

1 **Anterior cingulate cortex differently modulates fronto-parietal functional connectivity between**
2 **resting-state and working memory tasks**

3

4 Running title: ACC modulates fronto-parietal connectivity

5

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17 **Abstract**

18 Fronto-parietal regions and the functional communications between them are critical in supporting
19 working memory and other executive functions. The functional connectivity between fronto-parietal
20 regions are modulated by working memory loads, and are also shown to be modulated by a third region in
21 brain in resting-state. However, it is largely unknown that whether the third-region modulations remain
22 the same during working memory tasks or were largely modulated by task demands. In the current study,
23 we collected functional MRI (fMRI) data when the subjects were performing n-back tasks and in resting-
24 state. We first used a block-designed localizer to define fronto-parietal regions that showed higher
25 activations in the 2-back than the 1-back condition. Next, we performed physiophysiological interaction
26 (PPI) analysis using left or right middle frontal gyrus (MFG) and superior parietal lobule (SPL) regions,
27 respectively, in three continuous-designed runs of resting-state, 1-back, and 2-back conditions. No
28 regions showed consistent modulatory interactions with the seed pairs in the three conditions. Instead, the
29 anterior cingulate cortex (ACC) showed different modulatory interactions with the right MFG and SPL
30 among the three conditions. While increased activity of the ACC was associated with decreased
31 functional coupling between the right MFG and SPL in resting-state, it was associated with increased
32 functional coupling between them in the 2-back condition. The observed task modulations support the
33 functional significance of the modulations of the ACC on fronto-parietal connectivity.

34

35 **Keywords:** anterior cingulate cortex; higher-order brain connectivity; modulatory interaction;
36 physiophysiological interaction; working memory.

37

38 **1. Introduction**

39 Working memory involves distributed brain regions, most prominently the bilateral fronto-parietal
40 network (Barch et al., 2013; Menicarelli et al., n.d.; Owen, McMillan, Laird, & Bullmore, 2005).
41 Understanding the functional connectivity among the distributed regions is critical to understand the
42 implementation of working memory in brain. The bilateral fronto-parietal regions showed high
43 correlations even in resting-state, thus forming lateralized fronto-parietal networks when using data
44 driven methods such as independent component analysis (ICA) (Beckmann, DeLuca, Devlin, & Smith,
45 2005; Biswal et al., 2010; Di & Biswal, 2013). Because of the presence of functional connectivity during
46 resting-state, it would be more critical to investigate the changes of functional connectivity during
47 working memory tasks. Electroencephalogram (EEG) studies typically show increased connectivity in
48 the theta band and reduced connectivity in the alpha band between fronto-parietal regions (Babiloni et al.,
49 2004; Dai et al., 2017; Sauseng, Klimesch, Schabus, & Doppelmayr, 2005). As blood-oxygen-level
50 dependent (BOLD) signals measured by functional MRI (fMRI), the signal synchronizations between
51 some of the fronto-parietal regions were found to be reduced during working memory condition compared
52 with control condition, although these regions were more activated during the higher working memory
53 load condition (Di & Biswal, 2019).

54 In addition to task modulations, functional connectivity between two regions might also be
55 modulated by a third region (Di & Biswal, 2015a; Friston et al., 1997). In the context of working
56 memory, some executive or distractive signals from other brain region might facilitate or disrupt the
57 functional communications between fronto-parietal regions. This will result in higher order interactions
58 among three brain regions, which can be studied using physiophysiological interaction (PPI) model (Di &
59 Biswal, 2013; Friston et al., 1997) or nonlinear dynamic causal modeling (Stephan et al., 2008). Several
60 studies have been performed to characterize the modulatory interactions in resting-state (Di & Biswal,
61 2013, 2014, 2015a, 2015b). Specifically, we defined the fronto-parietal regions of interest (ROIs) by
62 using ICA and performed PPI analysis on the left or right fronto-parietal ROIs, respectively (Di & Biswal,
63 2013). We identified several medial frontal and parietal regions that showed negative modulatory

64 interaction with the fronto-parietal ROIs, indicating that the increases of activity of these regions are
65 accompanied by reduced fronto-parietal functional connectivity. However, this analysis was only
66 performed in resting-state data. It is unclear whether similar effects would be shown in task conditions,
67 or it could alter significantly upon task demands.

68 The goal of the current study is to examine whether modulatory interactions of the fronto-parietal
69 regions are modulated by task demands. We adopted a n-back paradigm with varying working memory
70 loads where the bilateral fronto-parietal regions are consistently activated (Barch et al., 2013; Owen et al.,
71 2005). We first used a block-designed localizer to identify the fronto-parietal regions that showed higher
72 activations during the 2-back than the 1-back condition. We then performed PPI analysis by using the
73 frontal and parietal ROIs in three separate continuous task conditions, i.e. resting-state, 1-back, and 2-
74 back conditions. We examined two competing hypotheses. First, there are modulatory interactions of a
75 third region with the two ROIs, and the effects are consistent across the conditions. In contrast, there may
76 be modulatory interactions of a third region with the two ROIs, but the effects highly depend on the task
77 conditions. We performed conjunction analysis to identify brain regions that may fulfill the first
78 hypothesis, and performed repeated measure one-way ANOVA to find regions that may fulfill the second
79 hypothesis.

80

81 **2. Methods**

82 **2.1. Subjects**

83 Fifty participants (26 females) were recruited for the current study. The mean age was 22.34 years (19 –
84 24 years, SD = 1.303). One subject was removed because of large head motion during MRI scan. All
85 participants reported normal auditory and normal or corrected-to-normal visual acuity, and were free of
86 neurological or psychiatric problems. All study procedures were carried out with written informed
87 consent of each subject. Each subject received honorarium of 200 RMB for the participation. The study
88 was approved by institutional review board.

89 **2.2. Study procedure**

90 At the beginning of the MRI scan session, the participants underwent a resting-state fMRI scan (8 min 30
91 sec). The participants were instructed to lay still with eyes open and staring at a white cross fixation on a
92 dark background. Four working memory task runs were then performed with the following order: two
93 block-designed runs with both 1-back and 2-back condition in each run (3 min 46 sec each), one
94 continuous run of 1-back condition (5 min 10 sec), and one continuous run of 2-back condition (5 min 10
95 sec). The participants also underwent a few other tasks, which were not relevant to the current study.
96 Lastly, a high resolution anatomical T1-weighted MRI was scanned at the end of the MRI session.

97 **2.2.1. N-back task**

98 The N-back task tests the participants' working memory of the spatial locations of the letters presented on
99 the screen. A white cross fixation was presented at the center of the dark screen throughout the
100 experiment. A random letter would be presented in 1 of the 4 visual field quadrants around the fixation.
101 In a n-back task condition (n =1 or 2), participants were asked to press the left button with the left thumb
102 when the location of the current letter matched with the one presented "n" item(s) back, and pressed the
103 right button with the right thumb when it didn't match the one presented "n" item(s) back. The letter
104 stimulus was presented for 500 ms, followed by an interstimulus interval of 2500 ms. One third of the
105 total trials were "matches". Participants were instructed to focus only on the location of the letter, but not
106 on the letter itself, and to classify the stimuli as accurately and quickly as possible. Visual stimuli were
107 presented and responses were collected using E-Prime (Psychology Software Tools).

108 The N-back task procedures were designed in two ways. First, in the two localizer runs, the n-
109 back stimuli were presented as separate blocks of 1-back or 2-back conditions. Each run started with a 10
110 s fixation. Then, each of the block consisted of 8 trials (24 sec), with a 24-s fixation period intercepted
111 between the task blocks. The orders of task blocks of the two runs were "ABBA" and "BAAB",
112 respectively. As a result, each run lasted for 3 min and 46 sec. Second, in the two continuous runs, the n-
113 back trials were presented continuously without long fixation period between them. The 1-back and 2-
114 back conditions were allocated in two separate runs. Each run started with a 10 s fixation period,
115 followed by 100 trials. Each run lasted for 5 min and 10 sec.

116 **2.2.2. MRI scanning parameters**

117 MRI data were acquired on a 3T GE Signa Scanner (General Electric Company, Milwaukee, WI), using
118 an 8-channel head coil. The parameters for the fMRI images were: TR (repetition time) = 2000 ms; TE
119 (echo time) = 30 ms; flip angle = 90°; FOV (field of view) = 240×240 mm²; matrix size = 64×64; axial
120 slice number = 42 with slice thickness = 3 mm and gap = 0). As a result, each resting-state run was
121 consisted of 255 images, each block-designed run was consisted of 113 images, and each continuous task
122 run was consisted of 155 images. Structural T1-weighted images were acquired using the following
123 parameters: TR = 6 ms; TE = Minimum; TI = 450 ms; flip angle = 12°; FOV = 256×256 mm²; matrix size
124 = 256×256; sagittal slice number = 156 with slice thickness = 1 mm.

125 **2.3. FMRI data analysis**

126 **2.3.1. Preprocessing**

127 FMRI images were processed using SPM12 (SPM, RRID:SCR_007037;
128 <https://www.fil.ion.ucl.ac.uk/spm/>) under MATLAB environment (R2017b). The anatomical image of
129 each subject was segmented into gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), and
130 other brain tissue types, and normalized into standard Montreal Neurological Institute (MNI) space. The
131 first five functional images of each run were discarded from analysis. The remaining images were
132 realigned to the first image of each run, and coregistered to the anatomical image. The deformation field
133 images obtained from the segmentation step were used to normalize all the functional images into MNI,
134 with a resampled voxel size of 3 x 3 x 3 mm³. All the images were spatially smoothed using an 8 x 8 x 8
135 mm³ Gaussian kernel.

136 We calculated frame-wise displacement for the translation and rotation directions, respectively, to
137 reflect the amount of head motions (Di & Biswal, 2015a). We adopted the threshold of maximum frame-
138 wise displacement of 1.5 mm or 1.5 degree (half voxel size), or mean frame-wise displacement of 0.2 mm
139 or 0.2 degree. The subjects with any of the five runs exceeding the threshold would be removed from the
140 analysis. As a result, one subject's data were discarded.

141 **2.3.2. Activation analysis of the block-designed runs**

142 We first defined general linear model (GLM) to perform voxel-wise analysis on the block-designed runs
143 to identify task activations between the 2-back and 1-back conditions. The two runs were modeled
144 together with their own task regressors, covariates, and constant terms. The 2-back and 1-back conditions
145 were defined as two box-car functions convolved with canonical hemodynamic response function (HRF).
146 The first eigenvector of signals in the WM and that in the CSF, 24 head motion regressors (Friston,
147 Williams, Howard, Frackowiak, & Turner, 1996) were added as covariates. There was also as high-pass
148 filtering (1/128 Hz) implicitly implemented in the GLM. After model estimation, a contrast of 2-back –
149 1-back was defined to reflect the differences of activations between the two conditions.

150 Group level analysis was performed using one sample test GLM with the input of the contrast
151 images of 2-back vs. 1-back. Activated clusters were first identified using a threshold of $p < 0.001$ of
152 two-tailed test (Chen et al., 2019), and the cluster extent was thresholded at cluster level false discovery
153 rate (FDR) of $p < 0.05$. Because we were interested in fronto-parietal regions, we searched the peak
154 coordinates of the resulting clusters as well as local maxima within large clusters that covered these
155 regions. As a result, we defined bilateral middle frontal gyrus regions (MNI coordinates: RMFG, 24, 11,
156 56; LMFG, -24, 8, 50) and superior parietal lobule (MNI coordinates: LSPL, -18, -70, 50; RSPL, 21, -67,
157 53) as ROIs.

158 **2.3.3. Physiophysiological interaction analysis of the continuous-designed runs**

159 We first defined GLMs for each continuous run and subject to define ROIs. The GLMs did not include
160 task regressors, but only had the WM/CSF, head motion, and constant regressors. There was also as high-
161 pass filtering (1/128 Hz) implicitly implemented in the GLM. After model estimation, the time series of
162 the LMFG, LSPL, RMFG, and RSPL were extracted within spherical ROIs of 6 mm radius centered at
163 the above mentioned MNI coordinates. All the effects of no-interests, i.e. WM/CSF signals, head motion
164 parameters, constant, and low-frequency drifts were adjusted during the time series extraction. PPI terms
165 were calculated for LMFG and LSPL, and RMFG and RSPL, respectively. The time series of the two
166 ROIs were deconvolved with canonical HRF, multiplied together, and convolved back with canonical
167 HRF to form a PPI term (Di & Biswal, 2013; Gitelman, Penny, Ashburner, & Friston, 2003).

168 Next, new GLMs were built with the time series of the two ROIs and the PPI term between them
169 for each of the ROI pairs and conditions. Other regressors of no-interests as well as the implicit high-pass
170 filter were also included in the GLMs. The beta estimates corresponding to the interaction term was the
171 effect of interest, which were used for the group level analysis.

172 The first goal of the group analysis is to identify regions that show modulatory interaction effects
173 consistently present in the three conditions. We performed conjunction analysis of the three conditions.
174 Second-level GLM was built for the LMFG-LSPL and RMFG-RSPL analyses separately using a one-way
175 analysis of variance (ANOVA) model. First, a t contrast of each condition was defined for both positive
176 and negative effects. Next, we examined the conjunction effects of the three conditions for the positive
177 and negative effects, respectively, using a threshold of one-tailed $p < 0.0005$ (corresponding to two-tailed
178 $p < 0.001$). Cluster level FDR of $p < 0.05$ was used for the cluster extent threshold. Because there were
179 no clusters survived at the two-tailed $p < 0.001$ threshold, we also explored lower threshold of two-tailed
180 $p < 0.01$ for potential effects.

181 The second goal is to identify regions that showed variable modulatory interactions in the three
182 conditions. Repeated measure one-way ANOVA model was used for this purpose, with the three
183 conditions as three levels of a factor. The significant results of the repeated measure ANOVA indicate
184 differences in the PPI effects between any two of the three conditions. The resulting statistical maps were
185 thresholded at $p < 0.001$ with cluster level FDR at $p < 0.05$.

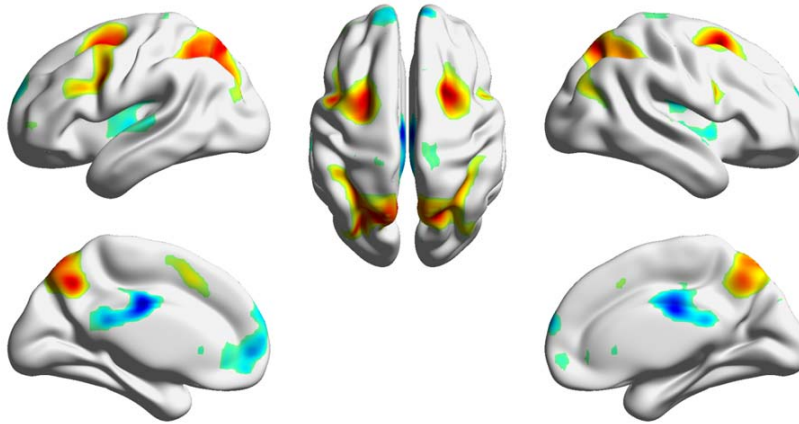
186

187 **3. Results**

188 **3.1. Task activations in the localizer runs**

189 We observed typical bilateral fronto-parietal regions that showed higher activations during the 2-back
190 condition compared with 1-back condition (Figure 1 and Table 1). The frontal clusters mainly covered
191 the bilateral middle frontal gyrus and precentral gyrus. The parietal clusters mainly covered the bilateral
192 superior parietal lobule and precuneus. The right cerebellum and left basal ganglia were also activated.

193 There were also reduced activations in the 2-back compared with 1-back condition, mainly in the default
194 model network and bilateral temporo-opercular regions.



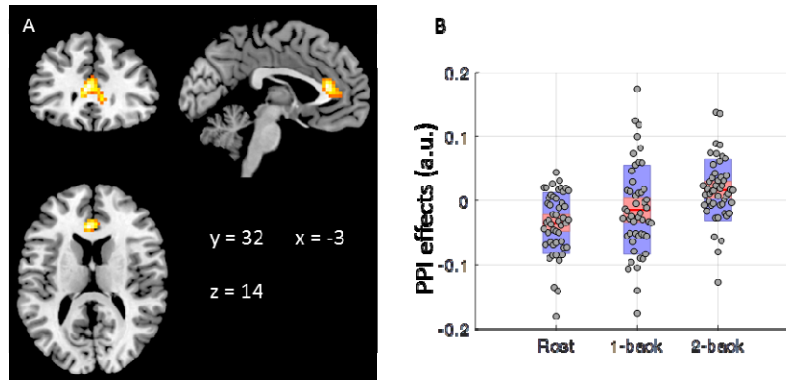
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196 **Figure 1** Increased (warm color) and decreased (cold color) activations in the 2-back condition compared
197 with the 1-back condition. The map was thresholded at $p < 0.001$ (two-tailed) with cluster-level false
198 discovery rate of $p < 0.05$. The surface presentation was made using BrainNet Viewer
199 (RRID:SCR_009446) (Xia, Wang, & He, 2013).

200

201 **3.2. Modulatory interactions during different task conditions**

202 We first performed conjunction analysis to identify regions that showed consistent PPI effects across the
203 three conditions. No statistical significant clusters were found of any sizes at $p < 0.001$ for both the
204 LMFG-LSPL and RMFG-RSPL analyses. We further checked the threshold of $p < 0.01$, and still there
205 were no clusters of any sizes survived.

206 Repeated measure one-way ANOVA showed only significant effects on the modulatory
207 interactions of RMFG and RSPL. As shown in Figure 2 and Table 2, the only cluster mainly covered the
208 anterior cingulate cortex (ACC). Post-hoc analysis showed that the PPI effect in the ACC was positive in
209 the 2-back condition but negative during resting-state (Figure 2B). Repeated measure one-way ANOVA
210 of the modulatory interactions of LMFG and LSPL showed a similar cluster in the ACC. However, the
211 cluster size could not pass the cluster-level threshold.

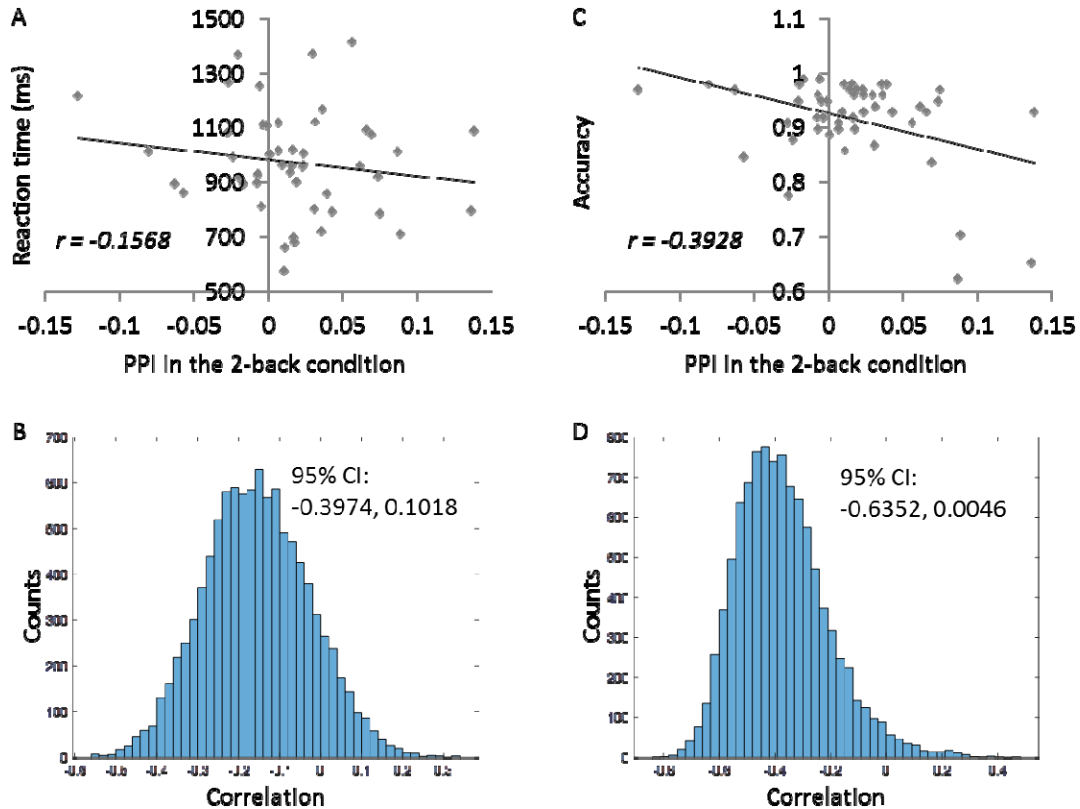


212

213 **Figure 2** A) Regions that showed different modulatory interactions effects with right middle frontal gyrus
214 (RMFG) and right superior parietal lobule (RSPL) among the three task conditions (repeated measure one
215 way analysis of variance: ANOVA). The map was thresholded at $p < 0.001$ with cluster level false
216 discovery rate (FDR) of $p < 0.05$. B) Mean modulatory interactions of the cluster in the in the three
217 conditions of continuous runs. The center red lines represent the mean effects, and the light red bars and
218 light blue bars represent 95% confidence interval and standard deviation, respectively. Panel B was made
219 by using notBoxPlot (<https://github.com/raacampbell/notBoxPlot>). A.u., arbitrary unit.

220

221 In order to better interpret the PPI effects in the ACC, we correlated the mean PPI effects in the
222 ACC cluster with RMFC and RSPL with behavioral measures of mean reaction time and accuracy (Figure
223 3). The PPI effect showed a very small correlation with reaction time ($r = -0.16$), and a moderate
224 negative correlation with the accuracy ($r = -0.39$). But it can be seen in Figure 3C that there were
225 potential outliers near the x axis that might introduce spurious correlations. We therefore performed
226 bootstrapping for 10,000 times to obtain a 95% confidence interval of the correlation (-0.6352, 0.0046)
227 (Figure 3D).



228

229 **Figure 3** Behavioral correlates of the mean modulatory interactions in the ACC with RMFG and RSPL

230 during the 2-back continuous run. A and B illustrate the scatter plot of correlations between the

231 modulatory interaction and reaction time and 10,000 bootstrapping distributions of the correlation. C and

232 D illustrate the scatter plot of correlations between the modulatory interaction and accuracy and 10,000

233 bootstrapping distributions of the correlation.

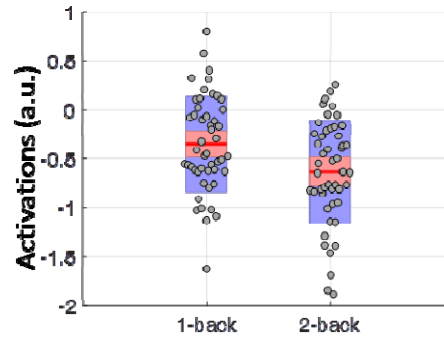
234

235 Lastly, we also extracted the mean task activations of the ACC in the block-designed runs (Figure

236 4). The ACC showed reduced activations in both the 1-back and 2-back conditions with reference to the

237 fixation baseline. But the activations were more negative in the 2-back condition than in the 1-back

238 condition (paired t test: $t(48) = 4.49, p < 0.001$).



239

240 **Figure 4** Mean task activations of the cluster in the block-designed runs. The center red lines represent

241 the mean effects, and the light red bars and light blue bars represent 95% confidence interval and standard

242 deviation, respectively. This figure was made by using notBoxPlot

243 (<https://github.com/raacampbell/notBoxPlot>). A.u., arbitrary unit.

244

245

246 **4. Discussion**

247 By comparing modulatory interactions of two key regions in working memory across three continuously

248 designed task conditions, the current analysis identified the ACC that showed different modulatory

249 interactions with the RMFG and RSPL in the resting-state, 1-back, and 2-back conditions. On the other

250 hand, no regions showed consistent modulatory interactions with the fronto-parietal regions across the

251 three conditions. The activity in the ACC was positively correlated with the connectivity of RMFG and

252 RSPL during the 2-back condition, but was negatively correlated with the connectivity of RMFG and

253 RSPL in resting-state. Due to the nature of regression model, this is impossible to infer the directions of

254 the modulations (Di & Biswal, 2013). However, the RMFG and RSPL were co-activated by the working

255 memory task and are also considered part of the same functional network (Biswal et al., 2010; Yeo et al.,

256 2011), while the ACC showed increased deactivation in the 2-back condition. We prefer to interpret the

257 results as that the ACC increase the functional connectivity between RMFG and RSPL during the 2-back

258 condition, and reduce the functional connectivity between the RMFG and RSPL.

259 Due to the fact that the ACC was negatively activated in the task conditions compared with the
260 fixation condition (Figure 4), it is likely that the ACC is part of the default mode network (Raichle et al.,
261 2001). It is consistent with our previous study in resting-state, which also showed some midline regions
262 from the default mode network having negative modulatory interactions with RMFG and RSPL (Di &
263 Biswal, 2013). The task positive network including the fronto-parietal regions and the default mode
264 network are anti-correlated both in resting-state (Fox et al., 2005) and during task executions (Shulman et
265 al., 1997). The current results together with our previous work (Di & Biswal, 2013) further confirm that
266 the competing nature of the task positive and default mode networks not only exist in first order
267 relationships but also in higher order interactions.

268 More interestingly, current analysis found that the modulatory interactions among ACC, RMFG,
269 and RSPL were largely modulated by task conditions. In contrast to resting-state, the ACC showed no
270 significant modulatory interactions in the 1-back condition, and positive modulatory interactions in the 2-
271 back condition. The task dependent effect is in line with some studies that have demonstrated task
272 modulated modulatory interactions in other brain systems by using higher order psycho-physio-
273 physiological interaction models (Gorka, Knodt, & Hariri, 2015; Stamatakis, Marslen-Wilson, Tyler, &
274 Fletcher, 2005). In neuronal level models, it has also been shown that higher order interactions present
275 only in certain task conditions (Ganmor, Segev, & Schneidman, 2011; Macke, Opper, & Bethge, 2011).
276 Taken together, all the evidence conversely suggests that high order interactions may be sensitive to
277 certain task conditions.

278 During the 2-back condition with higher working memory loads, the signals from the ACC were
279 associated with increased functional communications between the fronto-parietal regions. One of the
280 functions of the ACC is error detection and conflict monitoring (Bush, Luu, & Posner, 2000). Then, the
281 ACC activity may represent error related signals that would enhance the communications between the
282 fronto-parietal regions to maintain task performances. The brain-behavioral correlation analysis
283 supported this interpretation. The modulatory interactions in the 2-back condition were not correlated

284 with reaction time, but were negatively correlated with accuracy. In other words, the more errors one
285 made, the larger the modulatory interactions were among ACC, RMFG, and RSPL.

286 The current study adopted functionally defined ROIs of the MFG and SPL from a localizer for the
287 PPI analysis. The bilateral MFGs are a little anterior to the premotor regions and posterior to the
288 dorsolateral prefrontal cortex reported in a meta-analysis of N-back tasks (Owen et al., 2005). And the
289 bilateral SPLs are superior and posterior to the inferior parietal lobule region reported in (Owen et al.,
290 2005). The differences may represent discrepancies in task designs and control conditions compared with
291 other studies. But the fact that these regions showed the highest contrast between the 2-back and 1-back
292 condition in the current localizer task support the usage of these regions to represent regions that are
293 involved in working memory process. The fronto-parietal ROIs also do not exactly match those used in
294 the resting-state study (Di & Biswal, 2013). But similar to this paper, the current analysis showed
295 negative modulatory interactions in the middle line region of ACC with RMFG and RSPL (Di & Biswal,
296 2013).

297 The current analysis adopted a ROI-based approach, with ROIs identified directly from the
298 working memory task studied. This helped us to focus on specific brain regions that are related to the
299 task. The whole brain PPI analysis identified a region that are not a part of the fronto-parietal network
300 nor activated during the working memory tasks. It is reasonable because our previous study has shown
301 that modulatory interactions are more likely to take place among regions from different brain networks
302 (Di & Biswal, 2015a). There may be other brain regions that involve higher order interactions with one
303 of the fronto-parietal regions. But the potential interactions will increase exponentially when considering
304 the combinations of two brain regions outside the fronto-parietal network, making it difficult to do an
305 exhaustive search based on the current sample size. Further studies may adopt the whole brain approach
306 (Di & Biswal, 2015a) to examine the whole brain characterizations of modulatory interactions effects.

307 In conclusion, the current analysis extended our previous analysis in resting-state and showed that
308 the modulatory interaction among ACC and right fronto-parietal regions were highly modulated by task

309 demands. The results may provide new model on how error related signals affecting working memory
310 process through higher order interactions among brain regions.

311

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315

316 **Author contributions:**

317 X.D. conceived the idea. H.Z. designed the experiment and collected the fMRI data. X.D. performed the
318 data analysis and wrote the draft. All authors discussed the results, and contributed to the final manuscript.

319

320 **Conflict of interest statement:**

321 The authors declare that there is no conflict of interest regarding the publication of this article.

322

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408

409 **Table 1** Clusters that showed increased activations in the 2-back condition compared with 1-back
 410 condition in the block designed runs. The cluster was defined as two tailed $p < 0.001$, with cluster level
 411 false discovery rate $p < 0.05$.

p (cluster FDR)	voxels	Coordinates			peak T	Label
		x	y	z		
< 0.001	2108	24	11	56	11.65	Right middle frontal gyrus
		-24	8	50	10.72	Left middle frontal gyrus
		-48	5	32	9.810	Left precentral gyrus
< 0.001	2897	-6	-61	44	10.73	Precuneus
		-18	-70	50	10.68	Left superior parietal lobule
		21	-67	53	10.44	Right superior parietal lobule
0.004	120	48	5	23	7.00	Right precentral gyrus
0.003	149	27	-61	-37	6.92	Right cerebellum
		9	-73	-31	4.78	Right cerebellum
0.003	136	-18	5	11	5.84	Left caudate
		-30	26	2	5.75	Left anterior insula
0.038	63	-33	50	2	4.20	Left middle frontal gyrus
		-42	50	2	4.02	Left middle frontal gyrus
< 0.001	661	-3	-16	32	-8.73	Middle cingulate gyrus
		0	-37	20	-6.08	Posterior cingulate gyrus
		0	-28	44	-5.42	Posterior cingulate gyrus
< 0.001	660	39	-19	20	-6.54	Right parietal operculum
		36	-16	2	-5.56	Right posterior insula
		39	2	-1	-5.16	Right anterior insula
< 0.001	910	12	59	20	-6.11	Superior frontal gyrus
		-6	62	8	-5.86	Medial superior frontal gyrus
		-9	53	-1	-5.84	Medial superior frontal gyrus
< 0.001	498	-36	-10	-4	-5.39	Left posterior insula
		-63	-25	5	-4.73	Left superior temporal gyrus
		-39	-19	17	-4.64	Left central operculum
0.037	74	21	38	-1	-5.19	Anterior cingulate gyrus

412
 413 FDR, false discovery rate. X, y, and z coordinates are in (Montreal Neurological Institute) MNI space.

414

415 **Table 2** Clusters that showed different physiophysiological interaction (PPI) effects with right middle
416 frontal gyrus (RMFG) and right superior parietal lobule (RSPL) among the resting-state, 2-back, and 1-
417 back conditions in the continuous runs (repeated measure one way analysis of variance). The cluster was
418 defined as $p < 0.001$, with cluster level false discovery rate $p < 0.05$.

p (cluster FDR)	voxels	Coordinates			peak F	Label
		x	y	z		
0.005	133	-3	32	14	14.94	Anterior cingulate gyrus
		9	35	5	14.82	Anterior cingulate gyrus
		3	44	-4	8.27	Anterior cingulate gyrus

419
420 FDR, false discovery rate. X, y, and z coordinates are in (Montreal Neurological Institute) MNI space.

421