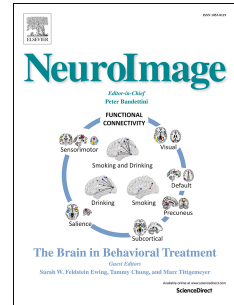


# Journal Pre-proof

Older adults benefit from more widespread brain network integration during working memory

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# Older adults benefit from more widespread brain network integration during working memory

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43 **Abstract**

44 Neuroimaging evidence suggests that the aging brain relies on a more distributed set of cortical  
45 regions than younger adults in order to maintain successful levels of performance during demanding  
46 cognitive tasks. However, it remains unclear how task demands give rise to this age-related expansion  
47 in cortical networks. To investigate this issue, functional magnetic resonance imaging was used to  
48 measure univariate activity, network connectivity, and cognitive performance in younger and older  
49 adults during a working memory (WM) task. Here, individuals performed a WM task in which they held  
50 letters online while reordering them alphabetically. WM load was titrated to obtain four individualized  
51 difficulty levels with different set sizes. Network integration—defined as the ratio of within- versus  
52 between-network connectivity—was linked to individual differences in WM capacity. The study yielded  
53 three main findings. First, as task difficulty increased, network integration decreased in younger adults,  
54 whereas it increased in older adults. Second, age-related increases in network integration were driven  
55 by increases in right hemisphere connectivity to both left and right cortical regions, a finding that helps  
56 to reconcile existing theories of compensatory recruitment in aging. Lastly, older adults with higher WM  
57 capacity demonstrated higher levels of network integration in the most difficult task condition. These  
58 results shed light on the mechanisms of age-related network reorganization by demonstrating that  
59 changes in network connectivity may act as an adaptive form of compensation, with older adults  
60 recruiting a more distributed cortical network as task demands increase.

61

## 62 Introduction

63 Despite substantial anatomical and functional decline, the aging brain retains a surprising degree of  
64 neural plasticity. In functional neuroimaging studies, for example, older adults often activate brain  
65 regions not engaged by younger adults during the same tasks (Cabeza and Dennis, 2013; Park and  
66 Reuter-Lorenz, 2009). Although over-recruitment in older adults is often interpreted as compensatory  
67 (Cabeza et al., 2018), it is unclear if and how the regions over-recruited by older adults are integrated  
68 with the network mediating task performance. To investigate this question, the current study assessed  
69 the effects of aging on network integration, an established concept of interest in characterizing brain  
70 dynamics (Tononi et al., 1994), during a working memory (WM) manipulation task. The study had three  
71 main goals.

72 The first goal of the study was to examine how the effects of age on network integration differ as a  
73 function of WM demands. As the number of items maintained in WM (load) increases, brain activity  
74 tends to rise monotonically in several regions, including dorsolateral prefrontal cortex (DLPFC) and  
75 lateral parietal cortex (LPC, Beauchamp et al., 2001; Braver et al., 1997; Rypma et al., 1999; Veltman  
76 et al., 2003). These activations tend to increase more rapidly in older than younger adults up to a  
77 certain level of WM demands (Cappell et al., 2010; Low et al., 2009; Schneider-Garces et al., 2010).  
78 According to the Compensation-Related Utilization of Neural Circuits hypothesis (CRUNCH, Reuter-  
79 Lorenz and Cappell, 2008), due to processing inefficiencies, older adults over-recruit neural resources  
80 at lower levels of task difficulty than younger adults. What is unclear from available CRUNCH evidence  
81 is whether the accelerated brain recruitment in older adults is limited to the activation of individual  
82 regions or whether it involves a reorganization of the underlying task network. Much recent work has  
83 focused on mapping functional brain networks in older adults, and a number of these more recent  
84 investigations of age-related changes in multivariate network connectivity have shown that PFC regions  
85 over-recruited by older adults often show stronger long-range functional connectivity outside of local  
86 cortical communities, and these changes are often associated with differences in cognitive performance

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87 (Damoiseaux et al., 2016; Geerligts et al., 2014; Geerligts et al., 2015; Geerligts et al., 2017). In the  
88 current study, therefore, we hypothesized that as task demands increase, the WM network would  
89 become more integrated with the rest of the brain and this effect would be greater for older than  
90 younger adults (Hypothesis 1).

91 The second goal of this study was to examine hemispheric differences in network integration for  
92 young and older adults. In functional neuroimaging studies, activations are often more bilateral in older  
93 adults than younger adults, an effect known as Hemispheric Asymmetry Reduction in Older Adults  
94 (HAROLD, Cabeza, 2002). For example, during a verbal WM task that yields left lateralized activations  
95 in younger adults, older adults may show additional activity in the right hemisphere (Reuter-Lorenz et  
96 al., 2000). As in the case of CRUNCH, most evidence for HAROLD is based on univariate activity in  
97 individual regions, and hence, the network mechanisms of age-related hemispheric differences remain  
98 uncertain. In the current study, we therefore hypothesized that during the left-lateralized verbal WM  
99 task, older adults would show greater demand-related network integration in the right-hemisphere  
100 (Hypothesis 2).

101 The third goal of the study was to investigate if age-related changes in network integration relate to  
102 individual differences in WM performance. It has been suggested that more widespread activity in older  
103 adults is beneficial for performance (Cabeza and Dennis, 2013; Park and Reuter-Lorenz, 2009), and  
104 both CRUNCH and HAROLD effects have been interpreted as compensatory. However, the evidence  
105 for compensation has been mostly based on univariate activity and evidence that network changes in  
106 older adults contribute to cognitive performance is largely missing (however, see Monge et al., 2018).  
107 We hypothesized that age-related WM network integration would be associated with WM ability in older  
108 adults (Hypothesis 3).

109 To test these hypotheses, participants completed a verbal WM manipulation task in which they  
110 briefly maintained consonants in memory while mentally rearranging them into alphabetical order. fMRI  
111 analyses focused on the effects of WM load on functional connectivity during the delay period, while the

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112 WM network was defined as regions activated by the task irrespective of load. Here, network  
113 integration was measured as the ratio of within- versus between-network connectivity, while network  
114 integration was compared within and between hemispheres, and correlated with WM capacity to test  
115 the three stated hypotheses.

## 116 Materials and Methods

### 117 Participants

118 Forty-four young adults aged 18 to 35 (21 females; mean age  $22.8 \pm 4.6$ ) and 32 older adults aged  
119 60 to 80 (15 females; mean age  $69.1 \pm 5.3$ ) participated in the study for monetary compensation and  
120 consented to the protocol approved by the Duke Medical School IRB (#Pro00065334). All subjects  
121 were self-reported right-handed. Older adults were screened for possible incidence of dementia, as  
122 measured by a Mattis Dementia Rating Scale-2 (DRS-2) total scaled score below 8 (Jurica et al., 2001).  
123 Qualifying participants were enrolled in a 6-day TMS protocol (Beynel et al., 2019; Beynel et al., in  
124 review), but only data from the screening session (Day 1) and MRI session (Day 2) are reported here.  
125 Participants had no history of psychiatric or neurological disorders and were not using psychoactive  
126 drugs. Participants were excluded because of poor functional imaging quality (excessive movement or  
127 falling asleep during data acquisition,  $n=3$ ), or due to poor task performance in the scanner (accuracy  
128 greater than two standard deviations below the group mean,  $n=6$ ). Thus, 37 young adults and 30 older  
129 adults were included in the final analysis.

### 130 Experimental Design and Statistical Analyses

#### 131 *Behavioral procedure and task design*

132 Participants performed a verbal *WM manipulation task* (**Fig. 1A**). In this task, an array of 3 to 9  
133 consonant letters was presented for 3 seconds followed by a 5-second delay period, during which  
134 participants mentally rearranged letters into alphabetical order. Vowels were excluded to prevent

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135 chunking. After the delay period, a letter and number were presented together for 4 seconds and the  
136 participants pressed one of three buttons to indicate if the probe letter (1) appeared in the position  
137 indicated by the number in the alphabetized list (*Valid*, 40% of trials), (2) was part of original set but the  
138 number did not match the position in the alphabetized list (*Invalid*, 40% of trials), or (3) was not part of  
139 the original set (*New*, 20% of trials). These three types of trials occurred in random order. During the  
140 subject-specific titration on Day 1 (see the following paragraph), the response phase was followed by a  
141 5-second inter-trial interval (ITI). During practice, participants were given feedback during this ITI on  
142 their accuracy after each trial, and at the end of each block. Twenty-five trials were included in each of  
143 the 6 blocks with a brief, self-paced rest interval between blocks.

144 *[Figure 1 here]*

145 As part of the overall protocol, subjects participated in up to 6 experimental sessions, but only the  
146 first two are relevant to this study. In the first session, participants performed the WM manipulation task  
147 outside the scanner in order to identify the range of WM loads producing parametric changes in  
148 performance for each participant. The optimal load was identified using 2-down-1-up staircase  
149 procedure: when a trial was answered correctly, the load was increased by 1, and when it was  
150 answered incorrectly, the load was decreased by 2. New trials were excluded from the analysis and  
151 accuracy data, collapsed across Valid and Invalid trials at each load, were then fitted to a sigmoid  
152 function with performance threshold criterion set at 82% accuracy. To ensure that the psychometric  
153 function was not strongly influenced by noise in loads with a low number of trials, 50% accuracy was  
154 used for the largest loads if less than 10 trials were tested. To achieve more stable curve fits, anchors  
155 were added by including points for loads of 1 and 2 at 100% accuracy and loads 10 and 11 at 50%  
156 accuracy. Four individualized difficulty levels were defined according to the intersection between the  
157 sigmoid curve and an 82% accuracy threshold, referred to here as WM capacity (for similar staircase  
158 approaches, see Garcia-Perez, 1998). The two loads below this intersection were defined as the Very  
159 Easy and Easy levels, and the two loads above were defined as the Medium and Hard levels. Thus, the

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160 four Absolute Loads selected for an individual depended on his/her WM ability (e.g., 3-4-5-6 letters in  
161 one participant, 4-5-6-7 in another participant) and therefore potentially reduced state-dependency that  
162 would be caused by fixed difficulty levels that do not match individual capabilities. Furthermore, given  
163 the intensive testing schedule inherent in our 6-session protocol, we excluded participants who could  
164 not accurately perform the WM task. Participants for whom this curve-fitting procedure (based on Day 1  
165 data) did not estimate a minimum set size of at least 3 letters were excluded from subsequent imaging  
166 and rTMS sessions. As such, for clarity the Very Easy, Easy Medium and Hard conditions are referred  
167 to as *WM Difficulty Levels*. Individual sigmoid curves for all young and older adults, and subsequent  
168 determination of their Starting Load (i.e. the Absolute Load value of the Very Easy condition), are  
169 shown in **Figure 1B**.

170 In the second session, participants performed the WM manipulation task inside the MRI scanner.  
171 Four blocks, each with 30 trials, were performed using the 4 individually-titrated Difficulty Levels. Stimuli  
172 were back-projected onto a screen located at the foot of the MRI bed using an LCD projector. Subjects  
173 viewed the screen via a mirror system located in the head coil and the start of each run was  
174 synchronized with the MRI acquisition computer. Trial-by-trial feedback was not given, but the overall  
175 block accuracy was presented at the end of each block. Behavioral responses were recorded with a 4-  
176 key fiber-optic response box (Resonance Technology, Inc.). Scanner noise was reduced with ear plugs,  
177 and head motion was minimized with foam pads. When necessary, vision was corrected using MRI-  
178 compatible lenses that matched the distance prescription used by the participant. The total scan time,  
179 including breaks and structural scans, was approximately 1 hour 40 minutes.

### 180 *MRI scanning and data preprocessing*

181 MRI was performed in a 3-T GE scanner at the at Duke Brain Imaging Analysis Center (BIAC).  
182 Structural MRI and diffusion-weighted imaging (DWI) scans were followed by performing 4 fMRI runs of  
183 the WM manipulation task. The anatomical MRI was acquired using a 3D T1-weighted echo-planar  
184 sequence (matrix = 256 x 256, time repetition (TR) = 7.15 ms, time echo (TE) = 2.7 ms, field of view

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185 (FOV) = 256mm<sup>2</sup>, slices = 196, slice thickness = 1 mm). In the fMRI runs, coplanar functional images  
186 were acquired using an inverse spiral sequence (64 × 64 matrix, TR = 2000 ms, TE = 25 ms, FOV =  
187 220mm<sup>2</sup>, 34 slices, 4 mm slice thickness, 280 images). Finally, DWI data were collected using a single-  
188 shot echo-planar imaging sequence (TR = 17000 ms, slices = 76, thickness = 2.0 mm, FOV = 256 ×  
189 256 mm<sup>2</sup>, matrix size 128 × 128, voxel size = 2 mm<sup>3</sup>, b value = 2000 s/mm<sup>2</sup>, diffusion-sensitizing  
190 directions = 26, total images = 960, total scan time = 7.5 min).

191 Functional images were preprocessed using image processing tools, including FLIRT and FEAT  
192 from the fMRIB Software Library (FSL), in a publicly available pipeline developed by the Duke Brain  
193 Imaging and Analysis Center ([https://wiki.biac.duke.edu/biac:analysis:resting\\_pipeline](https://wiki.biac.duke.edu/biac:analysis:resting_pipeline)). Images were  
194 corrected for slice acquisition timing, motion, and linear trend; motion correction was performed using  
195 MCFLIRT, and 6 motion parameters estimated from the step were then regressed out of each  
196 functional voxel using standard linear regression. A comparison of mean displacement across all  
197 functional runs between younger and older adults revealed no group differences ( $t_{66} = 1.21$ ).  
198 Nonetheless, motion regressors were used in all univariate models, and included in all subsequent  
199 correlational psychophysical interaction (cPPI) analyses (see below) to adjust for any potential  
200 confounds due to motion. Images were then temporally smoothed with a high-pass filter using a 190-  
201 second cutoff and normalized to the Montreal Neurological Institute (MNI) stereotaxic space. White  
202 matter and CSF signals were also removed from the data, using white matter/CSF masks generated by  
203 FSL's FAST and regressed from the functional data using the same method as the motion parameters.  
204 Spatial filtering with a Gaussian kernel of full-width half-maximum (FWHM) of 8 mm was applied.

### 205 *Behavioral analyses*

206 Accuracy and reaction times (RTs) of WM manipulation trials were analyzed for each individually-  
207 titrated WM Difficulty Level. RTs were analyzed, only for correct trials (74.6% of total trials), using a  
208 linear restricted maximum likelihood model. Accuracy was analyzed using a binomial logistic regression  
209 model including all trials. In both models, R (R Core Team, 2012) and lme4 (Bates et al., 2012) were

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210 used to perform mixed effects analysis. WM Difficulty Level was entered as a fixed effect, and both  
211 model intercepts and by-subject random slopes across WM Difficulty Levels were included as random  
212 effects. Gender and each subject's WM capacity were also included to account for standardizing  
213 difficulty levels across subjects and general differences in task ability. No deviations from  
214 homoscedasticity or normality were observed. P-values were obtained by likelihood ratio tests of the full  
215 model with the variable in question against a null model without the variable in question using an  
216 ANOVA to compare the model fits. There was no missing data, but in 1.8% of trials participants failed to  
217 respond within the 4-second response window (143 out of 8040 trials); these trials were excluded from  
218 all analyses.

### 219 *fMRI analyses*

220 A parametric approach was used to investigate how activity varied as a function of WM load. First-  
221 level voxel time-series analysis was carried out using general linear modeling (GLM); fixed effects  
222 models were carried out to examine the effects of load; separate events were modeled for the array  
223 presentation (duration: 3 seconds), delay period (duration: 5 seconds), and response (duration: subject  
224 reaction time), each with an onset at the beginning of the event. Four separate delay-period regressors  
225 were used to model each of the WM Difficulty Levels for each subject; correct valid and correct invalid  
226 responses were modeled under the same task regressor; despite decreasing accuracy in difficulty  
227 conditions, the number of correct trials in each condition was still sufficient for fMRI response estimation  
228 (mean trial count = 23, 23, 21, 20 across difficulty levels). Incorrect and non-response trials were  
229 modeled identically, but separately, and were not considered in the univariate results below.  
230 Subsequent to individual-level models, random-effects analysis was performed on parameter estimates  
231 of the delay-period regressors ( $p < 0.005$ ). Subsequent group-level analyses were performed across  
232 the four delay-period regressors in SPM12.

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233 *Cortical parcellation*

234 Before functional matrices were constructed, a consistent parcellation scheme was established  
235 across all subjects that reflects an accurate summary of full connectome effects (Bellec et al., 2015).  
236 Subjects' T1-weighted images were segmented using SPM12  
237 ([www.fil.ion.ucl.ac.uk/spm/software/spm12/](http://www.fil.ion.ucl.ac.uk/spm/software/spm12/)), yielding a grey matter (GM) and white matter mask in the  
238 T1 native space for each subject. The entire GM was then parcellated into 471 regions of interest  
239 (ROIs), each representing a network node by using a subparcellated version of the Harvard-Oxford  
240 Atlas (HOA), (Tzourio-Mazoyer et al., 2002), defined originally in MNI space. Subsequent follow-up  
241 analyses utilized a parcellation scheme defined by Yeo and colleagues (2011), also defined in MNI  
242 space. The T1-weighted image was then nonlinearly normalized to the ICBM152 template in MNI space  
243 using fMRIB's Non-linear Image Registration Tool (FNIRT, FSL, [www.fmrib.ox.ac.uk/fsl/](http://www.fmrib.ox.ac.uk/fsl/)). The inverse  
244 transformations were applied to the HOA atlas in the MNI space, resulting in native-T1-space GM  
245 parcellations for each subject. Then, functional time series were extracted from the above MNI-  
246 normalized functional data for each individual, each ROI, for subsequent functional connectivity  
247 analyses.

248 *Functional connectivity*

249 Functional connection matrices representing task-related connection strengths were estimated  
250 using a cPPI analysis used previously by our group (Davis et al., 2017) and others (Fornito et al., 2012)  
251 to estimate a whole-brain connectivity matrix that describes task-related interactions between brain  
252 regions. Briefly, the model relies on the calculation of a PPI regressor for each region (or node), based  
253 on the product of that region's time course and a task regressor of interest, in order to generate a term  
254 reflecting the psychophysical interaction between the seed region's activity and the specified  
255 experimental manipulation.

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256 The convolved task regressors from the univariate model described above were used as the  
257 psychological regressor, which were originally coded as the four Set-Size-modulated delay regressors  
258 (range = 1-4); all regressors are mean-adjusted in FSL; as such, our linear, mean-centered  
259 parameterization forms an effective contrast of [-1.5 -0.5 0.5 1.5] across Very Easy, Easy, Medium, and  
260 Difficulty item loads (respectively). The correct-trial delay-period regressors were each multiplied with  
261 two network time courses for region  $i$  and  $j$ . As is typical in most working memory paradigms, our delay  
262 period interval was of a fixed length (4 s), and therefore not jittered with the array presentation or  
263 response periods of the task. In order to address the possibility that this delay period-activity was thus  
264 contaminated by these other events, we repeated this partial correlation by including convolved  
265 regressors for array and response periods in the  $z$ -term. Nonetheless, the inclusion of these regressors  
266 had no influence, suggesting that the confound in isolating delay-period activity during fMRI of working  
267 memory cannot be solved under the current data design parameters. The partial correlation  $\rho_{PPI_i, PPI_j \cdot z}$   
268 was then computed, removing the variance  $z$ , which includes both the psychological regressor and the  
269 time courses for regions  $i$  and  $j$ , as well as constituent noise regressors including 6 motion parameters  
270 and noise regressors coding for the concurrent signal in white matter and CSF during each run. This  
271 cPPI analysis resulted in 4 separate output matrices, comprising connectivity delineated by WM load.  
272 Task-related connectivity was estimated from the resulting output matrices; negative connections were  
273 included in these analyses, as they may inform important, explicit interpretations about how networks  
274 may be segregated (Braun et al., 2012). Of note, our inclusion of the motion regressors did not have a  
275 significant effect on overall connectivity values; nonetheless, it remains an open question whether such  
276 an inclusion in task-related connectivity helps to control for the residual influence of motion not removed  
277 in initial preprocessing stages, or instead re-introduces noise into the data (see Lindquist et al., 2019).  
278 To facilitate future work, we have made available cPPI connectomes both with and without motion  
279 regressors included as controlling random variables.

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280 Lastly, in order to summarize system-wide behavior in the task-related network, a previously  
281 reported measure of system segregation was applied with modifications (Chan et al., 2014). This  
282 measure is calculated as the difference between the mean magnitudes of between-system correlations  
283 from the within-system correlations as a proportion of mean within-system correlation.

$$Segregation = \frac{\bar{Z}_w - \bar{Z}_b}{\bar{Z}_w}$$

284 Where  $\bar{Z}_w$  is the mean r-values between nodes of one partition, module, or system (similar to within-  
285 module degree or WMD), and  $\bar{Z}_b$  is the mean of r-values between nodes of separate partitions (similar  
286 to between-module degree or BMD, Davis et al., 2017). Accordingly, values greater than 0 reflect  
287 relatively lower between-system correlations in relation to within-system correlations (i.e., stronger  
288 integration of systems), and values less than 0 reflect higher between-system correlations relative to  
289 within-system correlations (i.e., diminished integration of systems). This measure was then modified by  
290 taking  $1 - Segregation$  to reflect system *integration*, or the inverse effect of segregation. In subsequent  
291 connectivity analyses, one older adult participant's average network integration value was greater than  
292 two standard deviations below the mean and was thus excluded from this analysis. All plots were  
293 created using R (R Core Team, 2012) and ggplot (Wickham and Wickham, 2007). All connectivity data  
294 was visualized using BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>).

## 295 Results

### 296 Behavioral results

297 There were no significant group differences between young and older adults in either Starting Load  
298 ( $t_{66} = 0.46$ ,  $p = 0.65$ ) or WM capacity values ( $t_{66} = 1.26$ ,  $p = 0.21$ ). This suggests that both age groups  
299 were fairly equivalent in baseline performance level. Results from the linear and logistic regression  
300 models demonstrated that increasing WM Difficulty Level corresponded to lower accuracy ( $\chi^2 = 86.84$ ,  $p$   
301  $< 2.2e-16$ ) and slower RTs ( $\chi^2 = 63.37$ ,  $p = 1.7e-15$ ). Additionally, while there was no main effect of

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302 group on accuracy (i.e., correctly recognizing old probes), older adults demonstrated significantly  
303 slower RTs ( $\chi^2 = 12.30$ ,  $p = 4.5e-4$ ). This lack of group difference in accuracy is not surprising given that  
304 low performers were screened out of the experiment, and previous studies have demonstrated that  
305 titrating for individual performance largely removes age differences in task performance that are  
306 typically found (Cappell et al., 2010; Schneider-Garces et al., 2010). Accuracy and response time was  
307 further summarized across difficulty level for valid, invalid, or new trials separately to further investigate  
308 performance differences across trial type (**Fig. S1A**; accuracies for the Valid/Invalid Position decision  
309 are presented in **Table S1B**, but not the focus of the current analysis). From these data, we see that  
310 older adult subjects correctly recognized both old probes (valid or invalid letter probes, which both  
311 constitute “old” trials) with a high degree of accuracy, (all subject means > 80%, even at the highest  
312 levels of difficulty). Furthermore, older adult subjects were also correctly identified lure probes (i.e., New  
313 trials; all subject means < 18%, even at the highest levels of difficulty). Higher WM capacity significantly  
314 predicted lower accuracy ( $\chi^2 = 10.98$ ,  $p=9.2e-4$ ) but not reaction time. Plots of response accuracy show  
315 a linear trend across WM Difficulty Level (**Fig. 2A & 2B**) wherein WM load strongly predicts  
316 performance, but no group-by-difficulty interactions were found. This titration therefore allows brain  
317 measures to be more directly compared both within and across age groups, as these differences would  
318 be unrelated to any disparity in task performance.

319 *[Figure 2 here]*

## 320 **fMRI results**

321 As described in the introduction section, the study had three main goals: (1) investigate how age  
322 effects on WM network integration vary as a function of WM demands; (2) examine hemispheric  
323 differences in network integration in young and older adults; and (3) investigate if age-related changes  
324 in network integration relate to individual differences in WM performance. Before turning to each of  
325 these analyses, the next section describes how the task-related network was identified.

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### 326 *Task-related network identification*

327 As illustrated by **Figure 3A**, when collapsing across WM loads, the network of activated regions  
328 consisted of frontal and parietal areas, similar to what is typically found in fMRI studies of WM (Cabeza  
329 and Nyberg, 2000). To select ROIs for network analyses, all commonly activated ROIs across young  
330 and older adults that had average ROI-level t-value above 2.59, corresponding to a significance of  $p <$   
331  $0.005$  uncorrected, were included in the task network. This resulted in a 35-node network consisting of  
332 bilateral frontoparietal and sensorimotor regions (see **Fig. 3B**). Next, we address whether age was  
333 associated with differences in the symmetry of task-network activation. Splitting the Task network  
334 activity by left and right ROIs, we then performed a Age x Hemisphere ANOVA on the univariate activity  
335 values to test this hypothesis (**Fig. S2**); As expected given the verbal nature of the task, average  
336 activity within this network was greater in the left hemisphere in young adults ( $F_{1,36} = 8.21, p = 0.007$ ),  
337 but this hemispheric asymmetry activity was not observed in older adults ( $F_{1,29} = 1.09, p = 0.31$ , **Fig.**  
338 **3C**); nonetheless, we found no significant hemisphere-by-age interaction. Average univariate activity in  
339 all task-related regions showed a weak inverse-U pattern as a function of WM load, with no significant  
340 differences between groups across difficulty level (**Fig. 3D**). This finding supports previous findings of  
341 load effects disappearing when normalized to individual performance (Schneider-Garces et al., 2010),  
342 and thus may be a better measure of directly comparing brain differences rather than WM capacity  
343 differences in aging. Thus, this task-based network is utilized to more effectively investigate changes in  
344 network connectivity, such as how task regions communicate with each other at network and whole-  
345 brain levels.

346 [Figure 3 here]

### 347 *Network integration and task difficulty*

348 The first goal of the study was to investigate how age effects on WM network integration vary as a  
349 function of WM demands. Specifically, we tested the hypothesis that *as task demands increase, the*

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350 *WM network becomes more integrated with the rest of the brain and this effect is greater for older than*  
351 *younger adults* (Hypothesis 1). In order to test this hypothesis we applied task-related connectivity (as  
352 defined by cPPI, see Davis et al., 2017; Fornito et al., 2012), which examines the degree to which the  
353 correlation of fMRI timeseries between a pair of cerebral regions may be modulated by the  
354 hemodynamic response associated with a cognitive event. As illustrated by **Figure 4**, the results were  
355 consistent with this hypothesis: as a function of WM Difficulty Level, network integration decreased  
356 slightly in young adults, but increased substantially in older adults. When entered into a 2-way group by  
357 difficulty ANOVA, there were significant differences in group ( $F_{1,64} = 6.19$ ,  $p = 0.015$ ) and no general  
358 Difficulty Level differences. The interaction between group and load was also significant ( $F_{1,196} = 5.72$ ,  $p$   
359  $= 0.018$ ). This effect emerged particularly in the hardest level (Level 4:  $t_{65} = -4.21$ ,  $p = 8.1e-05$ ). This  
360 finding is consistent with the univariate activity evidence for the CRUNCH hypothesis (Cappell et al.,  
361 2010; Low et al., 2009; Reuter-Lorenz and Cappell, 2008; Schneider-Garces et al., 2010), but it  
362 extends this evidence by showing that demand-related over-recruitment in older adults involves  
363 changes in network integration.

364 *[Figure 4 here]*

365

### 366 *Hemispheric differences in network integration*

367 The second goal of the study was to identify which regions are driving the integration effect by using  
368 informed decompositions of the networks examined above. First, we sought to test whether  
369 hemispheric differences in network integration in young and older adults help to explain the observed  
370 pattern above. This approach is motivated by the common finding that activations are less lateralized in  
371 older adults than younger adults. In particular, we tested the hypothesis that *during a left-lateralized*  
372 *verbal WM task, older adults show greater demand-related network integration in the right- than the left-*  
373 *hemisphere* (Hypothesis 2). To do so, integration measures were calculated separately within the left

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374 and right hemispheric components of the task network (**Fig. 5A**) and entered into a 3-way group by  
375 difficulty by hemisphere ANOVA. While the 3-way interaction was not significant, interactions emerged  
376 in group by difficulty ( $F_{1,456} = 10.06$ ,  $p = 0.002$ ) and group by hemisphere ( $F_{1,456} = 4.26$ ,  $p = 0.040$ ), with  
377 no interaction of difficulty by hemisphere. Thus, the lack of a significant 3-way interaction precludes that  
378 “older adults show increased difficulty-related network connectivity in the right, more than the left  
379 hemisphere.” Nonetheless, such a conclusion is based on a more explicit comparison of the left and  
380 right hemisphere; we therefore performed follow-up tests to characterize the connection profile left and  
381 right hemisphere independently. Thus, separate 2-way group by difficulty ANOVAs for each  
382 hemisphere were then computed to probe this possibility. Consistent with the Hypothesis 2, the  
383 difficulty by age interaction remained significant in the right hemisphere ( $F_{1,196} = 3.90$ ,  $p = 0.048$ ), but  
384 not in the left hemisphere ( $F_{1,196} = 1.68$ ,  $p = 0.19$ ; **Fig. 5B**). This finding suggests that age-related  
385 increases in network integration were driven by greater integration of the right hemisphere task nodes.  
386 To further investigate this effect, we split the connectivity of right-hemisphere task nodes with other  
387 right-hemisphere nodes (right-right) and with left-hemisphere nodes (right-left) focusing on the  
388 difference between Difficulty Levels 3 and 4 since these consecutive levels demonstrated the greatest  
389 interaction effect. As illustrated by **Figure 5C**, both right-right and right-left connections showed greater  
390 integration with WM demands in older adults. An age (young vs. old) by difficulty (Level 3 vs Level 4) by  
391 connection type (right-right, right-left) ANOVA showed a significant age by difficulty interaction ( $F_{1,192} =$   
392  $5.45$ ,  $p = 0.02$ ), but no other interactions. These results are consistent with univariate activity evidence  
393 for the HAROLD model (Cabeza and Dennis, 2013), but extends this evidence by showing that age-  
394 related contralateral recruitment is associated with greater between-network connectivity of the  
395 contralateral hemisphere network both within- and across-hemispheres.

396 *[Figure 5 here]*

397 A potential concern of the hemispheric differences in network integration is that it could be driven by  
398 differences in canonical intrinsic networks, such as the default mode network (DMN). A growing body of

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399 evidence suggests that older adults show less modular architecture (Betzel et al., 2014), and that  
400 relationships between frontal control and DMN regions become less decoupled with age (Spreng and  
401 Turner, 2019). To investigate this issue, our second approach was to investigate the alternative  
402 hypothesis that the task-based integration was driven by changes in the modularity of resting state  
403 networks. Each ROI in the 471-node network was assigned to one of the seven network parcellation  
404 schemes defined by Yeo and colleagues (2011) based on the greatest area of overlap. The regions  
405 were thus labeled as Visual, Somatomotor, Dorsal Attention, Ventral Attention, Limbic, Frontoparietal,  
406 and Default networks according to this standard atlas (**Fig. 5D**). In this analysis integration between  
407 nodes of each of the seven canonical resting-state modules (or networks) was calculated to determine  
408 whether the network integration effects observed in **Figure 5B** were present in any specific standard  
409 resting-state network (the task network was excluded from this analysis). Integration scores were  
410 assessed for each canonical network using a repeated-measures ANOVA for each module. The Limbic  
411 network, comprising regions in anterior temporal and orbitofrontal cortex, was the only resting state  
412 network to demonstrate a significant group by difficulty interaction after Bonferroni correction (**Fig. 5E**;  
413  $F_{1,196} = 8.25, p = 0.032$ ). There were no other significant interaction effects in any module, and there  
414 were no significant group or difficulty level effects in any module. It is noteworthy that while no limbic  
415 regions (e.g., hippocampus, inferior/anterior temporal cortex) exhibited greater univariate activity in the  
416 present study, sub-threshold activity in these regions may nonetheless be contributing to successful  
417 working memory performance. Many regions classified as Limbic in the Yeo atlas comprise loci  
418 implicated in multiple investigations of stimulus representation in working memory including age-related  
419 changes in anterior temporal connectivity during working memory (Nyberg et al., 2016; Viviano et al.,  
420 2019); nonetheless, there is no overlap between task-related working memory regions in the current  
421 study (which comprise largely frontoparietal regions), and regions in the Yeo Limbic module, suggesting  
422 that individuals in the current study may rely on connectivity-based support from an extended network  
423 of medial temporal lobe regions during increasingly difficult working memory conditions.

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424 Lastly, in order to address the possibility that connectivity differences were driven by simple BOLD  
425 differences, the relationship between task-network univariate activity and integration in the task-related  
426 regions (i.e., nodes) was also investigated across all task difficulty conditions. No significant  
427 relationships between BOLD activity within the task network regions and network integration emerged  
428 at any level. Even in the most difficult condition, there was no trend between integration and activity in  
429 older adults (OA:  $r_{30} = 0.00$ , **Fig. S3A**). Nonetheless, because the putative task network was defined  
430 across all levels of difficulty, we sought to test whether the observed age-related increases in  
431 integration may have emerged due to the recruitment of additional regions outside the task network at  
432 the highest levels of difficulty. Post hoc tests of older versus younger adults revealed age-related  
433 increases in activity in right inferior frontal cortex, right inferior temporal cortex, and inferior parietal  
434 cortex (see Supplemental Results, **Fig. S1**), consistent with other reports (Li et al., 2015; Luo et al.,  
435 2016). Activation within these regions was similarly uncorrelated with integration scores in older adults  
436 ( $r_{30} = -0.02$ , **Fig. S3B**). These null results suggest that the observed age-related increases in integration  
437 in the task network cannot be attributed to either increases or decreases in univariate activity, and that  
438 connectivity information offers new information not revealed by univariate activity differences.

#### 439 *Network integration and individual differences in WM performance*

440 The third goal of the study was to investigate if age-related changes in network integration relate to  
441 individual differences in WM performance. Specifically, we tested the hypothesis that *age-related WM*  
442 *network integration would be associated with WM ability in older adults* (Hypothesis 3). As illustrated by  
443 **Figure 6A**, the results were consistent with this hypothesis: in older adults, there was a significant  
444 correlation between network integration in the most difficult condition and WM capacity ( $r = 0.37$ ,  $p =$   
445  $0.048$ ). In younger adults, in contrast, this relationship was not significant ( $r = -0.26$ ,  $p = 0.18$ ); a  
446 Fischer r-to-z transform confirmed a significant difference in these relationships ( $z = 2.54$ ,  $p = 0.011$ ,  
447 two-tailed), providing further support for the idea that older adults rely more on the right hemisphere  
448 than their younger counterparts during difficulty working memory processing. The correlation of WM

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449 capacity with integration was also examined at the easiest difficulty level to determine whether this  
450 effect was specific to the highest difficulty level. Neither correlation was significant (young adults:  $r = -$   
451  $0.07$ ,  $p = 0.67$ ; older adults:  $r = 0.09$ ,  $p = 0.66$ ; **Fig. 6B**). A Fisher  $r$ -to- $z$  transformation was used to  
452 assess the significance of the difference between the brain-behavior correlations in younger and older  
453 adults. This difference was also significant only in the highest difficulty level ( $z = 2.54$ ,  $p = 0.01$ ),  
454 suggesting that network integration serves a different functional purpose in younger versus older adults.  
455 Nonetheless, to test for the possibility that individuals with higher WM capacity will also have a  
456 numerically higher number of items to maintain and manipulate in the most difficult condition (a natural  
457 consequence of our titrating procedure), we tested for any significant relationship between participant  
458 accuracies at the highest difficulties, and their WM capacity; we found no relationship between these  
459 measures (all  $|r| < 0.1$ ). Thus, the tendency for older adults with higher WM capacity to integrate more  
460 in the difficult task condition implies that this increase in integration is an adaptive benefit to WM. This  
461 pattern of correlations also suggests that in younger adults, the segregation of the task network from  
462 non-task regions is similarly adaptive, but in the reverse direction; such a pattern of greater segregation  
463 associated with positive outcomes for behavior is consistent with other studies finding a link between  
464 increase modularity and WM performance in younger populations (Braun et al., 2015; Stanley et al.,  
465 2014).

466 *[Figure 6 here]*

467 To better understand hemispheric influences, the same pattern of brain-behavior relationships was  
468 examined when integration scores were split across left and right hemisphere task regions. Only the  
469 highest difficulty level was examined in order to reduce the number of comparisons, which is justified by  
470 the age by difficulty effect observed above (**Fig. 4**); correlations with the easiest difficulty level are  
471 included for comparison. Of particular interest was whether younger and older adults exhibited  
472 qualitatively different brain-behavior relationships, specifically whether the age-related difference in the  
473 correlation between network integration and WM capacity was significant. After correcting for the

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474 remaining number of correlations compared, the right hemisphere showed a significant difference in  
475 correlation values in older, compared to young adults ( $z = 2.24$ ,  $p = 0.025$ ), while the left hemisphere  
476 did not show a significant difference ( $z = 1.59$ ,  $p = 0.11$ ; **Fig. 6C**). This indicates that older adults may  
477 rely more than their younger counterparts on right hemisphere network integration with the rest of the  
478 brain, and that the bilateral integration effects associated with WM capacity and age seen above (**Fig.**  
479 **6A**) are likely driven by the right hemisphere. This finding is in line with our result above, in the current  
480 analysis, that the age-related differences in network integration are largely attributable to the right  
481 hemisphere. Thus, an age-related difference in brain-behavior relationships is consistent with the  
482 interpretation that integration is good for older and bad for younger adult brains.

483 Correlations between average integration and accuracy during task performance at the highest  
484 difficulty level were also computed in both the bilateral task network and task network split by  
485 hemisphere; no significant relationships emerged ( $|r| < 0.2$ ), suggesting that the relationship of  
486 integration with behavior may be driven more strongly by individual differences rather than task-related  
487 recruitment of a so-called compensatory mechanism.

## 488 Discussion

489 The current study examined how aging affects network integration during the manipulation of  
490 information in working memory and how this integration influences individual differences in WM ability.  
491 Our analysis focused on the use of task-related whole-brain connectivity, which describes the  
492 modulation in the correlation of timeseries between cortical regions in response to a cognitive event.  
493 The study yielded three main findings. First, as task difficulty increased, network integration decreased  
494 in younger adults but increased in older adults. Second, the increase in network integration due to task  
495 demands that was observed in older adults was driven by stronger connectivity in the right hemisphere,  
496 which is less activated in younger adults during the WM task. Third, older adults with higher working  
497 memory capacity had significantly higher levels of task network integration in the most difficult

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498 condition, consistent with a compensation account as articulated in the HAROLD and CRUNCH  
499 models. These three findings are discussed in separate sections below.

## 500 **Age effects on network integration as a function of task demands**

501 The first finding of the study was that older adults showed a significant increase in network  
502 integration as a function of WM demands (load), whereas young adults showed the reverse pattern. To  
503 our knowledge, this is the first demonstration of a demand-related increase in task-related network  
504 integration in older adults, as well as the first report of a clear age-by-difficulty interaction in network  
505 connectivity. The age-related increase in network integration is generally consistent with studies  
506 observing load-related increases in PFC activity in older adults (Nagel et al., 2009), but it goes beyond  
507 univariate activation findings by showing that the task-related regions over-recruited by older adults are  
508 selectively integrated with the broader cortical network. This result also extends findings of age-related  
509 increases in bivariate functional connectivity (Daselaar et al., 2006; Dennis et al., 2008; St. Jacques et  
510 al., 2009) by showing the effect at the level of whole-brain networks and revealing the global context for  
511 these bivariate interactions. Finally, while the current results fit with previous evidence of age-related  
512 increases in network integration during rest (Chan et al., 2017; Chan et al., 2014), they also expand this  
513 evidence by showing a clear link between network integration and task demands.

514 In contrast with older adults, integration decreased in younger adults as a function of difficulty.  
515 There is not currently a consensus on what the benefits of more widespread network community  
516 integration may be, and there is evidence showing task demands can be associated with either  
517 increased integration (Braun et al., 2015; Hearne et al., 2017) or decreased integration (Davis et al.,  
518 2018; Mattar et al., 2018), depending on task investigated. Furthermore, there is evidence that,  
519 depending on the task, greater integration can be associated with better (Braun et al., 2015; Cohen and  
520 D'Esposito, 2016) or worse (Cohen and D'Esposito, 2016) performance. In the current study, the task  
521 was the same and opposite effects of task demands on integration were seen for older versus younger  
522 adults. Given that networks tend to show less functional segregation in older adults (Betzel et al., 2014;

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523 Chan et al., 2014; Cohen and D'Esposito, 2016), one possibility is that older adults benefit more from  
524 integration than younger adults. Opposing effects of univariate activity on WM performance in older and  
525 younger adults have been previously shown (Peira et al., 2016; Rypma and D'Esposito, 2000).,  
526 suggesting that younger and older adults recruit task-sensitive regions differently in response to shifting  
527 cognitive demands.

528 The first finding that older adults showed increased network integration is consistent with univariate  
529 activity supporting the CRUNCH hypothesis (Cappell et al., 2010; Low et al., 2009; Reuter-Lorenz and  
530 Cappell, 2008), while also showing that faster recruitment in older adults at higher task demands is not  
531 limited to the activity of individual regions. In univariate fMRI studies, manipulating WM load typically  
532 results in an inverted-U fMRI activity pattern, first increasing with task difficulty but then declining at  
533 higher levels of difficulty (Cappell et al., 2010; Low et al., 2009; Schneider-Garces et al., 2010; Vidal-  
534 Pineiro et al., 2017). In older adults, activity increases faster at lower levels of difficulty, but it also  
535 declines faster at higher difficulty levels. These findings are postulated to result from processing  
536 inefficiencies in older adults who over-recruit neural resources at lower levels of demands and, as a  
537 result, do not have additional resources at high demand levels. In contrast to univariate activity, network  
538 integration did not decrease at the highest difficulty level, despite clear limits in working memory  
539 capacity at this level (see **Fig. 2**). This pattern suggests that connectivity may represent a  
540 fundamentally different neural signal, one which remains more adaptive in aged participants.

#### 541 **Hemispheric differences in network integration in young and older adults**

542 The second finding of the study was that increases in demand-related network integration in older  
543 adults were driven by connectivity changes in the right hemisphere. This finding fits with evidence for  
544 the HAROLD model (Cabeza and Dennis, 2013) showing age-related increases in univariate activity in  
545 the hemisphere less activated in younger adults, such as the right hemisphere in the current verbal WM  
546 task. Previous results speak in favor of the idea that bilateral activation patterns in the PFC are often  
547 associated with higher task demands across the lifespan (Belger and Banich, 1992; Davis and Cabeza,

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548 2015), and therefore suggest a flexible bilateral cortical mechanism by which older adults may maintain  
549 youthful levels of performance. The current laterality findings, however, provide new insight by showing  
550 the consequence of these changes as expressed across whole-brain networks. Interestingly, right-  
551 hemisphere network integration increases in older adults were mediated by both connections within the  
552 right hemisphere and by connections between the right and the left hemisphere. The latter observation  
553 is consistent with previous results showing greater bivariate connectivity between left and right DLPFC  
554 in older than younger adults (Davis et al., 2012). This therefore suggests that the bilateral  
555 compensatory pattern may not be limited to strictly contralateral regions of the brain.

556 A central debate cognitive neuroscience of aging is whether or not age-related increases in  
557 recruitment of neural processes outside those recruited by younger adults reflect an adaptive  
558 compensation for the deleterious effects of age, or instead reflect more non-specific neural activity that  
559 fails to contribute meaningfully to cognition. The more specific question of how best to interpret age-  
560 related increases in right-hemisphere BOLD activation in the context of memory-related behaviors has  
561 traditionally relied on indirect relationships between activation and performance (Mattay et al., 2006;  
562 Suzuki et al., 2018), while nonetheless ignoring how such bilateral neural systems emerge from more  
563 traditional unilateral networks. In a consensus opinion article, compensation was defined as a  
564 cognition-enhancing over-recruitment of neural resources in response to cognitive demands (Cabeza et  
565 al., 2018). Thus, there are two essential criteria for attributing brain responses to compensation: they  
566 increase as a function of task demands and are associated with better cognitive performance. In the  
567 current results we found that age-related increases in task-related, right hemisphere network  
568 connectivity both increased with task difficulty and were significantly related to WM ability. Thus, in the  
569 present paradigm the age-related increase was clearly adaptive, given the strong parametric increases  
570 in connectivity in response to increasing task demand (**Fig. 4**) and right hemisphere connectivity in  
571 particular was related to successful performance (**Fig. 6**), fulfilling two of the aforementioned criteria for  
572 successful compensation. Having clarified the utility of this approach, it is important for future work to

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573 clarify the reasons why such a neural mismatch in neural resources emerges—namely declines in  
574 structural brain health. Furthermore, the justification for considering the left and right hemispheres  
575 separate in this respect is clear once one considers that this verbal task is left-lateralized (see Davis et  
576 al., 2018), and hence increased integration within the right hemisphere is consistent with contralateral  
577 recruitment (Davis et al., 2012). However, we found no concomitant increase in bilateral connectivity in  
578 OAs, suggesting that the task-related increase in right hemisphere connectivity in response to task  
579 difficulty is not reliant on signaling from the contralateral hemisphere. Such observations would not be  
580 possible by relying only on BOLD activation of left and right hemispheres. Thus, while this debate is  
581 typically formulated in terms of univariate activation, the current manuscript offers support that  
582 connectivity modulation in response to task difficulty may be more sensitive to right-hemisphere  
583 recruitment (for a generally left-lateralized lexical working memory task) than univariate activity.

584 When our connectivity patterns were decomposed by their membership to canonical resting state  
585 networks, rather than by hemisphere, only the Limbic network showed a significant age by difficulty  
586 interaction in network integration (**Fig. 5E**). Interestingly, the resting state-derived Frontoparietal  
587 network did not demonstrate an interaction, suggesting that canonical parcellations may not be as  
588 sensitive to such task-related changes in network connectivity. Furthermore, a post hoc test of the  
589 correlation comparing between-network connectivity (between the task network and any of the resting  
590 state networks defined by the Yeo atlas) and behavioral performance (either WM capacity or  
591 performance during the task) failed to identify any significant brain-behavior relationships (all  $r < 0.4$ , all  
592 N.S. after Bonferroni correction). Despite the popularity of resting state networks, it is unlikely that these  
593 partitions are fully representative of task-based networks (Cole et al., 2014; Davis et al., 2016), which  
594 could explain lack of integration in all but one of the resting state networks, and a lack of behavioral  
595 impact for connectivity in these subnetworks. Thus, while a growing body of evidence from resting state  
596 data suggests that older adults show less modular architecture (Betzel et al., 2014), our finding

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597 highlights the importance of task specificity in the context of investigating network connectivity, the use  
598 of more standardized network labels may obscure effects specific to a unique task-related network.

599 Notably, task-related connectivity has been assessed previously using similar techniques to  
600 describe age-related changes in network organization (Geerligs et al., 2014; Grady et al., 2016). Large-  
601 scale descriptions of network organization have largely focused on resting-state connectivity, findings  
602 (Betzel et al., 2014; Vij et al., 2018); we and others have cautioned that the inferences available from  
603 these “task-free” data is limited (Campbell and Schacter, 2017; Davis et al., 2016; Spreng et al., 2016).  
604 Nonetheless, the current data suggest that Task Difficulty is a highly salient modulator of connectivity,  
605 specifically within regions activated by the task. Nonetheless, the generalizability of our task-based  
606 parcellation scheme rests on the fact that a bilateral frontoparietal activation pattern during working  
607 memory comprises one of the most ubiquitous patterns in cognitive neuroscience (Owen et al., 2005).  
608 To be sure, the data-driven nature of resting state analysis has afforded the field new capacities to  
609 determine highly reliable network definitions based on consistent intra- and inter-subject consistencies  
610 in coactivation (Gordon et al., 2017; Power et al., 2011; Yeo et al., 2014), local homogeneity in  
611 activation (Gordon et al., 2016), or convergent multimodal information (Glasser et al., 2016). The  
612 influence of a parcellation scheme on functional network properties is therefore an underappreciated,  
613 but growing domain of study (Romero-Garcia et al., 2012; Zhong et al., 2015). Clearly more systematic  
614 work in this domain is needed, and an increase in data- and code-sharing practices will enable this  
615 work to proceed.

## 616 **Network connectivity and WM capacity**

617 The third main finding of the study was that older adults with higher WM capacity showed  
618 significantly higher network integration in the most difficult condition. While the association between  
619 higher integration and better behavioral performance has been shown in resting state data (Sala-Llonch  
620 et al., 2014), this is, to our knowledge, the first time this relationship is found in task-based functional  
621 connectivity. Interestingly, while WM capacity was found to relate to task network integration, no such

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622 pattern emerged with overall accuracy or reaction time at any given WM difficulty level. It is possible  
623 that the individual titration of difficulty may have obscured such effects, or that this finding reflects a  
624 relationship with individual ability rather than successful task performance. The lack of difference in  
625 behavioral performance between groups, thus, may be attributed to different patterns of network  
626 integration at high difficulty levels being utilized as alternative, and equally successful, processing  
627 strategies, resulting in equivalent WM capacity between age groups.

628       The significant difference in brain-behavior correlations between younger and older adults (**Fig. 6E**)  
629 provides some evidence for this interpretation. Given that network integration in the current study  
630 increased with task demand and was driven by the hemisphere less engaged by younger adults, the  
631 link between more widespread connectivity and WM performance provides further support for the  
632 compensatory interpretation of both CRUNCH and HAROLD (Cabeza and Dennis, 2013; Park and  
633 Reuter-Lorenz, 2009). Taken together, these findings point to the possibility that younger and older  
634 adults differ fundamentally in their approach to the WM task. The factors driving this age-related  
635 reorganization in processing are unknown, but the current study sheds some light on the topology of  
636 that reorganization. Working memory tasks, in particular, have been associated with 5Hz theta-band  
637 coupling between frontal and parietal regions during the memory retention period (Jensen and Tesche,  
638 2002; Siegel et al., 2009) which increase parametrically with memory load. Empirical findings  
639 demonstrate that WM representations can be maintained in the absence of sustained activity during the  
640 delay in a distributed set of regions linked by oscillatory activity (LaRocque et al., 2013). The extent to  
641 which distributed activation/connectivity and distributed representation drive age-related reorganization  
642 has not been studied, but a recent analysis suggests these measures are largely decoupled (Morcom  
643 and Henson, 2018). In a recent definition of compensation, the possibility was outlined that functional  
644 compensation in older adults reflects not simply the same cognitive process extended to new cortex,  
645 but rather the recruitment of additional cognitive processes not utilized in younger adults (Cabeza et al.,  
646 2018). Thus, the finding that successful performance in older adults relies on greater integration

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647 suggests that this group may rely on a more distributed set of processing cues, or a more flexible  
648 cognitive strategy, to perform the same task as younger adults.

649

## 650 **Conclusions**

651 In sum, this study yielded three main findings. First, as task difficulty increased, younger adults  
652 showed decreased network integration, whereas older adults showed increased network integration.  
653 Second, age-related increase in network integration was driven by increases in right hemispheric  
654 connectivity to both left and right cortical regions. Lastly, older adults with higher working memory  
655 capacity demonstrated significantly higher levels of network integration in the most difficult condition.  
656 These findings are generally consistent with two popular theories regarding age effects on brain  
657 function, CRUNCH and HAROLD, as well as with the compensatory interpretation of these effects,  
658 while also extending the evidence for these theories from univariate activity to network architecture.

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## 861 Tables

862 Table 1. ANOVA of factors affecting accuracy and RTs

Effect	Estimate	Std. Error	$\chi^2$ Value	Pr >  t
<i>Accuracy</i>				
Intercept	7.76	0.66		
Age Group	-0.05	0.54	0.01	0.92
WM Difficulty Level	-0.99	0.10	86.84	<2.2e-16
Age x WM Difficulty	-0.09	0.13	0.40	0.52
WM Capacity	-0.37	0.11	10.98	9.2e-4
<i>RTs</i>				
Intercept	1210.63	236.10		
Age Group	328.68	90.98	12.30	4.5e-4
WM Difficulty Level	231.09	22.37	63.37	1.7e-15
Age x WM Difficulty	-34.43	34.18	1.04	0.30
WM Capacity	37.71	39.37	0.89	0.35

863 Note:  $\chi^2$  statistics and p-values were obtained by likelihood ratio tests of the full model with the effect in question  
864 against the model without the effect in question.

865

## 866 Captions

867 **Figure 1.** Task paradigm and individual WM load determination. **(A)** Illustration of WM manipulation during an  
868 array of 3 to 9 letters was presented, followed by a delay during which participants were asked to rearrange the  
869 original array in alphabetical order and subsequently report if a probe number matches the serial position of a  
870 probe letter in the alphabetized array. **(B)** Individually-titrated Difficulty Levels were determined using sigmoid  
871 curves fitted to individual performance data from screening visit, based on accuracy.

872 **Figure 2.** Behavioral performance on Valid and Invalid trials in each group across difficulty, with figures  
873 representing **(A)** showing average Accuracy  $\pm$  standard error and **(B)** RTs  $\pm$  standard error. Linear mixed effects  
874 models for the effects of Age Group and WM Difficulty were performed on both forms of data. While clear  
875 Difficulty effects are present in both measures, Group differences are present for Reaction Time ( $\chi^2 = 12.3$ ,  $p =$   
876  $4.5e-4$ ), but not for Accuracy ( $\chi^2 = 0.01$ ,  $p = 0.92$ ).

877 **Figure 3.** Converting univariate information into multivariate topology ( $p < 0.05 = *$ ,  $p < 0.01 = **$ ). **(A)**  
878 Thresholded average delay-period maps, averaging responses within each ROI in the HOA471, used to identify  
879 regions responsive to the task. **(B)** Nodes of the network with a  $t$ -value greater than 2.57 common to both groups  
880 were then assigned to the task network. **(C)** Average activity was higher in left than right hemisphere task regions,  
881 with a significant main effect in younger adults. **(D)** While task network activity was higher for younger than older  
882 adults, univariate activity within the task network did not differ across WM Difficulty Level between age groups.

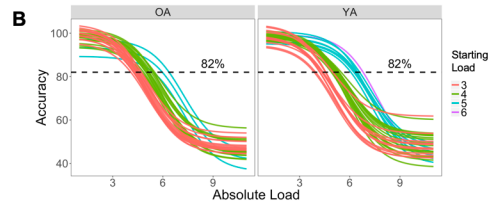
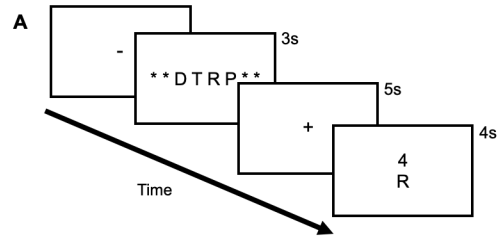
883 **Figure 4.** Components of integration value determination and parametric effects of WM Difficulty Level on  
884 network integration ( $\pm$  standard error, across WM Difficulty Level;  $p < 0.05 = *$ ,  $p < 0.01 = **$ ).

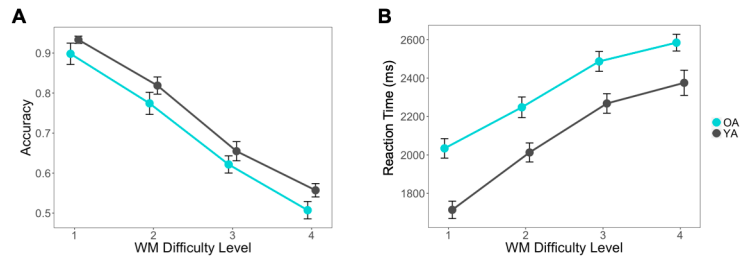
885 **Figure 5.** Network integration of subdivided task and resting-state networks ( $p < 0.05 = *$ ,  $p < 0.01 = **$ ). **(A)**  
886 Parcellation of the task network split by hemisphere. **(B)** Average integration  $\pm$  standard error of left-hemisphere  
887 and right-hemisphere task networks treated separately. **(C)** Right hemisphere task region between-network  
888 connectivity with right and left non-task regions. **(D)** Data-driven parcellation of modules determined by average  
889 resting state data across young and older adults. **(E)** Average integration  $\pm$  standard error of each module as  
890 defined by resting state.

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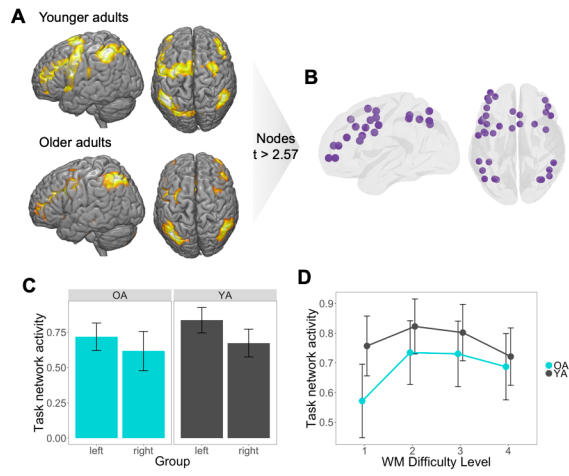
891 **Figure 6.** Relationship of task-network integration and WM capacity ( $p < 0.05 = *$ ,  $p < 0.01 = **$ ). **(A)** Task-network  
892 integration in the most difficult task condition positively correlates with individual WM capacity scores in older  
893 adults. **(B)**  $r$  values of these correlations are significant for older adults with a significant difference across group  
894 only in the high difficulty level. **(C)** Split by hemisphere, the difference in correlation values is significant only for  
895 the Right hemisphere in the high difficulty level.

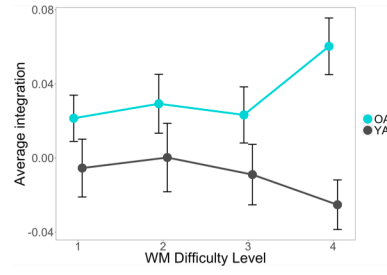
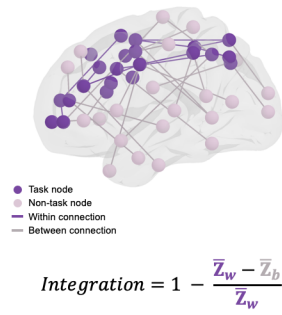
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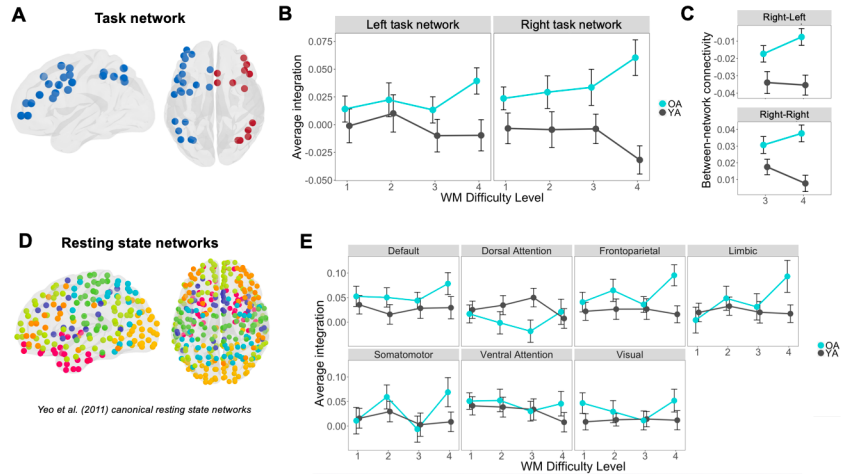


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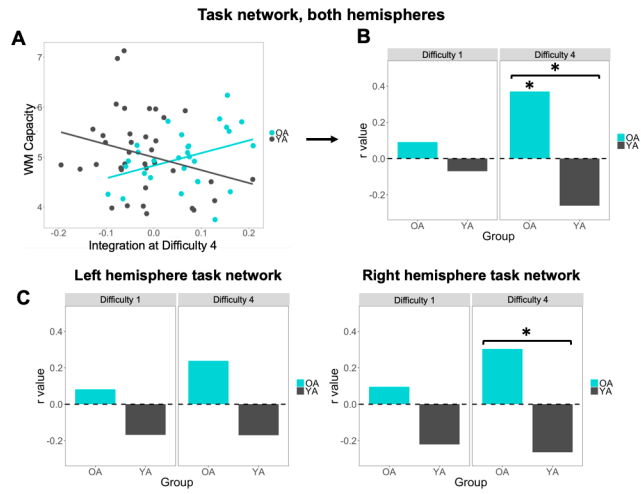




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## 1 Credit Author Statement

2 **Crowell, C.A.:** Methodology, Software, Formal Analysis, Investigation, Writing – Original Draft, Writing  
3 – Review & Editing; **Davis, S.W.:** Methodology, Software, Formal Analysis, Investigation, Writing –  
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