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**Alterations in resting-state functional connectivity associated to the age-related decline in time-based prospective memory**

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Running title: Neural substrates of prospective memory decline in aging

### Abstract

Time-based prospective memory (TBPM) is defined as the ability to remember to perform intended actions at a specific time in the future. TBPM is impaired in ageing, and this decline has been associated with white matter alterations within the superior fronto-occipital fasciculus. In the present study, we used resting-state functional magnetic resonance imaging from 22 healthy young ( $26 \pm 5.2$  years) and 23 older ( $63 \pm 6.1$  years) participants to investigate how age-related alterations in resting-state functional connectivity are related to TBPM performance, and whether these alterations are associated with the white matter disruptions we have previously observed with diffusion tensor imaging. Whole-brain analyses revealed lower resting-state functional connectivity in older participants compared to younger ones, which in turn correlated with TBPM performance. These correlations were mainly located in the salience network and the parietal part of the fronto-parietal network. Our findings suggest that resting-state functional connectivity alterations contribute to the age-related decline in TBPM.

**Keywords:** *Aging; Resting state functional connectivity; Structural connectivity; Memory; Prospective memory*

## 1 Introduction

2 Prospective memory (PM) or memory of future intentions is defined as the ability to  
 3 remember to execute an action at a specific moment or after a defined amount of time. The  
 4 retrieval of intentions can be triggered either by the occurrence of a prospective visual cue  
 5 (e.g., “remember to drop off a letter when you will see the post office”), referred to as event-  
 6 based PM (EBPM), or after a given amount of time or at a precise time (e.g., “take the roast  
 7 out of the oven after 30 minutes”), referred to as time-based PM (TBPM) since there are no  
 8 cue given to the subject to perform the intention (Einstein and McDaniel 1990). Usually,  
 9 intentions have to be retrieved while being engaged in concurrent activities, referred to as the  
 10 *ongoing task*. Many studies have reported a decline in PM in older individuals compared to  
 11 young ones. In this context, TBPM has been found to be more affected by age than EBPM  
 12 (Einstein et al. 1995; Park et al. 1997). This greater sensitivity of time-based intentions has  
 13 been attributed to the fact that they require more self-initiated processes (i.e., executive  
 14 control to manage time) than EBPM, which are impaired in ageing (Einstein et al. 1995; Park  
 15 et al. 1997). Understanding PM deficits in ageing will provide essential information for  
 16 developing more efficient recall strategies to older individuals to compensate for their  
 17 difficulties in daily life.

18 The neural substrates of the decline of TBPM are still poorly understood.  
 19 Neuroimaging studies of TBPM conducted in healthy young adults reported specific  
 20 activation patterns for EBPM (i.e., middle occipital and lingual gyri) and TBPM (i.e., superior  
 21 and middle prefrontal cortex, precuneus) (Gonneaud et al. 2017). In contrast, older  
 22 participants did not show such a functional specialization according to the nature of the task.  
 23 Increased activations in frontal and parietal regions, in the supplementary motor area, the  
 24 fusiform gyrus and precuneus were found in older individuals compared to young ones in a

EBPM task (Gao et al., 2014 ; Gonneaud et al., 2017). Such results, also reported by Peira et al. (2016), support the dedifferentiation hypothesis according to which older people recruit fewer specific networks compared to young individuals, reflecting difficulties in implementing task-specific cognitive processes. This inability to use efficient strategic monitoring processes and dedicated neural networks according to the requirements of the PM task may contribute to a decrease in PM performance. As a result, older individuals will activate more strongly some non-task-critical regions such as the supplementary motor area and the precuneus (Gao et al., 2014; Gonneaud et al., 2017), but will also recruit less other critical regions such as the frontal, prefrontal, cingulate and parietal cortices (Lamichhane et al., 2018; Peira et al., 2016; Scalici et al., 2021). Finally, reduced activity within the fronto-parietal network, involved in attentional monitoring and cue detection, appears to be associated with the age-related decline in prospective memory (Lamichhane et al., 2018).

Recently, we showed that lower TBPM performance in older adults was associated with decreased white matter integrity, especially in tracts of the superior fronto-occipital fasciculus, whereas no correlations with gray matter volume were found (Morand et al., 2021). These results suggest that age-related decline in TBPM may be due to a disconnection phenomenon, rather than neuronal loss. Besides, functional connectivity also changes in the course of ageing, partly due to decreased white matter integrity, altering the communication between regions belonging to various resting-state networks (Andrews-Hanna et al. 2007; Honey et al. 2009). Therefore, resting-state functional connectivity appears as an interesting approach to indirectly explore the neuronal organization at rest and its modification during ageing, overcoming the difficulties older adults may have in performing complex cognitive tasks in the MRI scanner.

Many studies have shown that some brain areas remain active, or are even more active, in the absence of any external stimulation (*i.e.* at rest) compared to a situation in which

participants are performing a task (Biswal et al. 1995; Damoiseaux et al. 2006). Consistently, several neural networks (*i.e.* brain regions that are functionally connected) have been identified from resting-state functional imaging (Damoiseaux et al. 2006; Doucet et al. 2019). These networks include the *default mode network (DMN)*, the *frontoparietal network (FPN)*, the *cingulo-opercular “salience” network*, the *ventral attention network (VAN)*, the *dorsal attention network (DAN)* and the *somatomotor*, the *auditory* and the *visual networks* (Smith et al. 2009; Power et al. 2011; Yeo et al. 2011; Doucet et al. 2019). A large number of studies have reported reduced activity in the DMN in ageing (Damoiseaux et al., 2008; Esposito et al., 2008; Mak et al., 2017 for review). Lower functional connectivity in older adults has also been observed in the FPN (Campbell et al. 2012; Madhyastha and Grabowski 2014; Marstaller et al. 2015), the DAN (Madhyastha and Grabowski 2014; Varangis et al. 2019), and the salience network (Meier et al. 2012; Onoda et al. 2012) in comparison to young adults. In addition, lower connectivity within the DMN was associated with a decline in verbal episodic memory (Wang et al. 2010; Salami et al. 2014; Ward et al. 2015; Staffaroni et al. 2018). Similarly, the decline in visuospatial memory has been associated with decreases in resting-state functional connectivity in regions belonging to either the DMN, FPN or somatomotor network (Suri et al. 2017). Reduced connectivity within the DMN has also been associated with the age-related decline in working memory, leading to difficulties in resources allocation and cognitive control (Sambataro et al. 2010). Performance on tasks assessing executive functions has been associated with a functional hypoconnectivity within the salience network (Onoda et al., 2012) and the FPN (Zhao et al. 2020) in older adults.

Previous studies suggest an association between structural and functional connectivity in ageing (Betz et al., 2014; Damoiseaux et al., 2017 for review). Across the brain, fractional anisotropy, a measure of white matter integrity, is correlated with resting-state functional connectivity within the DMN and the FPN (Ferreira and Busatto, 2013 for review;

Marstaller et al., 2015). Only one study investigated in older adults the impact of both structural connectivity and resting-state functional connectivity alterations on cognition (Andrews-Hanna et al. 2007). This study revealed that lower episodic memory performance in older adults was associated with functional alterations within the DMN, and with white matter disruption in the posterior corona radiata, superior longitudinal fasciculus and cingulum.

To our knowledge, the impact of age-related changes in resting-state functional connectivity on TBPM decline has not been investigated so far. In light of the resting-state functional connectivity changes occurring during ageing and their impact on cognition, we expected lower functional connectivity in the DMN, the FPN and the salience network in older adults compared to young ones. Furthermore, as these networks are associated with episodic memory, executive functions and attentional control, respectively, we hypothesized that changes in these networks are related to poorer TBPM performance in older adults. Finally, to better understand the substrates of the age-related decline in TBPM, we investigated the association between TBPM-related resting-state functional connectivity and TBPM-related structural connectivity alterations, which were previously identified in the same sample of participants using diffusion imaging (Morand et al., 2021).

## Materials and Methods

### Participants

We analyzed data of 22 young healthy adults (18-35 years old) and 23 healthy older adults (51-76 years old), who were already included in our previous study focusing on structural connectivity (Morand et al. 2021). All participants were native French speakers, right-handed, had normal or corrected-to-normal vision, and had completed at least seven years of education. They did not have any medical history of neurological or psychiatric disorders. In addition, older participants were screened for the absence of cognitive deficits

using the Mini Mental State Examination (MMSE, Folstein et al., 1975) and the Mattis Dementia Rating Scale (Mattis 1976). This study was approved by the regional ethics committee (CPP Nord Ouest III, Caen), and written informed consent was obtained from each participant prior participation. Participants' characteristics are presented in Table 1.

\*\*\*\*\*Table 1\*\*\*\*\*

### **Prospective memory assessment**

Participants were invited to perform a semantic categorization task, either alone (ongoing task only) or along with a TBPM task. A total of six sets were proposed, three with the ongoing task only, and three with the ongoing task + TBPM. The task was performed within the MRI scanner (see Gonneaud et al. 2014; 2017, for the detailed method and brain activity patterns).

- Ongoing task – General procedure

Participants were asked to categorize color pictures as *natural* or *manmade* items. Each picture was displayed within a 280 x 280-pixel white square. A digital countdown was displayed in the upper right-hand corner of the screen, and was used for the TBPM condition (as described below). To avoid any difficulty arising from a failure to correctly remember the response keys (counterbalanced between participants), a reminder was displayed at the bottom of the screen, representing the forefinger (left/right)-category (natural/manmade) association. Each experimental block took place as follows (Figure 1): first, the instructions were displayed on the screen for 8 seconds; in order to create an interval between the instructions and the beginning of the task, participants were then asked to predict their performance. Participants were asked to predict their performance on a 5-point scale ranging from 1 (*Very badly*) to 5 (*Very well*). The question remained on the screen for 8 seconds, and was followed by a fixation cross for 1 second, after which 40 pictures were displayed one by one. Each



picture remained on the screen for 2 seconds, followed by a mask for 1 or 2 second(s). Participants were asked to classify each item as natural *or* manmade, as quickly and accurately as possible. The order of presentation was entirely randomized across participants, who had to categorize 6 sets of 40 pictures. At the end of each set, they had to assess their performance on this block (using the same scale as the performance prediction). After 8 seconds, a fixation cross appeared and a new set began.

- TBPM task

For some experimental blocks design, a TBPM instruction was added. Participants had to perform simultaneously the ongoing activity (semantic categorization) and the TBPM task. Simultaneously with the ongoing task, participants were instructed to press an additional key with their middle finger every 30 seconds. To avoid the TBPM task to rely only on time estimation abilities, a countdown was provided to the participant. This countdown was continuously displayed in the upper right-hand corner of the screen so that participants had to voluntarily direct their eyes to monitor the time. Five TBPM answers were expected by block and three TBPM blocks were realized. A total score for TBPM was calculated on 15 points.

## **MRI acquisition**

MR images were all acquired on a 3T MR Philips imager (Achieva 3.0 T TX) at the Cyceron neuroimaging center (Caen, France). A high-resolution T1-weighted anatomical image was acquired for each participant, using a three-dimensional fast-field echo sequence (T1 resolution =  $1\text{mm}^3$ , repetition time = 20 ms, echo time = 4.6ms, flip angle =  $10^\circ$ , 180 slices, slice thickness = 1 mm, field of view =  $256 \times 256\text{ mm}^2$ , matrix =  $256 \times 256$ ).

Resting-state functional MRI data were acquired using an interleaved 2D T2\* SENSitivity Encoding EPI sequence designed to reduce geometric distortions (2D-T2\*-FFE-EPI axial, SENSitivity Encoding EPI factor = 2, 42 axial slices, bottom to top, 2.8 mm thickness, TR = 2.382 s, TE = 30 ms, flip angle =  $80^\circ$ , field of view =  $224 \times 224$ , no gap, in-

plane voxel size =  $2.8 \times 2.8 \text{ mm}^2$ , 280 volumes, acquisition time = 7.6 min). During this acquisition, subjects were asked to relax, to keep their eyes closed without falling asleep and to let their thoughts flow freely.

For the diffusion tensor imaging (DTI) acquisition, 70 axial slices were acquired with spin echo sequence (32 directions at  $b = 1000 \text{ s/mm}^2$ , repetition time = 10 000 ms, echo time = 82 ms, flip angle =  $90^\circ$ , field of view =  $224 \times 224 \text{ mm}^2$ , acquisition matrix =  $112 \times 112$  pixels, acquisition voxel size =  $2 \times 2 \text{ mm}^3$ , and non-diffusion weighted picture at  $b = 0 \text{ s/mm}^2$ ). The analysis of DTI data was the subject of another publication (Morand et al., 2021) in which the preprocessing steps and analyses were fully described.

### **Imaging data preprocessing**

Data preprocessing was conducted using the Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) implemented in MATLAB (R2019) (MathWorks Inc., Natick, MA) (see Figure 1). T1-weighted scans were segmented and normalized to the Montreal Neurological Institute (MNI) template using the unified segmentation and spatial normalization routine from SPM12 (Ashburner and Friston, 2005).

Resting-state fMRI scans (also called EPI volumes) were processed following the procedure recommended by Whitfield-Gabrieli & Nieto-Castanon (2012). Briefly, resting-state functional MRI volumes were checked for artifacts due to head motion or abnormal variance distribution using the TSDiffana toolbox (<https://imaging.mrc-cbu.cam.ac.uk/imaging/DataDiagnostics>), implemented in Matlab. For each individual, the EPI volumes were corrected for slice timing and realigned on the first volume. Data were then spatially normalized to reduce geometrical distortions effects (Villain et al. 2010). This procedure included (1) coregistration including the alignment between the mean EPI and the non-EPI T2\* volumes, then between the non-EPI T2\* and T2 volumes, and then between the

T2 and T1 volumes, (2) normalization of the mean EPI volume to match the non-EPI T2\* volume, (3) segmentation of T1 volume using the VBM12 procedure to extract gray matter, white matter and cerebrospinal fluid, (4) normalization of the coregistered T1, non-EPI T2\*, and EPI volumes were normalized, to matching analogous anatomical regions in a common space (MNI), using the parameters obtained from the T1-weighted segment routine previously described. (final dimension 79×95×79 and final voxel size 2×2×2 mm<sup>3</sup>), and (5) smoothing of EPI volumes using a 4mm FWHM (full-width at half-maximum) Gaussian kernel.

For further processing, the CONN Toolbox was used for resting-state functional connectivity processing and analysis too (Functional connectivity Toolbox; <https://www.nitrc.org/projects/conn>, Whitfield-Gabrieli & Nieto-Castanon, 2012) and included the following steps: noise reduction preprocessing (see Figure 2), first-level (individual) analysis, and second-level (group) analysis.

*Noise reduction preprocessing.* The denoising step was applied on all preprocessed data to minimize the influence of physiological sources (head motion, heart rate, and breathing), and reduce inter-subject variability. EPI volumes were filtered with the covariates from the T1 volume segmentation, including gray matter, white matter and cerebrospinal fluid. Temporal frequencies below 0.008 Hz or above 0.09 Hz were then removed from the Blood Oxygenation Level Dependent (BOLD) time series (Hallquist et al. 2013).

# \*\*\*\*\*Figure 1\*\*\*\*\*

## Statistical analyses

### *Whole brain comparison of resting-state fMRI connectivity between young and older adults*

*First level analysis.* Brain regions were identified using the Harvard-Oxford probabilistic anatomical brain atlas combined with the Automated Anatomical Labeling atlas (Desikan et al., 2006; Tzourio-Mazoyer et al., 2002) composed of 48 seed cortical regions

called region of interest (ROI). For each individual, the CONN toolbox created subject-specific files including connectivity means of the 48 seed regions of the brain atlas. Then, bivariate Pearson's correlation coefficients were calculated for each participant between the time course of each region from the atlas and the time course of all the other regions of the atlas ( $48 \times 48$  matrices). Correlation coefficients were then converted to normally distributed scores using Fisher Z-transformation. These matrices were used for whole-brain ROI-to-ROI connectivity in the second level analysis.

*Second level analysis.* Following the computation for each subject of connectivity matrices, a ROI-to-ROI functional connectivity analysis was performed to compare all functional brain connection patterns between the groups of young and older participants. The 48 ROIs of the Harvard-Oxford atlas were considered, with a total of 1152 possible pairs of regions. We used two-sample t-tests with the hypothesis of a decrease in resting-state functional connectivity in older adults compared to young ones. The reverse contrast was also performed. Type I error was controlled by cluster-level false discovery rate (FDR) correction ( $p < 0.05$ ).

### ***Comparison of PM scores between young and older adults***

TBPM scores and those obtained for the ongoing task were compared between groups using Student *t* tests. To measure the magnitude of the effects, we also computed Cohen's *d* (Cohen 1988). Cohen defines effect sizes as small when *d* is approximately 0.2, medium when *d* is approximately 0.5, and large if *d* exceeds 0.8. TBPM scores were used in regression analyses between performance and resting-state functional measures.

### ***Regression analyses***

After the second level (i.e., group) analysis, for all participants, connectivity values (correlation coefficients Fisher Z-transformed) for each significant pairwise regions obtained in the second level ROI-to-ROI analysis were extracted. In other words, we obtained a mean

measure of resting-state functional connectivity between two regions that were functionally connected (named pairwise ROI-to-ROI). Then, pairs of regions with resting-state functional hypoconnectivity in older adults compared to young ones were correlated separately with TBPM scores of older adults (68 regressions). In order to compare, the pattern of results between groups, regressions were also performed in the group of young participants, Resting-state functional connectivity values associated with TBPM scores were then correlated with fractional anisotropy in white matter tracts associated with TBPM performance in ageing. For this second step, we focused on white matter tracts that were identified in our previous study conducted in the same sample of participants (Morand et al., 2021).

Statistical analyses were carried out using R-based open-source software Jamovi (<https://www.jamovi.org>). As we assumed both positive (i.e., hyperconnectivity) or negative (i.e., hypoconnectivity) between resting-state functional connectivity and TBPM scores, and between resting-state functional connectivity and white matter fractional anisotropy, the significance threshold was set at  $p < 0.05$ , two-tailed.

## Results

### *Effect of age on TBPM*

Group comparisons on TBPM performance revealed that, while the two groups had equivalent performance for the ongoing task ( $t_{43} = 0.78$ ,  $p = 0.48$ ,  $d = 0.23$ ; Figure 2), older adults recalled fewer intentions than young ones ( $t_{43} = 4.06$ ,  $p < 0.001$ ,  $d = 1.21$ ; Figure 2).

\*\*\*\*\*Figure 2\*\*\*\*\*

### *Age-related changes in resting-state functional connectivity*

When performing the ROI-to-ROI analyses, older adults showed lower connectivity in 68 pairs of regions throughout the brain compared to young participants (Figure 3, see Appendix A for details). Lower functional connectivity involved posterior regions more than

anterior ones, notably occipital regions (temporo-occipital and occipital fusiform gyri, intra- and supra-calcarine cortex, lingual gyrus, cuneal cortex and occipital pole), parietal areas (supplementary motor area, pre- and post-central gyri, parietal operculum cortex), temporal areas (superior and middle temporal gyri, Heschl's gyrus, planum temporale, central operculum cortex) as well as the amygdala and parahippocampal gyrus. Only one pairwise connectivity, between the right supplementary motor area and the right inferior frontal gyrus, was found to be higher in older adults compared to young ones.

**\*\*\*\*\*Figure 3\*\*\*\*\***

***Relationships between resting-state functional alterations and TBPM performance***

Each pair of regions that were hypoconnected at rest in older adults was then entered in a regression analysis to investigate the association between resting-state functional alterations and TBPM performance. This analysis revealed positive correlations (see Figure 4 and Appendix B for details) between TBPM scores and pairwise ROI-to-ROI resting-state functional connectivity, mainly involving the left precentral gyrus with the right central operculum ( $r = 0.57$ ,  $p < 0.01$ ), the left temporo-occipital fusiform gyrus with the right supplementary motor area ( $r = 0.49$ ,  $p < 0.05$ ), and the right planum temporale with the right postcentral gyrus ( $r = 0.45$ ,  $p < 0.05$ ). In addition, we have decided to keep the trends as these results are also interesting. Trends were also observed between the central operculum region, either right (with the left supplementary motor area [ $r = 0.42$ ,  $p = 0.069$ ]), or left (with the right supplementary motor area [ $r = 0.44$ ,  $p = 0.054$ ], with the right precentral gyrus [ $r = 0.42$ ,  $p = 0.067$ ]). Moreover, age-related TBPM decline is associated to reduced connectivity between the left central operculum cortex and the right central operculum cortex ( $r = 0.44$ ,  $p = 0.051$ ). A negative correlation with TBPM was observed as a trend between the right postcentral gyrus with the left intracalcarine cortex ( $r = -0.43$ ,  $p = 0.059$ ).

The hyperconnectivity identified between the supplementary motor area and the inferior frontal gyrus operculum cortex was not related to TBPM performance.

To control for the specificity of relationship between lower connectivity associated with TBPM performance, regression analyses were conducted with scores obtained during the ongoing task. This analysis did not revealed any significant correlations between lower connectivity and performance on the ongoing task.

\*\*\*\*\***Figure 4**\*\*\*\*\*

***Relationships between white matter disruption and resting-state functional alterations associated with TBPM decline***

To better understand the relationships between structural and functional connectivity alterations on TBPM decline in aging, regression analyses were performed between significant resting-state functional connectivity alterations related to TBPM performance (=3 pairs) and white matter alterations measured by fractional anisotropy also correlated with TBPM performance (=5 white matter tracts). These tracts, previously identified in the same individuals (Morand et al., 2021), include the right posterior corona radiata, the right fornix, the right external capsule, the left retrolenticular part of the internal capsule and the right posterior thalamic radiation. Thus, each of the hypoconnected pairs was correlated to each of the white matter tracts.

These analyses did not reveal any significant associations between the integrity of the right posterior corona radiata and resting-state functional alterations. Only trends were observed and reported, namely concerning the right central operculum with the left precentral gyrus ( $r = 0.40$ ,  $p = 0.07$ ), and the right planum temporale with the right postcentral gyrus ( $r = 0.42$ ,  $p = 0.06$ ).

## Discussion

The main objective of the present study was to investigate whether alterations in resting functional connectivity in older adults may play a role in the age-related decline in TBPM. We also explored the relationship between white-matter integrity and resting-state functional connectivity alterations, and whether these changes subserved the age-related decline in TBPM.

Our findings indicate that TBPM performance was lower in older adults compared to young individuals, while both groups performed similarly on the ongoing task. As previously reported in the literature, older adults have greater difficulties with executive control to monitor time, which impairs their TBPM performance (Einstein et al., 1995).

The analysis of resting-state functional connectivity revealed a functional hypoconnectivity between middle and posterior regions (i.e., temporal, parietal, and occipital areas) in older adults compared to young ones. These results are consistent with previous resting-state functional MRI studies in normal ageing (Jockwitz et al. 2017; Varangis et al. 2019). Although some studies also showed a hypoconnectivity between frontal regions included in the DMN and the fronto-parietal network (Damoiseaux et al. 2008; Koch et al. 2010), we did not find resting-state hypoconnectivity in anterior regions in the present study. This can be explained by the fact that our group of older adults was slightly younger (mean age 62.5 years) than the participants included in the studies reporting hypoconnectivity within anterior regions (for instance 70 years in average in Damoiseaux et al., 2008). These results suggest that resting-state functional connectivity of anterior regions may be affected later than that of posterior ones. This result is supported by the study by Staffaroni et al. (2018) showing that frontal resting-state connectivity increased between 55 and 65 years old. According to the neurocognitive models of ageing, the difference in resting-state connectivity between anterior



and posterior regions fits well with the PASA (i.e. Posterior-Anterior Shift in Aging) model (Davis et al. 2008). This model suggests that the pattern of neural activity changes with age and results in a decrease in activity in posterior regions, while anterior regions increase their activity due to compensatory processes. These alterations concern brain regions involved in the salience network, the posterior part of the FPN, the somatomotor network, as well as the visual network, previously shown to be affected in ageing (Onoda et al. 2012; Betzel et al. 2014; Madhyastha and Grabowski 2014; Marstaller et al. 2015).

Our findings, although exploratory and some trends, suggest for the first time that alterations of resting-state functional connectivity contribute to TBPM decline in ageing. Interestingly, the central operculum cortex, whose functional connectivity at rest with the precentral gyrus is impaired, is associated with TBPM performance. The operculum cortex is a part of the cingulo-opercular “salience” network (Touroutoglou et al. 2012) which is considered as an attentional system, allowing to identify relevant stimuli in the environment in order to guide behavior (Menon and Uddin 2010; Uddin 2015). Brain areas belonging to the cingulo-opercular salience network (i.e., the central operculum cortex) may play a role in the detection of relevant stimuli in the environment. They also may be involved in the attentional shift between bottom-up information (salient information) and top-down information. In our paradigm, this network may be recruited to monitor and detect the appropriate moment to execute TBPM intentions during the ongoing task (McDaniel et al. 2013; Cona et al. 2015; Shelton and Scullin 2017). The salience network is interconnected with the fronto-parietal executive network (Menon and Uddin 2010; Nomi et al. 2018). We found that at rest, the central operculum cortex is hypoconnected with the supplementary motor area, which is part of the fronto-parietal executive network (Mălîia et al. 2018) and the precentral gyrus, involved in the somatomotor network (Yeo et al. 2011). The FPN is involved in clock check response, monitoring, and integration of time intervals (Oksanen et

al. 2014). In this network, the supplementary motor area may subserve cognitive control, in particular the preparation of responses adapted to goals and actions programming (Nachev et al. 2008; Coxon et al. 2016) and task switching (Rushworth et al. 2002). Both networks are involved in attention/motor control processes (Hoffstaedter et al. 2015; Coxon et al. 2016; Jockwitz et al. 2017; Hausman et al. 2020). Our results also suggest that alterations in the somatomotor network (i.e., the planum temporale, the precentral and postcentral gyri) may have an impact on TBPM performance, potentially through difficulties in intention maintenance along the task.

TBPM is subserved by the fronto-parietal executive functional network (Gonneaud et al., 2014 ; Momennejad & Haynes, 2012). This network includes the insula, involved in the recognition of target time (Menon & Uddin, 2010), and the supplementary motor area involved in intention execution (Gonneaud et al., 2014). The postcentral gyrus would be involved in intention encoding and retrieval (Eschen et a., 2007), and the precuneus would subserve attentional processes and time monitoring (Momennejad & Haynes, 2012). The alterations in resting-state connectivity that we found concern regions involved in PM and belonging to resting state networks: i) the sensorimotor network involved in intention encoding, ii) the cingulo-opercular cognitive control network involved in visuo-spatial attention and task alternation (ongoing and PM task), and iii) the fronto-parietal executive network involved in intention retrieval and execution. Overall, we found that resting-state hypoconnectivity of cortical regions involved in the salience, fronto-parietal and somatomotor networks may explain difficulties of older adults to monitor time, switch between the ongoing and TBPM tasks and maintain self-initiated processes.

Our results suggest a direct link between age-related decline in TBPM performance and specific resting-state functional connectivity alterations. Given these results, the question that arises now is how alterations in functional connectivity at rest can impact functional

connectivity during a cognitive task. We hypothesized that with ageing, alterations in resting-state networks may lead to defects in synchronization between these regions. The fact that regions communicate less efficiently will alter their deactivation during cognitive tasks. Thus, when older individuals perform a PM task, they may have difficulties to disengage resting-state networks.. In the same group of participants, Gonneaud et al. (2017) reported that PM functional networks became less specific with ageing. Indeed, specific patterns of brain activation were observed for EBPM and TBPM in young adults. However, similar analyses in older individuals failed to reveal a functional specialization according to the type of intention. These results suggest a dedifferentiation process in the course of ageing, explained by difficulties to recruit specific neuronal mechanisms and to disengage some regions during the task. This dedifferentiation process could be a consequence of an insufficient deactivation of resting-state functional networks (Malagurski et al. 2020).

Resting-state networks are composed of many anatomically distinct cortical regions. Structural connectivity contributes to functional communication at rest between these regions (Greicius et al. 2009; van den Heuvel and Hulshoff Pol 2010), and relies notably, on the integrity of white matter bundles that support information transfer between regions. Our study also aimed at determining whether the decline in prospective memory is related to both alterations in functional connectivity at rest and white matter bundle damage. Contrary to our expectations, age-related functional connectivity at rest was not significantly associated with changes in white matter connections. The lack of association may be explained by the small size of the group of older adults, or by the fact that structural and functional changes do not occur according to the same temporality. Interestingly, if the functional and structural communication between these regions is impaired, this may lead to difficulties in maintaining and retrieving intentions (Morand et al. 2021).

Since the sample size remains relatively small, we could only do an exploratory analysis and therefore not correct for multiplicity at the risk of discarding potentially interesting results (Schulz and Grimes, 2005). FDR corrections for multiple comparisons were applied to identify the regions that have a certain variability with respect to age at the group level. We wanted to make sure, as much as possible, that these results were not driven by false positives. The exploratory nature of this study potentially provides new insights into the relationship between neural substrates and decline in prospective memory in ageing that should be replicated in larger cohorts. Although exploratory, this study adds to the actual knowledge on cognitive decline in ageing and its neural correlates. It would be interesting in future studies to combine resting state fMRI with activation fMRI in order to explore network dynamics over time when a prospective memory task is added.

## **Conclusions**

Our study reveals that alterations in resting-state functional connectivity, especially in the salience and the fronto-parietal networks, contribute to age-related decline in TBPM. PM deficits are frequent in the aging, even more so in patients with Alzheimer's disease. A better understanding of the neural substrates of these deficits will allow for a better management of patients, enabling them to better preserve their autonomy with age.

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## **Ethics approval**

This study was approved by the Nord-Ouest III French Ethics Committee.

## **Conflict of interest**

418 The authors have no conflicts of interest to disclose.

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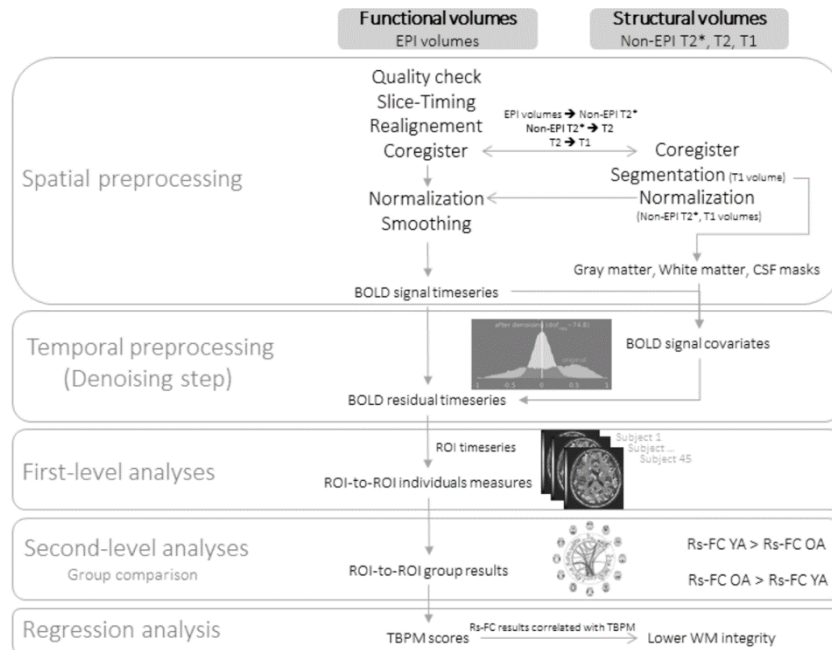
## Tables

**Table 1. Demographic data for healthy young and older adults.**

|   | Young adults ( $n = 22$ ) | Older adults ( $n = 23$ ) | $p$ value            |
|---|---------------------------|---------------------------|----------------------|
| Sex ratio (M/F)                               | 10/12                     | 11/12                     | .87 <sup>1</sup>     |
| Age (years) ( $\pm$ SD)                       | 25.4 ( $\pm$ 5.19)        | 62.5 ( $\pm$ 6.05)        | < 0.001 <sup>2</sup> |
| [Age range]                                   | [18–35]                   | [51–76]                   | -                    |
| Education (years) ( $\pm$ SD)                 | 14.3 ( $\pm$ 2.55)        | 14.4 ( $\pm$ 2.61)        | .67 <sup>2</sup>     |
| MMSE score /30 ( $\pm$ SD)                    | na                        | 28.7 ( $\pm$ 0.82)        | -                    |
| Mattis Dementia Rating Scale /144 ( $\pm$ SD) | na                        | 141.1 ( $\pm$ 2.49)       | -                    |

Note. na: not applicable, SD: standard deviation. <sup>1</sup> $\chi^2$  test; <sup>2</sup> Student t-test

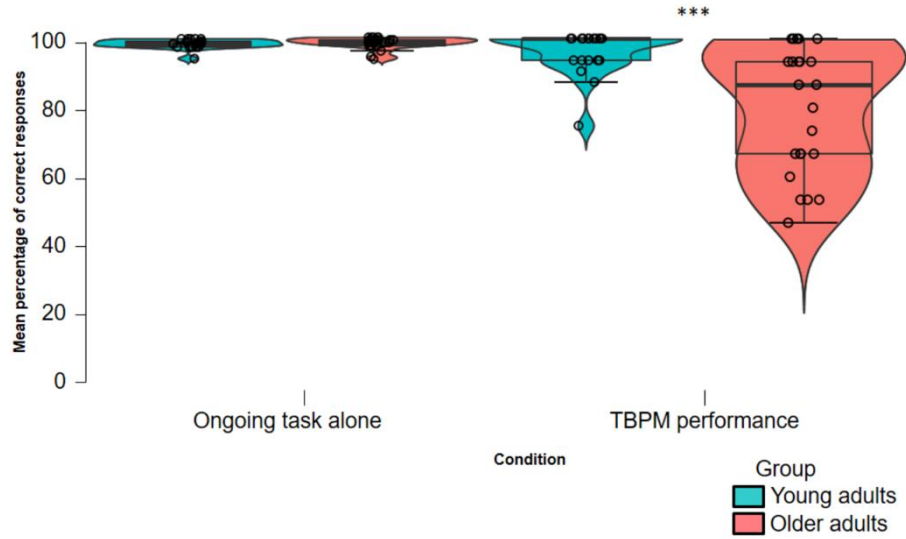
## Figures



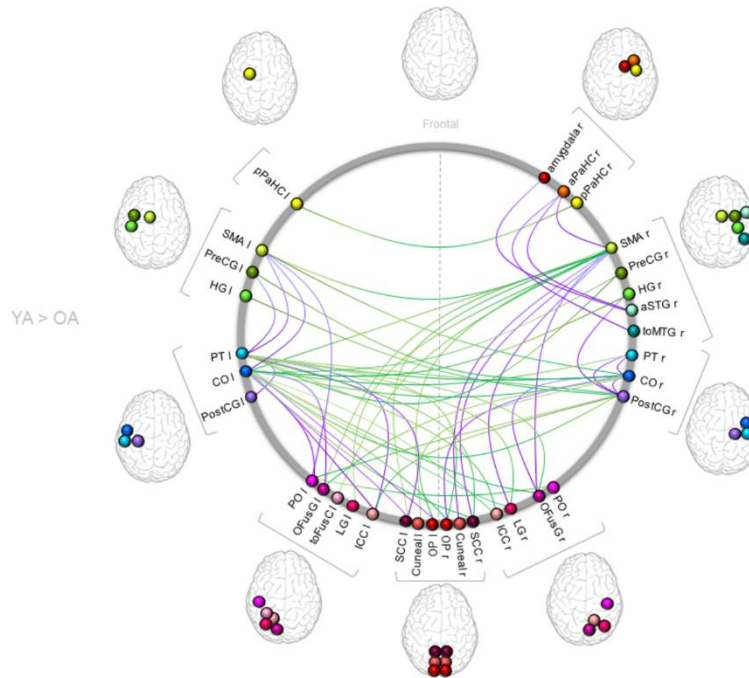
**Figure 1.** Schematic representation of the different steps of resting-state functional connectivity preprocessing and analyses. BOLD: Blood Oxygenation Level Dependent, CSF:



cerebrospinal fluid, OA: older adults, ROI: region of interest, Rs-FC: resting-state functional connectivity, TBPM: time-based prospective memory, YA: young adults, WM: white matter.

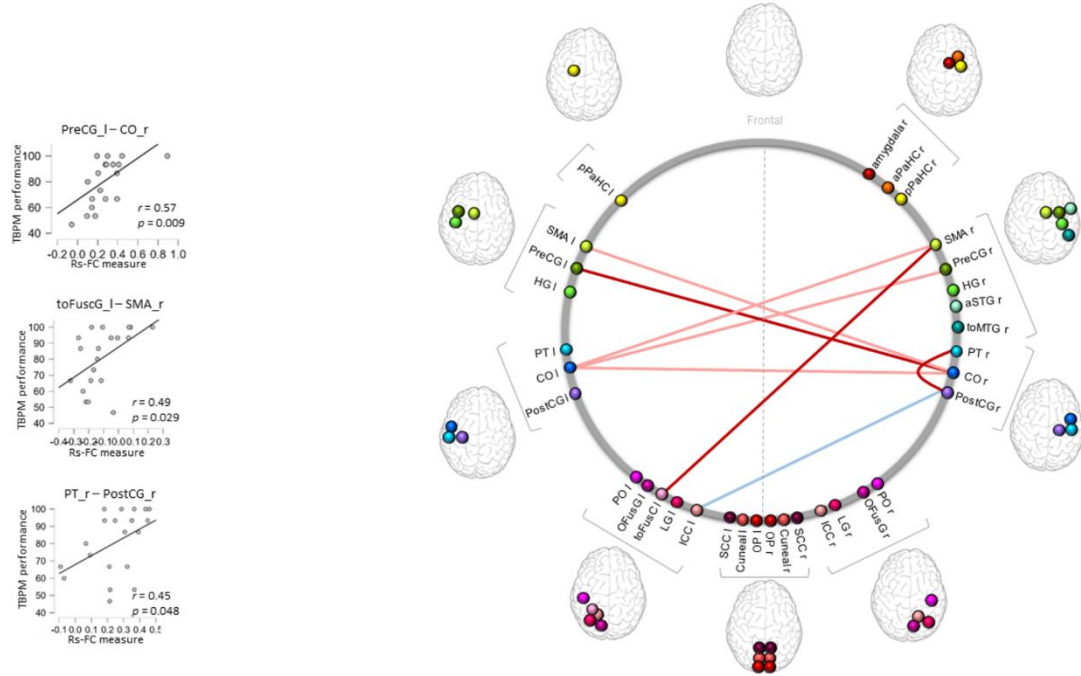


**Figure 2. Prospective memory performance in young and older adults.** Mean percentage of correct responses during the ongoing task and the TBPM task (i.e., prospective items correctly executed) for young and older adults. \*\*\*  $p < 0.001$ .



**Figure 3. Connectogram of significant pairwise functional hypoconnectivity in older adults compared to young ones (young > older adults).** Results are obtained with ROI-to-ROI analyses contrasting young adults minus older ones, at  $p$  FDR-corrected  $< .05$ . purple lines: intra-hemispheric connectivity, green lines: inter-hemispheric connectivity. Abbreviations: **aPaHC**: anterior parahippocampal cortex; **aSTG**: anterior superior temporal

gyrus; **CO**: central operculum cortex; **Cuneal**: cuneal cortex; **HG**: Heschl's gyrus; **ICC**: intracalcarine cortex; **LG**: lingual gyrus; **pPaHC**: posterior parahippocampus; **OFusG**: occipital fusiform gyrus; **OP**: occipital cortex; **PostCG**: postcentral gyrus; **PO**: parietal operculum cortex; **PreCG**: precentral gyrus; **PT**: planum temporale; **toFUSC**: temporo-occipital fusiform cortex; **SCC**: supracalcarine cortex; **SMA**: supplementary motor area. **r** = Right hemisphere, **l** = Left hemisphere.



**Figure 4. Connectogram of the associations between TBPM scores and pairwise resting-state functional hypoconnectivity in older adults.** The scatterplots on the left represent regressions results between TBPM scores and significant hypoconnected ROIs (i.e., significant inter-correlations of ROIs). The figure on the right represents a connectogram of hypoconnected pairwise ROIs associated with TBPM scores. Strong red lines represent positive significant correlations at two-tailed threshold whereas lighter red represent trend correlations. The lighter blue lines represents negative trend correlation. Abbreviations: **aPaHC**: anterior parahippocampal cortex; **aSTG**: anterior superior temporal gyrus; **CO**: central operculum cortex; **Cuneal**: cuneal cortex; **HG**: heschl's gyrus; **ICC**: intracalcarine cortex; **LG**: lingual gyrus; **pPaHC**: posterior parahippocampus; **OFusG**: occipital fusiform gyrus; **OP**: occipital cortex; **PostCG**: postcentral gyrus; **PO**: parietal operculum cortex; **PreCG**: precentral gyrus; **PT**: planum temporale; **toFUSC**: temporo-occipital fusiform cortex; **SCC**: supracalcarine cortex; **SMA**: supplementary motor area. **r** = right hemisphere, **l** = left hemisphere.

