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

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30 Running title: Neural substrates of prospective memory decline in aging

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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 ± 5.2 years) and 23 older (63 ± 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

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

37 Recently, we showed that lower TBPM performance in older adults was associated
38 with decreased white matter integrity, especially in tracts of the superior fronto-occipital
39 fasciculus, whereas no correlations with gray matter volume were found (Morand et al.,
40 2021). These results suggest that age-related decline in TBPM may be due to a disconnection
41 phenomenon, rather than neuronal loss. Besides, functional connectivity also changes in the
42 course of ageing, partly due to decreased white matter integrity, altering the communication
43 between regions belonging to various resting-state networks (Andrews-Hanna et al. 2007;
44 Honey et al. 2009). Therefore, resting-state functional connectivity appears as an interesting
45 approach to indirectly explore the neuronal organization at rest and its modification during
46 ageing, overcoming the difficulties older adults may have in performing complex cognitive
47 tasks in the MRI scanner.

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

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

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

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

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

91 **Materials and Methods**

92 **Participants**

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

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

103 *****Table 1*****

104 **Prospective memory assessment**

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

110 • Ongoing task – General procedure

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

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

129 • TBPM task

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

138 **MRI acquisition**

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

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

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

151 For the diffusion tensor imaging (DTI) acquisition, 70 axial slices were acquired with
152 spin echo sequence (32 directions at $b = 1000 \text{ s/mm}^2$, repetition time = 10 000 ms, echo time
153 = 82 ms, flip angle = 90° , field of view = $224 \times 224 \text{ mm}^2$, acquisition matrix = 112×112
154 pixels, acquisition voxel size = $2 \times 2 \text{ mm}^3$, and non-diffusion weighted picture at $b = 0$
155 s/mm^2). The analysis of DTI data was the subject of another publication (Morand et al., 2021)
156 in which the preprocessing steps and analyses were fully described.

157 **Imaging data preprocessing**

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

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

173 T2 and T1 volumes, (2) normalization of the mean EPI volume to match the non-EPI T2*
174 volume, (3) segmentation of T1 volume using the VBM12 procedure to extract gray matter,
175 white matter and cerebrospinal fluid, (4) normalization of the coregistered T1, non-EPI T2*,
176 and EPI volumes were normalized, to matching analogous anatomical regions in a common
177 space (MNI), using the parameters obtained from the T1-weighted segment routine previously
178 described. (final dimension 79×95×79 and final voxel size 2×2×2 mm³), and (5) smoothing of
179 EPI volumes using a 4mm FWHM (full-width at half-maximum) Gaussian kernel.

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

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

191 *******Figure 1*******

192 **Statistical analyses**

193

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

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

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

205 *Second level analysis.* Following the computation for each subject of connectivity
206 matrices, a ROI-to-ROI functional connectivity analysis was performed to compare all
207 functional brain connection patterns between the groups of young and older participants. The
208 48 ROIs of the Harvard-Oxford atlas were considered, with a total of 1152 possible pairs of
209 regions. We used two-sample t-tests with the hypothesis of a decrease in resting-state
210 functional connectivity in older adults compared to young ones. The reverse contrast was also
211 performed. Type I error was controlled by cluster-level false discovery rate (FDR) correction
212 ($p < 0.05$).

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

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

219 *Regression analyses*

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

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

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

237 **Results**

238 *Effect of age on TBPM*

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

242 *******Figure 2*******

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

244 When performing the ROI-to-ROI analyses, older adults showed lower connectivity in
245 68 pairs of regions throughout the brain compared to young participants (Figure 3, see
246 Appendix A for details). Lower functional connectivity involved posterior regions more than

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

254 *******Figure 3*******

255
256 ***Relationships between resting-state functional alterations and TBPM performance***

257 Each pair of regions that were hypoconnected at rest in older adults was then entered
258 in a regression analysis to investigate the association between resting-state functional
259 alterations and TBPM performance. This analysis revealed positive correlations (see Figure 4
260 and Appendix B for details) between TBPM scores and pairwise ROI-to-ROI resting-state
261 functional connectivity, mainly involving the left precentral gyrus with the right central
262 operculum ($r = 0.57$, $p < 0.01$), the left temporo-occipital fusiform gyrus with the right
263 supplementary motor area ($r = 0.49$, $p < 0.05$), and the right planum temporale with the right
264 postcentral gyrus ($r = 0.45$, $p < 0.05$). In addition, we have decided to keep the trends as these
265 results are also interesting. Trends were also observed between the central operculum region,
266 either right (with the left supplementary motor area [$r = 0.42$, $p = 0.069$]), or left (with the
267 right supplementary motor area [$r = 0.44$, $p = 0.054$], with the right precentral gyrus [$r = 0.42$,
268 $p = 0.067$]). Moreover, age-related TBPM decline is associated to reduced connectivity
269 between the left central operculum cortex and the right central operculum cortex ($r = 0.44$, $p =$
270 0.051). A negative correlation with TBPM was observed as a trend between the right
271 postcentral gyrus with the left intracalcarine cortex ($r = -0.43$, $p = 0.059$).

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

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

278 *******Figure 4*******

279

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

282

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

292 These analyses did not reveal any significant associations between the integrity of the
293 right posterior corona radiata and resting-state functional alterations. Only trends were
294 observed and reported, namely concerning the right central operculum with the left precentral
295 gyrus ($r = 0.40$, $p = 0.07$), and the right planum temporale with the right postcentral gyrus ($r =$
296 0.42 , $p = 0.06$).

297 **Discussion**

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

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

307 The analysis of resting-state functional connectivity revealed a functional
308 hypoconnectivity between middle and posterior regions (i.e., temporal, parietal, and occipital
309 areas) in older adults compared to young ones. These results are consistent with previous
310 resting-state functional MRI studies in normal ageing (Jockwitz et al. 2017; Varangis et al.
311 2019). Although some studies also showed a hypoconnectivity between frontal regions
312 included in the DMN and the fronto-parietal network (Damoiseaux et al. 2008; Koch et al.
313 2010), we did not find resting-state hypoconnectivity in anterior regions in the present study.
314 This can be explained by the fact that our group of older adults was slightly younger (mean
315 age 62.5 years) than the participants included in the studies reporting hypoconnectivity within
316 anterior regions (for instance 70 years in average in Damoiseaux et al., 2008). These results
317 suggest that resting-state functional connectivity of anterior regions may be affected later than
318 that of posterior ones. This result is supported by the study by Staffaroni et al. (2018) showing
319 that frontal resting-state connectivity increased between 55 and 65 years old. According to the
320 neurocognitive models of ageing, the difference in resting-state connectivity between anterior

321 and posterior regions fits well with the PASA (i.e. Posterior-Anterior Shift in Aging) model
322 (Davis et al. 2008). This model suggests that the pattern of neural activity changes with age
323 and results in a decrease in activity in posterior regions, while anterior regions increase their
324 activity due to compensatory processes. These alterations concern brain regions involved in
325 the salience network, the posterior part of the FPN, the somatomotor network, as well as the
326 visual network, previously shown to be affected in ageing (Onoda et al. 2012; Betzel et al.
327 2014; Madhyastha and Grabowski 2014; Marstaller et al. 2015).

328 Our findings, although exploratory and some trends, suggest for the first time that
329 alterations of resting-state functional connectivity contribute to TBPM decline in ageing.
330 Interestingly, the central operculum cortex, whose functional connectivity at rest with the
331 precentral gyrus is impaired, is associated with TBPM performance. The operculum cortex is
332 a part of the cingulo-opercular “salience” network (Touroutoglou et al. 2012) which is
333 considered as an attentional system, allowing to identify relevant stimuli in the environment
334 in order to guide behavior (Menon and Uddin 2010; Uddin 2015). Brain areas belonging to
335 the cingulo-opercular salience network (i.e., the central operculum cortex) may play a role in
336 the detection of relevant stimuli in the environment. They also may be involved in the
337 attentional shift between bottom-up information (salient information) and top-down
338 information. In our paradigm, this network may be recruited to monitor and detect the
339 appropriate moment to execute TBPM intentions during the ongoing task (McDaniel et al.
340 2013; Cona et al. 2015; Shelton and Scullin 2017). The salience network is interconnected
341 with the fronto-parietal executive network (Menon and Uddin 2010; Nomi et al. 2018). We
342 found that at rest, the central operculum cortex is hypoconnected with the supplementary
343 motor area, which is part of the fronto-parietal executive network (Mălîia et al. 2018) and the
344 precentral gyrus, involved in the somatomotor network (Yeo et al. 2011). The FPN is
345 involved in clock check response, monitoring, and integration of time intervals (Oksanen et

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

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

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

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

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

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

406 **Conclusions**

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

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415 **Ethics approval**

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

417 **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 ¹
Age (years) (\pm SD)	25.4 (\pm 5.19)	62.5 (\pm 6.05)	< 0.001 ²
[Age range]	[18–35]	[51–76]	-
Education (years) (\pm SD)	14.3 (\pm 2.55)	14.4 (\pm 2.61)	.67 ²
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. ¹ χ^2 test; ² Student t-test

Figures

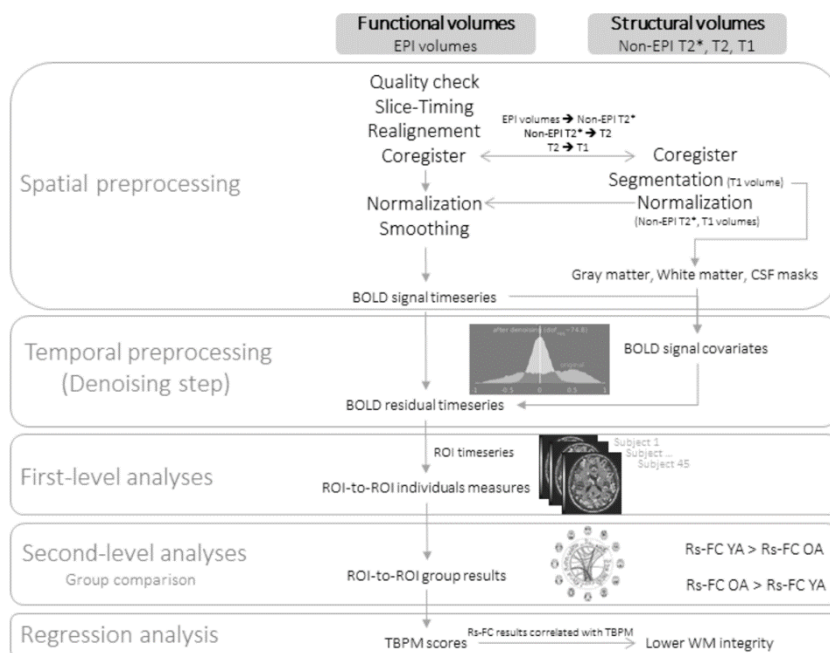


Figure 1. Schematic representation of the different steps of resting-state functional connectivity preprocessing and analyses. BOLD: Blood Oxygenation Level Dependent, CSF:

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.

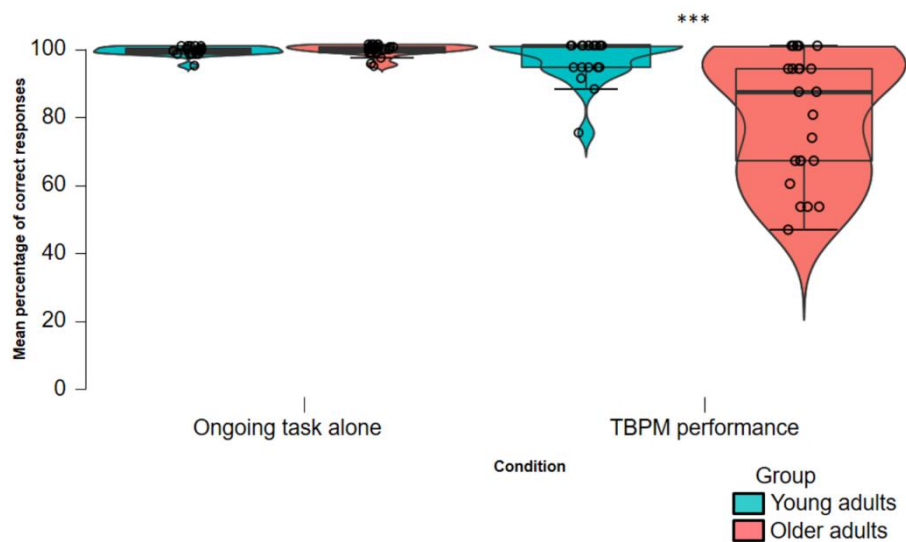


Figure 2. Prospective memory performance in young and older adults. Mean percentage of correct responses during the ongoing task and the TBPM task (i.e., prospective items correctly executed) for young and older adults. *** $p < 0.001$.

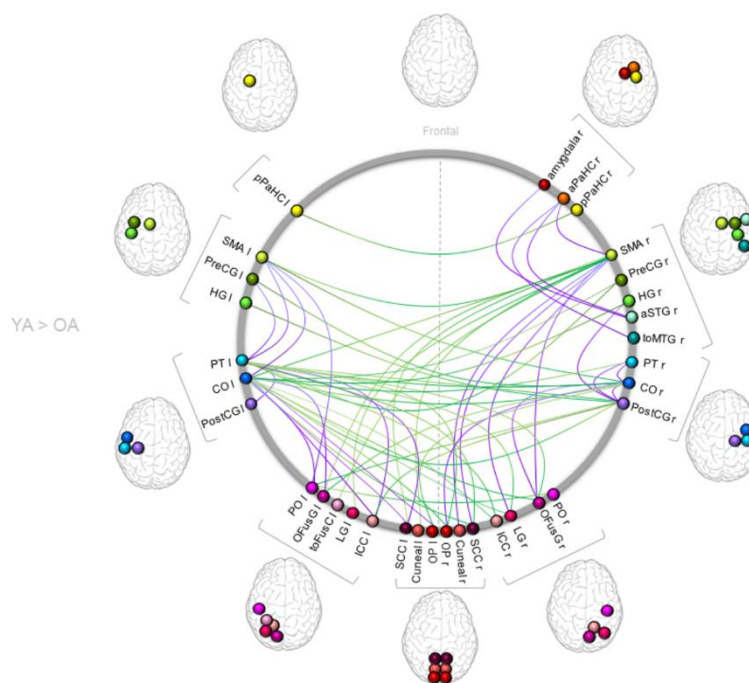


Figure 3. Connectogram of significant pairwise functional hypoconnectivity in older adults compared to young ones (young > older adults). Results are obtained with ROI-to-ROI analyses contrasting young adults minus older ones, at p FDR-corrected $< .05$. purple lines: intra-hemispheric connectivity, 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.

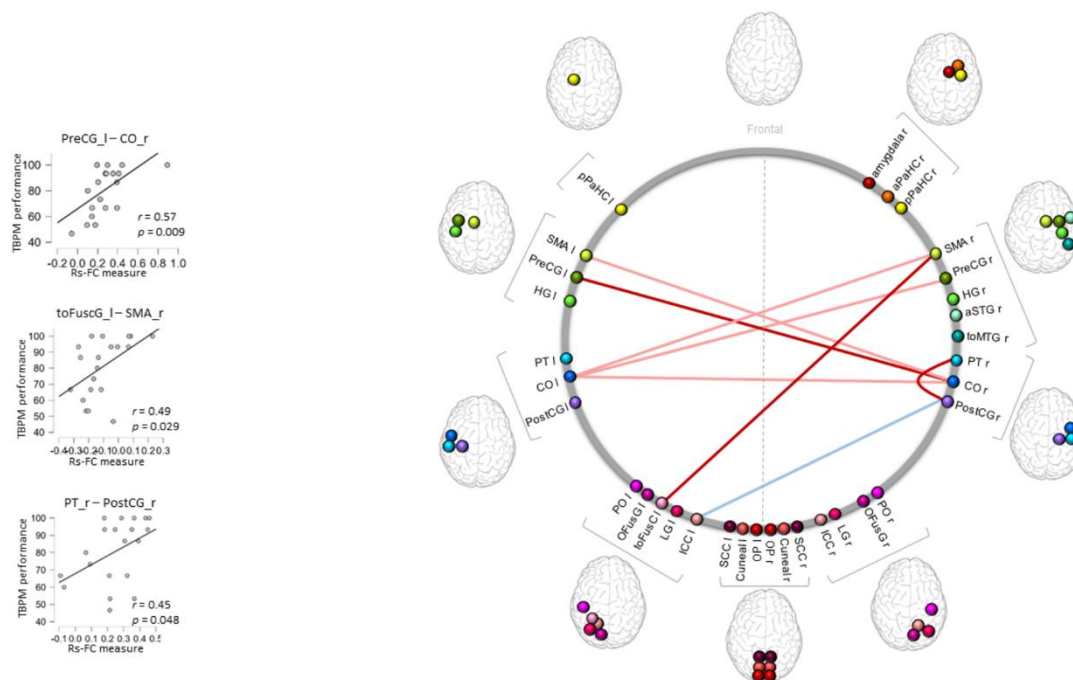


Figure 4. Connectogram of the associations between TBPM scores and pairwise resting-state functional hypoconnectivity in older adults. The scatterplots on the left represent regressions results between TBPM scores and significant hypoconnected ROIs (i.e., significant inter-correlations of ROIs). The 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.

