activation related to lexico-semantic representations. For older adults, our results reveal the existence of bi-directional interaction between the IFC and MTC, but not between the IFC and LTC – which in turn suggests that older adults adapt a new strategy, via supplemental access to conceptual access and semantic retrieval processes. This neural compensation strategy would be facilitated by a top-down mechanism from the IFC to the MTC. We discuss our results in the context of the possible additional strategies used by older compared to younger adults, to retrieve and produce words.

1. Introduction

Unlike executive functions, memory, and processing speed, which decline rapidly with age (Salthouse, 2009), language remains stable longer, or can even improve with age (Kave, Samuel-Enoch, & Adiv, 2009; Ramscar, Hendrix, Shaoul, Milin, & Baayen, 2014; Salthouse, 2009). Although reduced lexical production efficiency has been observed in older adults at a behavioral level (Burke & Shafto, 2004; Gollan & Brown, 2006; Verhaegen & Poncelet, 2013), they usually exhibit normal response accuracy for a typical production task such as object naming (Boudiaf et al., 2016; Evrard, 2002). This suggests that lexico-semantic knowledge is preserved during aging (Verhaeghen, 2003). At the cerebral level, the normal response accuracy observed in older adults is reflected by the modulation of activity and functional connectivity in the cerebral networks subserving lexical production (Baciu et al., 2016; Cotelli et al., 2010; Fertonani, Brambilla, Cotelli, & Miniussi, 2014; Lacombe, Jolicoeur, Grimault, Pineault, & Joubert, 2015; Wierenga et al., 2008). Such cerebral modulation of cerebral activity in older adults may be reflected either by increased recruitment of a dedicated functional network (i.e. a neural reserve mechanism), or by the recruitment of functional networks that are not normally involved in that function (neural compensation mechanism) (Barulli & Stern, 2013; Steffener & Stern, 2012; Stern, 2002).

In a previous fMRI study involving an object naming task, we found that relative to younger adults, older adults exhibited greater left fronto-temporal asymmetry, along with increased temporal region activity (Hoyau et al., 2017). This may be attributable to a compensatory mechanism used by older adults to maintain a normal accuracy level for lexical production, and can be regarded as an instance of either (a) neural reserve, i.e. an heightened activation of the semantic representations stored in the temporal regions (McIntosh et al., 1999; Schon, Quiroz, Hasselmo, & Stern, 2009; Simons and Spiers, 2003); or (b) neural compensation, i.e. supplementary access to concepts and semantic knowledge that is mediated by top-down processes (Ansado,

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Marsolais, Methqal, Alary, & Joanette, 2013; Boudiaf et al., 2016; Lacombe et al., 2015). Based on these findings (Hoyau et al., 2017), we hypothesized that neural reserve and neural compensation mechanisms involve different networks described below.

Within the core lexical production network, the left lateral posterior temporal cortex (LTC; fusiform and infero-temporal gyri) is thought to be mainly involved in object recognition and the semantic processing of visual attributes (Binder, Desai, Graves, & Conant, 2009; Chao, Haxby, & Martin, 1999; Simons, Koutstaal, Prince, Wagner, & Schacter, 2003). The left LTC is also involved in semantic processing of categories (i.e. shared features between concepts; Tyler et al., 2013), whereas the left inferior frontal cortex (IFC) is involved in retrieval and cognitive control processes. In younger adults, the left IFC is connected to left LTC (Duffau, Moritz-Gasser, & Mandonnet, 2014), reflecting a direct semantic pathway. Then, we hypothesize for younger adults, that word retrieval involves the IFC-LTC path.

A study by Whatmough and Chertkow (2007) found that left LTC and hippocampal activity co-varied during two semantic retrieval tasks. This result highlights the role of the medial temporal cortex (MTC; hippocampal and parahippocampal regions) in supporting and facilitating conceptual access and semantic retrieval processes. The left hippocampus is also involved in the initial stages of associations between the various modalities of concept acquisition. It is thought that, once a concept has been acquired, the neocortex (the left LTC in this case) alone can adequately retrieve semantic information – which in younger adults translates into reduced involvement of the MTC (Breitenstein et al., 2005; Squire and Zola Morgan, 1991). Furthermore, left MTC activity has been related to feature-based semantic processing (i.e., distinctiveness between concepts; Tyler et al., 2013) and object-name binding processes (Hamamé, Alario, Llorens, Liégeois-Chauvel, & Trébuchon-Da Fonseca, 2014). Also, patients with left temporal lobe epilepsy secondary to hippocampal sclerosis show decreased naming performance (see Bonelli et al., 2011), which suggests that the left MTC plays a crucial part in word production. Catheline et al. (2015) observed that reduced left MTC atrophy in older adults is predictive of higher scores of verbal fluency. Hence we hypothesized that word retrieval strategy is mediated by the left MTC in older adults. The fact that semantic knowledge is preserved or even improved in aging (Verhaeghen, 2003; Laver and Burke, 1993) may mean that older adults rely more on semantic knowledge for word retrieval. It thus follows that heightened connectivity between the left MTC and left LTC mechanism that is used for word retrieval in older adults may indicate the existence of the additional recruitment of networks related to stored semantic knowledge. On the other hand, the left IFC has also been found to be involved as a compensatory mechanism (Park & Reuter-Lorenz, 2009; Turner & Spreng, 2012). Thus in older adults a second mechanism of word retrieval processes, a top-down from the left IFC to left MTC, can be observed in older adults. The left MTC may play two different roles when it comes to facilitating lexical production during aging: (a) according to neural reserve, increased connectivity between the left MTC and the LTC may support the classical IFC-LTC path; or (b) according to neural compensation, the left MTC may facilitate semantic access and retrieval processes, thus indicating a strategic change in finding semantic representations, which are normally accessed via the left LTC.

Assessments of inter-regional connectivity are particularly helpful in determining whether neural reserve or neural compensation is the compensatory mechanism involved in lexical production during aging, a concept also supported by our working hypoheses. One methodological approach that can be used to evaluate connectivity between regions of interest is the dynamic causal modeling (DCM; Friston, Harrison, & Penny, 2003; Penny, Stephan, Mechelli, & Friston, 2004).

In our DCM study, we investigated the effect of aging on effective connectivity between the three regions of interest involved in lexical production network: the left IFC, the left MTC (including the hippocampal and parahippocampal gyri) and the left LTC (including the fusiform and middle/inferior temporal gyri). A fourth region, the occipital region (OC), has also been included, as an input access of the lexical production network activated by the object naming task. We investigated the reciprocal interactions between these regions in two groups (younger and older adults). We expect that older adults use compensatory mechanisms in terms of (a) neural reserve, with increased MTC-LTC connectivity adjacent to the classical left IFC-LTC pathway, or (b) neural compensation, with supplementary involvement of left IFC-MTC.

2. Material and methods

2.1. Participants

Our cohort consisted of 29 participants as follows: a Younger group, YG (N = 15, 5 females, M = 39.73, SD = 7.87, min = 30 y, max = 56 y) and an Older group, OG (N = 14, 3 females, M = 71.21, SD = 6.93, min = 59 y, max = 85 y). They were all right-handed (Edinburgh Handedness Inventory; Oldfield, 1971), had normal or corrected-to-normal vision, and exhibited no cognitive impairments (Mini Mental State Examination, MMSE; Folstein, Folstein, & McHugh, 1975), psychiatric symptoms (Hospital Anxiety and Depression, HAD; Zigmond & Snaith, 1983) or episodic memory deficits (5-words test, Dubois et al., 2002). All of the participants were highly educated native speakers of French (Poitrenaud questionnaire; Kalafat, Hugonot-Diener, & Poitrenaud, 2003). The relevant demographic information can be found in Table 1. Participants provided their informed consent for this study, which was approved by the local ethics committee (CPP N°: 2014-A00569-38).

2.2. Picture naming (PN): Stimuli and procedure

The participants performed a picture naming (PN) task whose 80 black and white stimuli represented objects and animals (DO-80 test; Metz-Lutz et al., 1991; see Fig. 1) in a block-design paradigm alternating four times between task and control periods. During the task periods, 20 images per period were shown (each image for 2 s with an inter-stimulus interval of 500 ms) that the participants were asked to name as accurately and quickly as possible. The same number of simple images (circles and squares) were presented during each control period. During the task periods, the participants were asked to name the images; during the control periods they were asked to say either “square” or “round”. The stimuli were displayed using E-prime software (E-prime Psychology Software Tools Inc., Pittsburgh, Pennsylvania) and were rear-projected, using a video projector, onto a translucent screen located behind the MR scanner. The participants viewed this screen, at a distance of about 114 cm, via a mirror attached to a head coil. The oral responses were recorded using an MRI-compatible microphone (FORMI™ II, version 1.2) that was attached to the coil. Computation of correct-response rates (%CR) and mean correct-response reaction times (RT, in milliseconds) was based on audio recordings of the participants’

Table 1
Demographic information and cognitive evaluation.

	Groups					
Gender ratio (M/F)	Younger group 10/5		Older group 11/3			
	Mean	SD	Mean	SD	*T test (ddl = 27)*	*P value*
Age	39.73	7.87	71.21	6.93	−11.391	< 0.05*
ESC	4.0	0.00	3.85	0.36	1.526	0.139
MMSE	29.6	0.63	29.07	1.20	1.492	0.147
HAD - anxiety	6.26	2.63	6.21	1.96	0.060	0.952
HAD - depression	2.8	2.54	3.92	2.84	−1.129	0.269
EM (5wD)	10.0	0.00	9.92	0.26	1.036	0.309

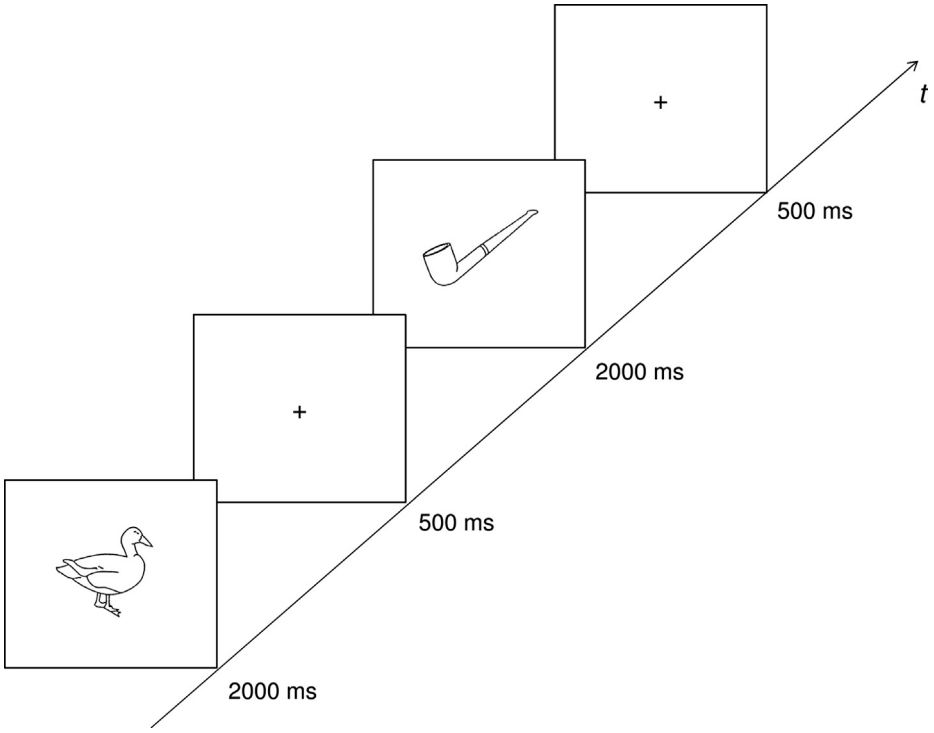

Fig. 1. Examples of stimuli presented in the picture naming task.

oral responses. Praat software (Boersma, 2002) was used to measure each participant's RT values separately from the recorded files. The functional run lasted 7.06 min.

2.3. FMRI acquisition

The experiment was performed in a whole-body 3 T MR scanner (Philips Achieva) with a 32-channel head coil at the MRI facility. For functional scans, the manufacturer-provided gradient-echo/T2*-weighted EPI method was used. Forty-four adjacent axial slices parallel to the bi-commissural plane were acquired in an interleaved mode. The slice thickness was 3 mm. The in-plane voxel size was 2.3 × 2.3 mm (220 × 220 mm field of view acquired with an 88 × 85 pixel data matrix. This was reconstructed to 96 × 96 pixels with zero filling). The main sequence parameters were TR = 2.5 s, TE = 30 ms, and flip angle = 80°. Finally, a T1-weighted high-resolution three-dimensional anatomical volume was acquired, using a 3D T1 TFE sequence (field of view = 256 × 240 × 160 mm; resolution: 0.89 × 0.89 × 1 mm; acquisition matrix: 272 × 250 × 160 pixels; reconstruction matrix: 288 × 288 × 160 pixels).

2.4. Data processing

2.4.1. fMRI data analysis

The general linear model (Friston et al., 1994, 1995) in SPM12 (Welcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB 2014 (Mathworks Inc., Sherborn, MA, USA) was used. The first preprocessing step was the creation of a study-specific template (SST). The SST consisted of an anatomical age-related template. The T1-weighted anatomical volumes were co-registered to the mean images created by the realignment procedure and segmented using the six tissue probability map with DARTEL. We created a SST by matching all the tissue class images previously calculated during the segmentation step, and we normalized this template to the MNI space. The use of a SST for aging studies is recommended to avoid methodological bias based on morphometric variations between individuals (Fillmore, Phillips-Meek, & Richards, 2015; Huang et al., 2010). After the creation of the SST, we performed the temporal correction of the realigned volumes. The T1-weighted anatomical volumes were normalized to the SST. Anatomical normalization parameters were subsequently used for the normalization of functional volumes. Finally, each functional volume was smoothed with an 8-mm FWHM (full width at half maximum) Gaussian kernel. The time series for each voxel was high-pass filtered (1/128 Hz cutoff for the PN task).

The FMRI signal was analyzed using a single-participant general linear model. For each participant, two conditions of interest (PN, Control) were modeled, comprising two regressors constructed as box-car functions convolved with a canonical hemodynamic response function. Movement parameters derived from realignment correction were entered into the design matrix as additional regressors of no interest, to account for motion-related variance. Analyses were performed at the individual subject level to examine the contrast between the two conditions ([PN > Control]), and to identify four regions (IFC, LTC, MTC, and OC) used as regions of interest (ROIs).

2.4.2. Dynamic causal modeling analysis

Time series were extracted from these four ROIs, for each participant individually. For each ROI, we first defined a search space on the basis of the activation peak identified in the second-level analysis (group-level analysis), with the [PN > Control] contrast. To ensure that the search spaces were not dominated by one of the groups, we privileged the peak of each group (YG and OG; Table 2a). In agreement with conventional methods (Stephan et al., 2010), we then localized the subject-specific maximum for each participant and for each ROI by selecting the nearest individual peak to the YG and OG group-level peak (for a similar peak selection procedure, see Benetti et al., 2009; Frässle et al., 2016; Kellermann, Scholle, Schneider, & Habel, 2016), using a *p*-value threshold of $p < .001$ uncorrected for multiple comparisons. A more liberal threshold of $p < .1$ was used to find a peak in the MTC in one young participant, and in the IFC in one older participant. Mean coordinates of the individual peaks for each ROI and each group are summarized in Table 2b. It should be noted that in some cases, the nearest maximum was located in a different anatomical region to the

Table 2
Picture naming activation in Younger and Older participants (group and individual analyses).

(a)	YG - group analysis			OG - group analysis		
	x	y	z	x	y	z
Left OC	−43	−82	−4	−39	−80	−13
Left LTC	−43	−59	−13	−43	−48	−16
Left MTC	−27	−11	−22	−25	−3	−22
Left IFC	−41	16	26	−55	21	29

(b)	YG - individual analyses						OG - individual analyses					
	Mean x		Mean y		Mean z		Mean x		Mean y		Mean z	
Left OC	−43	± *4.38*	−79	± *1.79*	−3	± *4.03*	−39	± *3.75*	−79	± *3.59*	−10	± *3.29*
Left LTC	−43	± *4.29*	−57	± *4.61*	−15	± *2.65*	−44	± *3.64*	−48	± *3.2*	−17	± *2.27*
Left MTC	−26	± *5.95*	−12	± *6.95*	−20	± *8.31*	−24	± *5.78*	−10	± *6.21*	−19	± *5.03*
Left IFC	−42	± *6.27*	22	± *0.78*	20	± *9.81*	−50	± *7.62*	19	± *5.71*	25	± *6.42*

region of interest, in which case we looked at the other nearby maxima, with the following anatomical constraints: For OC, the peak had to be in the inferior or middle occipital gyrus, jointly with the Brodmann area (BA) 18 or 19. For LTC, the peak had to be situated in the fusiform gyrus or in the inferior temporal gyrus, jointly with BA 37. For MTC, the peak had to lie in the hippocampal and parahippocampal gyri, jointly with BA 28 or 34. For IFC, the peak had to be placed in the inferior frontal gyrus. In this way, ROIs were defined based on both functional (group-level related) and anatomical constraints. After identification of individual peaks for all selected ROIs, we extracted principle eigenvariates (adjusted for the participant's effect of interest) from 6-mm spheres centered on subject-specific maxima.

We then defined alternative models (Fig. 2) including these ROIs and a set of connections to test our specific hypotheses. We began by defining a basic model (Model 1) comprising four hubs (OC, LTC, MTC, and IFC), from which alternative models were then derived. We specified connections from OC to LTC and MTC, from LTC and MTC to IFC, as well as bidirectional connections between LTC and MTC (Catani, Jones, & Donato, 2003; Duffau et al., 2014; Sehatpour et al., 2008; Smith et al., 2009). We also specified a connection from OC to IFC. According to persuasive models on visual perception, these fast and direct connections may play a major part in rapid object recognition (e.g., Kauffmann, Chauvin, Pichat, & Peyrin, 2015; Kveraga, Boshyan, & Bar, 2007; Peyrin et al., 2010). This basic model was then declined into seven different models, including the basic connections as well as our various hypothesized top-down connections from the IFC (Fig. 2). Hence, the models differed according to the target regions of the connections from the IFC. Model 2: connections lead from the IFC to MTC;

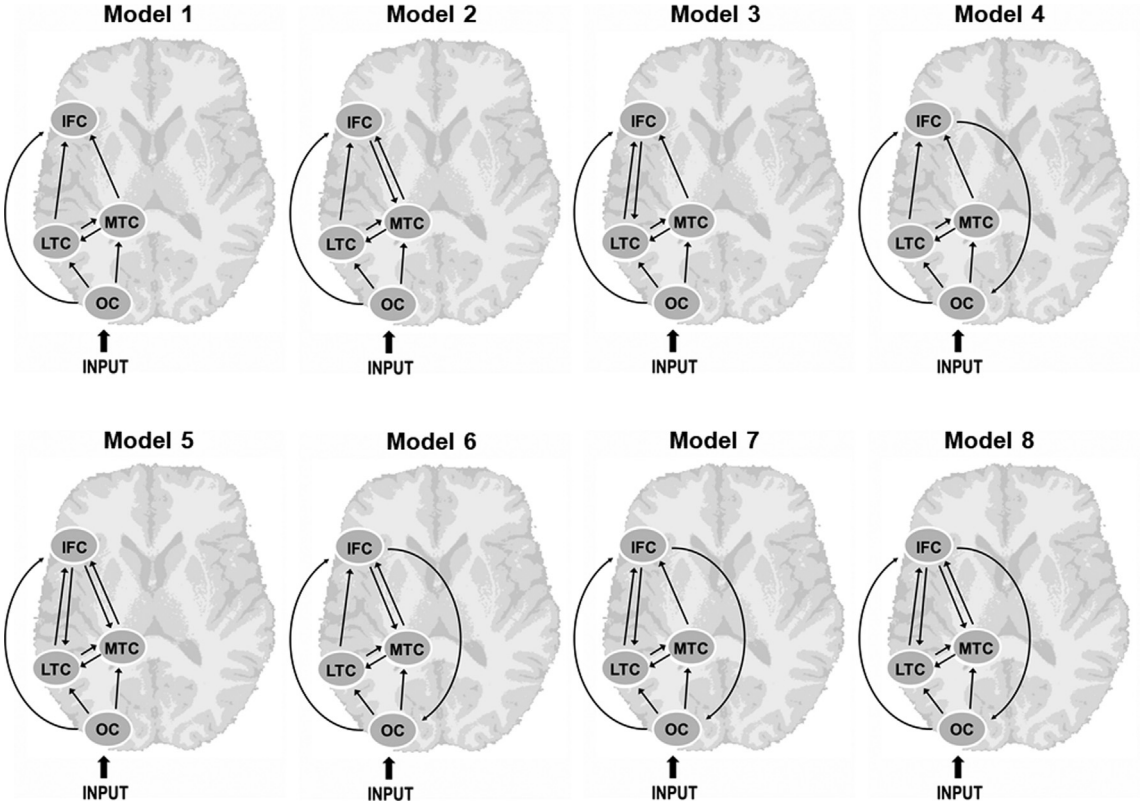

Fig. 2. Illustration of the model space (Models 1–8). Endogenous connections are represented by arrows. External visual input is first processed by the posterior occipital cortex (OC) and is represented by a solid arrow. OC: Left occipital cortex; LTC: Left lateral inferior temporal cortex; MTC: Left medial temporal cortex; IFC: Left inferior frontal cortex.

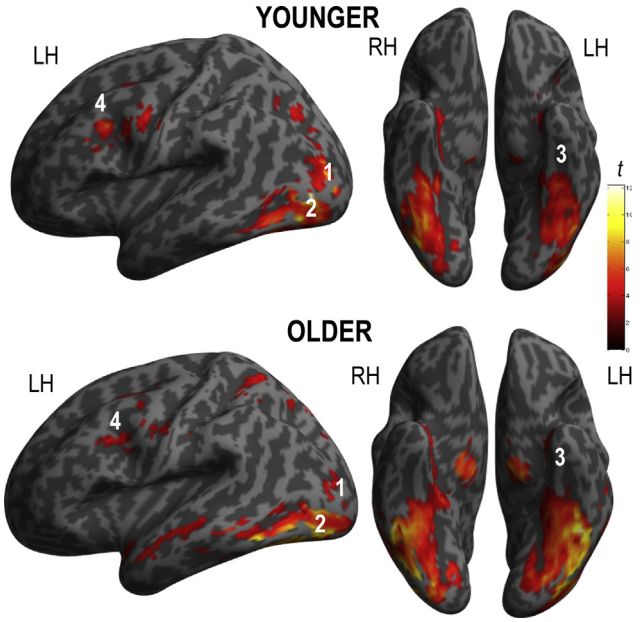

Fig. 3. Cerebral regions that are activated in the statistical contrast between the picture naming task and the control task for the younger and older groups: (1) Left posterior occipital cortex, OC; (2) Left lateral temporal cortex, LTC; (3) Left medial temporal cortex, MTC; (4) Left inferior frontal cortex, IFC.

Model 3: connections from the IFC to LTC; Model 4: connections from the IFC to OC; Model 5: connections from the IFC to MTC and LTC; Model 6: connections from the IFC to MTC and OC; Model 7: connections from the IFC to LTC and OC; Model 8: connections from the IFC to MTC, LTC and OC. For each specified model, endogenous parameters are estimated at the neuronal level using a hemodynamic forward model, to compare the predicted functional responses (i.e. predicted by the defined models) to the measured responses (i.e. extracted time series). Endogenous connection parameters reflect the effective baseline connectivity between regions (i.e. how the rate of change in the activity of one target region is influenced by an increase in activity in the source region). A positive parameter means that an increase in the activity in the source region results in an increase in the activity in the target region. Conversely, a negative parameter means that an increase in the activity in the source region results in a decrease in the activity in the target region. These parameters are expressed in Hertz (Hz). The evidence provided by the model, i.e. the probability of observing the measured data given a particular model, was then computed. The evidence of each model is approximated to the negative variational free-energy (Penny, 2012; Stephan, Penny, Daunizeau, Moran, & Friston, 2009). This approximation is thought to point out the optimal compromise between the accuracy and complexity of a given model. Alternative models were thus specified and compared based on their model evidence, using the Bayesian model selection (BMS) procedure to identify which model(s) best predict(s) the data (i.e. the likelihood that a given model could generate the observed data). The relative superiority of one model, compared to all the others, is given by the exceedance probability, i.e. the probability that this model is more likely than any other, given the data. We then applied the Bayesian model averaging procedure (BMA) to obtain a single model with new connectivity parameters, which correspond to the average connectivity of all models, but where each parameter used to calculate the average connectivity for endogenous parameters is weighted by the model evidence. Thus, models with high evidence contribute more to the "compound" model than models with lower evidence. Finally, the inference on parameters was made, to assess the significance of endogenous parameters (complete details on DCM methodology can be found in Seghier, Zeidman, Neufeld, Leff, & Price, 2010; Stephan et al., 2010, 2009).

Model comparison was implemented using random effects (RFX) BMS in SPM12, with the DCM tool (DCM12 version) to compute exceedance and posterior probabilities (i.e. likelihood of a model given the data) at the group level (Stephan et al., 2009). It should be noted that exceedance probabilities sum to 1 over all the models tested. An exceedance probability of 0.9 for a particular model therefore indicates that this model is 90% more likely to be better than any other model tested, given the data. We used a RFX analysis (Stephan et al., 2009) given that this approach is appropriate for cognitive tasks, which can be performed with various cognitive strategies. The analysis takes into account variability of models across participants and hence prevents outliers from having too much influence on the results (on the contrary, a fixed effect analysis, FFX, is more suitable in cases where the winning model is *a priori* most likely to be the same for all participants, which is not the case here). We performed one BMS for the Younger Group (YG) and one for the Older Group (OG). The results are reported in terms of exceedance probability (probability that the models outperform others).

3. Results

3.1. Behavioral results

No significant difference was observed between the two age groups for PN, in terms of either %CR ($T_{(25)} = -1.032$, $p = 0.311$; YG: mean = 98.13%, SD = 1.9; OG: mean = 98.79%, SD = 1.3) or RTs ($T_{(27)} = -1.121$, $p = 0.272$; YG: mean = 864 ms, SD = 141; OG: mean = 917 ms, SD = 107).

3.2. fMRI results

In a first step, the differences identified at individual level between the two conditions (PN and control) were included into a second-level analysis for all participants, using a one-sample *t*-test. This whole brain analysis revealed brain regions specifically involved in PN, for both YG and OG. Compared to the control condition, the PN condition ([PN > Control] contrast, $p < 0.05$; family wise error corrected for multiple comparisons with a minimum cluster extent of 10 voxels, see Fig. 3) elicited stronger activation in the bilateral lateral temporal cortex (LTC, including the fusiform and infero-temporal gyri), the bilateral medial temporal cortices (MTC, including the hippocampus and parahippocampus), and the left inferior frontal cortex (IFC, in the lower part of the left precentral gyrus and the left inferior frontal gyrus), all of which being involved in word production tasks. We also observed bilateral activation of the OC (BA 19), which was related to visual picture analysis. The same regions were activated for the YG and OG individually ($p < .001$ uncorrected for multiple comparisons; see Fig. 2). The activation peaks identified in the YG and OG (Table 2a) were used to localize the subject-specific maximums for each participant in each ROI in the DCM analysis. Using these activations and our hypotheses as a basis, we investigated effective connectivity between the left IFC, left LTC, and left MTC for the two groups. The OC was included as the access to the network. We focused on the left hemisphere based on our previous findings, which showed that aging modifies left frontal-temporal cerebral asymmetry during word retrieval (Hoyau et al., 2017). In that study, we hypothesized that aging modifies connectivity between the left IFC and left MTC and/or connectivity between the left IFC and left LTC during PN. The OC was included as an information input region.

3.3. DCM results

For the YG, BMS revealed that Model 7 easily outperformed the other models, with an exceedance probability of 0.62. In Model 7, IFC exerts a modulating effect on LTC and OC, but not on MTC. The second

best model for this group was Model 6, whose exceedance probability was 0.21 and in which IFC exerts a modulating effect on MTC and OC, but not on LTC. For the OG, BMS revealed that Model 8 was superior to the others, with an exceedance probability of 0.38. This model is characterized by the IFC exerting modulation on MTC, LTC, and OC. The second best model was Model 6, with an exceedance probability of 0.26. Model 6 is characterized by IFC exerting modulation on MTC and OC, but not on LTC.

Next, BMA was applied over the model space to obtain a single model with an average of the connectivity parameters, which are weighted by the evidence of their own models (i.e. by the probability of observing the measured data given by the model) for endogenous parameters. We performed inference on the parameters within the Bayesian framework, in line with the previous inference concerning model space (for a similar procedure, see Desseilles et al., 2011; Kauffmann et al., 2015; Richardson, Seghier, Leff, Thomas, & Price, 2011; Seghier et al., 2010). BMA generates posterior distributions of model parameters with 10 000 Gibbs samples. The significance of each connectivity parameter can be assessed based on the proportion of samples from the posterior distribution that differs from zero. Significant effects are reported at a posterior probability threshold of $p > 0.95$ for the positive connectivity parameters (excitatory influence) and at a posterior probability threshold of $p < 0.05$ for the negative connectivity parameters (inhibitory influence).

BMA was applied to the eight models for each group separately, to obtain a single model with average connectivity parameters (weighted by the evidence of their models). The results are summarized in Table 3 and Fig. 4. Concerning the YG, BMA revealed excitatory (positive) connections from OC to MTC (0.36 Hz) and LTC (0.37 Hz), an excitatory connection from LTC to MTC (0.20 Hz – the opposite connection was not significant), and bidirectional excitatory connections between LTC and the IFC (LTC to the IFC: 0.16 Hz; IFC to LTC: 0.07 Hz). Connections between MTC and the IFC were not significant. Finally, there was no significant connection from OC to the IFC, but an opposite inhibitory connection was revealed (−0.33 Hz). With respect to the OG, BMA demonstrated excitatory connections from OC to MTC (0.37 Hz) and to LTC (0.28 Hz), bidirectional excitatory connections between MTC and LTC (0.06 Hz each), and bidirectional excitatory connections between MTC and the IFC (MTC to IFC: 0.13 Hz; the IFC to MTC: 0.08 Hz). For this group, connections between LTC and the IFC were not significant. As for the YG, there was no significant connection from OC to the IFC, but the opposite connection was significant (−0.39 Hz, inhibitory). In summary, for the YG, there was an excitatory connection from the IFC to LTC, but not from the IFC to MTC. In contrast, for the OG, there was an excitatory connection from the IFC to MTC, but not from the IFC to LTC.

4. Discussion

In this study we investigated younger and older adults to explore the effect of age on effective connectivity in a distributed network that is activated by an object naming task. Our goal was to identify new strategies and compensatory mechanisms that older adults can use in order to perform a lexical production task. To this end, we assessed the role of the left MTC in lexical production by investigating the interplay between the anterior frontal (left IFC) and posterior temporal (left LTC and left MTC) regions of the brain, which are involved in word production and semantic retrieval processes. We hypothesized the following: (a) compared to younger ones, older adults would recruit the left MTC, suggesting additional conceptual access, whereas (b) compared to older ones, younger adults would recruit the direct semantic pathway, depicted by the interaction between the left IFC and LTC. In addition, for older adults, two main compensatory mechanisms could be observed, one reflecting the neural reserve mechanism with an increased connectivity between the left LTC and the left MTC next to the direct semantic pathway, and another one reflecting the neural compensation mechanism, with additional top-down access from frontal (IFC) to temporal (MTC) regions involved in semantic processing.

With regard to intrinsic connections and according to the best explanatory model reflected by our analyses (see Fig. 4), our results in the YG indicate significant bidirectional connections between the left IFC and left LTC, a significant unidirectional connection from the left IFC to left OC, but not from the left IFC to the left MTC. This finding indicates that occipito-temporo-frontal regions interact with each other, in agreement with their involvement in semantic retrieval. These depend on specific cerebral substrates and, in line with previous studies, on the anatomo-functional correlates of word production (2000; Indefrey & Levelt, 2004; Indefrey, 2011). In the OG, the left IFC interacts bilaterally with left MTC, but not with LTC, in agreement with the neural compensation hypothesis. Overall, older adults may use different strategies involving increased access to conceptual knowledge – which explains why the medial temporal regions are recruited. These findings are considered according to models of lexical production and semantic retrieval processes in the context of neurocognitive models of aging.

4.1. Effective connectivity in younger adults: The direct semantic pathway

According to several lexical-production models (Caramazza, 1997; Levelt, 1989; Levelt, Roelofs, & Meyer, 1999), the main stages of lexical production are conceptual representation, word form analysis (lexico-semantic and lexico-phonologic representations) and articulation (Indefrey, 2011). These stages depend on a set of regions that appear to constitute the core components of word production. In the left cerebral hemisphere, these components are the precentral gyrus, middle and posterior parts of the superior and middle temporal gyri, LTC, the

Table 3
Endogenous parameters for DCM connections across models in Younger and Older participants. Significant parameters with posterior probabilities of $p < 0.05$ (negative parameter, inhibitory connection) or $p > 0.95$ (positive parameter, excitatory connection) are highlighted in bold.

Younger group					Older group				
Connection		Mean	Standard deviation	Posterior probability	Connection		Mean	Standard deviation	Posterior probability
From	*To*				*From*	*To*			
IFC	**OC**	**−0.335**	0.020	0.000	**IFC**	**OC**	**−0.392**	0.027	0.000
OC	**LTC**	**0.375**	0.023	1.000	**OC**	**LTC**	**0.280**	0.020	1.000
MTC	LTC	0.027	0.022	0.889	**MTC**	**LTC**	**0.065**	0.023	0.998
IFC	**LTC**	**0.068**	0.022	0.999	IFC	LTC	0.005	0.023	0.589
OC	**MTC**	**0.359**	0.022	1.000	**OC**	**MTC**	**0.372**	0.021	1.000
LTC	**MTC**	**0.197**	0.024	1.000	**LTC**	**MTC**	**0.062**	0.026	0.993
IFC	MTC	0.027	0.020	0.916	**IFC**	**MTC**	**0.081**	0.021	1.000
OC	IFC	0.032	0.021	0.940	OC	IFC	0.029	0.020	0.924
LTC	**IFC**	**0.161**	0.025	1.000	LTC	IFC	0.011	0.026	0.667
MTC	IFC	0.007	0.023	0.626	**MTC**	**IFC**	**0.127**	0.024	1.000

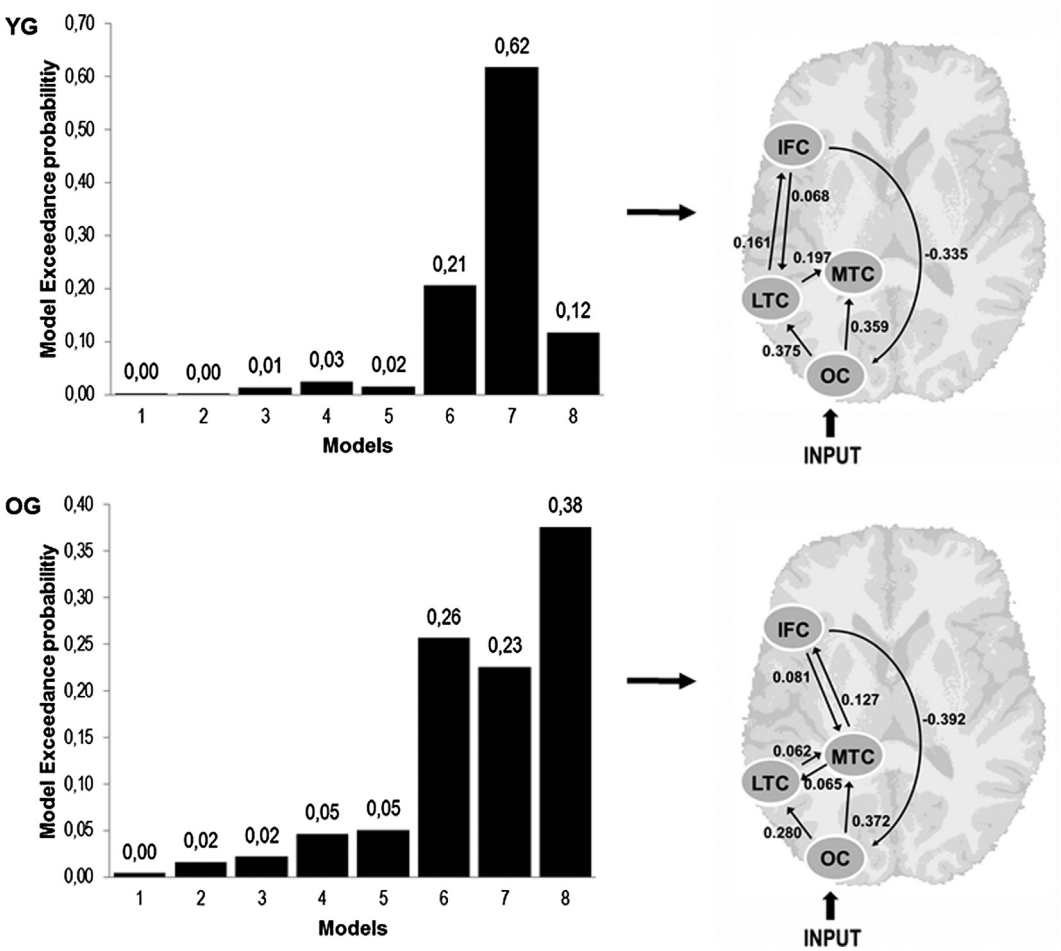

Fig. 4. Group results for the two DCM considered. For each group, the exceedance probabilities for the eight models tested and the BMA analysis results for endogenous connections are expressed in Hz. Only significant parameters with posterior probabilities of $p < 0.05$ (negative parameter, inhibitory connection) or $p > 0.95$ (positive parameter, excitatory connection) are shown. OC: posterior occipital cortex; LTC: lateral temporal cortex; MTC: medial temporal cortex; IFC: inferior frontal cortex; YG: Younger group; OG; Older Group. The main results illustrated by this figure are: Lexico-semantic operations path IFC → LTC for YG; Conceptual access and lexical retrieval path IFC-MTC for OG.

anterior insula, thalamus, and cerebellum (see Indefrey & Levelt, 2004). It is significant in this context that other auxiliary regions are also involved in lexical production such as medial temporal regions (including the hippocampal and parahippocampal gyri), involved in accessing concepts and knowledge from the semantic memory (Binder et al., 2009). Though not part of the core word production system (Indefrey, 2011), these regions are recruited during lexical production. Thus, our results on the intrinsic interactions between the left IFC, left LTC, left MTC and OC in YG are consistent with the core system network of lexical production (Duffau et al., 2014).

Furthermore, our findings show excitatory connections from OC to MTC and to LTC, and excitatory connections from LTC to MTC in YG, in addition to bidirectional excitatory connections between LTC and the IFC (see Fig. 4). Surprisingly, we observed a negative value indicating inhibition between the IFC and OC in the YG. Other researchers have also observed an inhibitory connection from the IFC to OC, which may suggest enhancement of performance within the core lexico-semantic domain-specific system involving LTC, IFC, and MTC (Chen, Chou, Song, & Madden, 2009; Poch et al., 2015). More precisely, Poch et al. (2015) suggested that to remove ambiguity from object recognition in high semantic demanding-tasks, inhibitory connections from the IFC to OC might inhibit the examination of irrelevant items.

4.2. Effective connectivity in older adults: The neural compensation mechanism and top-down connectivity to semantic memory

Most studies tend to emphasize that the role of cerebral anterior frontal regions is reflective of compensatory mechanisms that are invoked by older adults. Specifically, frontal recruitment in older adults suggests attempts to compensate for posterior changes occurring in the aging brain and improve behavioral performance (Cabeza et al., 1997; Goh & Park, 2009; Grady, 2000; Reuter-Lorenz & Cappell, 2008). It has also been posited that reduced selectivity of posterior brain areas may be attributable to less effective inhibitory modulation from frontal regions (Gazzaley et al., 2008). Other authors found that frontal and temporal regions involved in lexical production are sensitive to aging (Baciu et al., 2016; Bartzokis et al., 2001; Obler et al., 2010; Wierenga et al., 2008). In terms of connectivity, Agarwal, Stamatakis, Geva, and Warburton (2016) found that left hemisphere language areas display increased functional connectivity in older adults with intact performance, and that their role appears to be compensatory, in order to preserve the function. Overall, compensatory mechanisms might take different forms. In this study, we aimed to determine which compensatory mechanism is used by the older adults to correctly perform an object naming task, either a neural reserve or a neural compensation mechanism.

In line with the neural compensation mechanism, we observed in the OG, bidirectional interactions between the IFC and MTC, but not

between the IFC and LTC. This finding may be attributable to decreased efficiency of the lateral temporo-frontal path. For example, Chee et al. (2006) suggested that the decline of binding processes in older adults during scene perception might be explained by insufficient information processing of the ventral visual pathway. Furthermore, Gilbert and Moran (2016) observed that object recognition in younger adults was driven by bottom-up processes from the early visual cortex, and in older adults, by both bottom-up and top-down processes from the IFC, suggesting a decline of low-level bottom-up processes. Another explanation is that older adults recruit the IFC-MTC because of greater task-difficulty compared to younger adults. Some studies have shown (Addis & McAndrews, 2006; Rissman, Gazzaley, & D'Esposito, 2008) that IFC-MTC connections are recruited for difficult tasks, while IFC-LTC connections are recruited for easier tasks. According to this view, older adults would need more cognitive resources to correctly perform the task, which involves additional involvement of the IFC-MTC in order to access semantic memory. However, our findings did not indicate increased task-demands based on accuracy and response latencies on the object naming task. One explanation would be that older adults use a different strategy compared to younger ones, to access the semantic memory. Specifically, older adults might access semantic representations through a feature-based strategy (IFC-MTC path), whereas younger adults access semantic representations through an exemplar-based strategy (IFC-LTC path) (Tyler et al., 2013, 2004).

Our results revealed the presence of similar excitatory connections from the OC to the MTC and to LTC, and from the LTC to MTC in older than in the YG. Excitatory connections from the MTC to the LTC were also observed in the OG that were absent in the YG. The OG also maintains inhibitory connections from the IFC to the OC, probably in order to facilitate or reinforce domain-specific processes in the core system and maintain performance levels akin to those of younger adults.

5. Conclusions

Our results show that lexical production in aging is associated with changes in brain connectivity, as reflected by the interactive connectivity between the regions involved in semantic retrieval and cognitive control. Top-down connectivity from frontal to temporal regions reflects change of strategies in older adults, which consists of strengthening mechanisms that facilitate the access to semantic memory (interactions between the IFC and MTC). Older adults appear to use compensatory mechanisms for lexical production, based on increased semantic memory access that under the influence of frontal control (IFC-MTC). This concept is consistent with the theory that semantic knowledge is invoked to a greater degree for purposes of lexical production in aging, via changes in brain connectivity (Ansado et al., 2013; Boudiaf et al., 2016; Hoyau et al., 2017).

6. Statement of significance

Aging modulates the brain connectivity, as reflected by increased link between regions involved in semantic retrieval and cognitive control. To perform lexical production, older adults need more access to semantic memory (medial temporal cortex) via a top-down mechanism (inferior frontal cortex). This compensatory mechanism is used in the context of reduced efficiency of the direct semantic pathway for lexical retrieval, reflected by reduced connectivity between the inferior frontal and lateral temporal cortices.

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