1 **Full title**

2 **Intrinsic functional reorganisation of the attention network**

3 **in the blind**

4 **Running title: Attention network reorganisation in the blind**

5 Wen Qin [1, *], Yong Liu [2], Tianzi Jiang [2], and Chunshui Yu [1]

6 [1] Department of Radiology and Tianjin Key Laboratory of Functional Imaging,

7 Tianjin Medical University General Hospital, Tianjin 300052, China

8 [2] Brainnetome Center and National Laboratory of Pattern Recognition, Institute of

9 Automation, Chinese Academy of Sciences, Beijing 100190, China

10 ***Correspondence to:** Wen Qin, MD, Department of Radiology, Tianjin Medical

11 University General Hospital, No. 154, Anshan Road, Heping District, Tianjin 300052,

12 China; E-mail: wayne.wenqin@gmail.com. Phone: +86-22-60363760; Fax:

13 +86-22-60362206

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17 **Keywords:** attention network; blindness; functional connectivity strength; functional

18 coupling; functional magnetic resonance imaging; resting-state, visual network; visual

19 deprivation.

20

Abstract

21

22   Attention can bias visual perception by modulating the neuronal activity of visual

23   areas. However, little is known if blindness can reshape the intrinsic functional

24   organisation within the attention networks and between the attention and visual

25   networks. A voxel-wise network-based functional connectivity strengthen mapping

26   analysis was proposed to thirty congenitally, thirty early and thirty late blind subjects,

27   and thirty sighted controls. Both the blind and sighted subjects exhibited similar

28   spatial distributions of the intrinsic dorsal (DAN) and ventral (VAN) attention

29   networks. Moreover, compared to the sighted controls, the blind subjects showed

30   increased functional coupling within the DAN, and between the DAN and VAN, and

31   between the attention sub-networks and visual areas, suggesting an increased

32   information communication by visual deprivation. However, the onset age of

33   blindness had little impact on the functional coupling of the attention network,

34   indicating that non-visual sensory experience is enough for driving the development

35   of intrinsic functional organization of the attention network. Finally, a positive

36   correlation was identified between the duration of blindness and the functional

37   coupling of the posterior inferior frontal gyrus with the visual network, representing

38   an experience-dependent reorganisation after visual deprivation.

Introduction

40 Attention is a cognitive process to focus our limited brain resources to preferentially

41 process certain external stimuli or internal ideas while ignoring irrelevant ones (Raz

42 and Buhle 2006). Attention is thought to be controlled by two segregated functional

43 networks: a bilaterally distributed dorsal attention network (DAN) which is mainly

44 composed of the frontal eye field (FEF) and intraparietal sulcus (IPS) and involves in

45 endogenous and exogenous orienting of attention; and a right-lateralized ventral

46 attention network (VAN) which is mainly consisting of the anterior insula (aINS) and

47 temporoparietal junction (TPJ) and involves in reorienting of attention in response to

48 salient stimuli (Corbetta and Shulman 2002; Corbetta et al. 2008). These two attention

49 networks dynamically interact to determine which aspects of sensory information will

50 be perceived (Buschman and Miller 2007; McMains and Kastner 2011). Both genetic

51 and environmental factors can shape the organisation of the attention networks

52 (Rueda et al. 2005; Bellgrove et al. 2007; Neufang et al. 2015). For example, visual

53 attention training can improve the attention performance and reshape the attention

54 networks in sighted subjects (Rueda et al. 2005; Rueda et al. 2012).

55 As blindness interrupts the main information transfer system of the human brain,

56 long-term visual deprivation may affect attention behavior and reshape the

57 organisation of the attention networks. In fact, superior auditory/tactile attention

58 abilities have been observed in blind subjects (Roder et al. 1999; Collignon et al. 2006;

59 Forster et al. 2007). The congenitally (CB) and early blind (EB) subjects have shown

60 increased activation in the FEF and IPS of the DAN than the sighted control (SC)

61 when performing attention-demanding tasks (Burton et al. 2004; Garg et al. 2007;

62 Stevens et al. 2007; Burton et al. 2010). These findings indicate that visual

63 deprivation can reshape regional activity of the attention networks. However, it is still

64 unknown if and how visual deprivation reshapes the intrinsic functional couplings of

65 the attention networks.

66　　　　In the SC, the attention networks dynamically interact with the visual network

67　　VN). Stimulus-driven signals from the VN can selectively recruit the VAN based on

68　　their salience and relevance; and top-down signals from the DAN can modulate the

69　　activity of visual areas to improve the perception of specific aspects of visual stimuli

70　　(Buchel et al. 1998a; Tootell et al. 1998; Jack et al. 2006; Silver et al. 2007; Cate et al.

71　　2009; Bressler and Silver 2010). In the CB/EB, despite of the structural reorganisation

72　　(Shimony et al. 2006; Ptito et al. 2008; Jiang et al. 2009; Shu et al. 2009), the

73　　functional specification (location, motion, object, or language processing) of the

74　　occipital cortex is relatively preserved (Amedi et al. 2007; Renier et al. 2010;

75　　Collignon et al. 2011; Reich et al. 2011; Wolbers et al. 2011). However, it is unclear if

76　　the intrinsic functional organisation of the attention networks is also preserved in the

77　　blind. The cross-modal activation of the occipital cortex in the blind is frequently

78　　reported in the attention-demanding nonvisual tasks (Bavelier and Neville 2002;

79　　Collignon et al. 2009; Sathian and Stilla 2010), whereas simple passive

80　　auditory/tactile tasks cannot activate the occipital cortex (Sadato et al. 1996; Sadato et

81　　al. 1998; Weeks et al. 2000). Furthermore, the occipital cortex of the EB can be

82　　activated by pure top-down attention signals, which is very similar with the visual

83　　attention-induced response in the visual cortex in the SC (Gougoux et al. 2005;

84　　Stevens et al. 2007; Renier et al. 2010). These findings suggest that even after visual

85　　deprivation, functional interactions between the attentional and occipital regions still

86　　exist. However, little is known how visual deprivation impacts the intrinsic functional

87　　coupling between the attention and visual networks.

88　　　　　Visual deprivation-induced reorganisation may depend on the development

89　　maturity degree of the brain at the time of onset of blindness. Compared to the late

90　　blind (LB), the CB/EB exhibit different reorganisation patterns in cortical thickness

91　　(Jiang et al. 2009; Park et al. 2009; Kupers et al. 2011), glucose metabolism

92　　(Wanet-Defalque et al. 1988; Veraart et al. 1990), task-evoked activation (Buchel et al.

93　　1998b), and functional connectivity density (FCD) (Qin et al. 2015) in the occipital

94 cortex. Using the same auditory attention task, although both the EB and the LB

95 demonstrated improvement in attention performance, the temporal and spatial

96 alteration patterns in event-related potentials are largely different (Roder et al. 1999;

97 Fieger et al. 2006). Nevertheless, we are unclear whether the developmental maturity

98 degree of the brain at the time of onset of blindness has an effect on the intrinsic

99 functional organisation of the attention networks in the blind.

100 Most of our knowledge on the functional organisation of the attention networks

101 comes from the task-based functional magnetic resonance imaging (fMRI) that detects

102 regional blood-oxygen-level-dependence (BOLD) activation evoked by a specific task

103 (reflecting functional segregation). In contrast, the resting-state fMRI primarily

104 focuses on the synchronization of spontaneous activity among brain regions

105 (reflecting functional integration). A pioneer study has segregated the DAN and VAN

106 by resting-state functional connectivity (rsFC) analysis (Fox et al. 2006). A following

107 study further reveals a correlation between attention performance and the rsFC

108 between the DAN and VAN in normal subjects (Wen et al. 2012). These findings

109 indicate that rsFC analysis is a promising technique to evaluate the intrinsic functional

110 organisation of the attention networks.

111 In this study, we recruited gender- and age-matched CB, EB, LB and SC (thirty

112 subjects in each group), and proposed a voxel-wise network-based functional

113 connectivity strength (FCS) mapping (NB_FCSM) method to compare intergroup

114 FCS differences within each attention network (DAN and VAN), between the DAN

115 and VAN, and between the attention and visual networks (DAN-VN and VAN-VN).

116 Based on previous findings in the blind, we proposed four hypotheses: (1) the intrinsic

117 functional organisation of the attention networks is preserved in the blind because the

118 same brain regions show activation in non-visual attention tasks in the blind and in

119 visual attention tasks in the SC (Garg et al. 2007; Stevens et al. 2007; Corbetta et al.

120 2008; Burton et al. 2010); (2) the blind subjects have increased functional couplings

121 in the attention network since they show superior non-visual attention performance,

122   and increased activation in the network during non-visual attention tasks (Roder et al.

123   1999; Collignon et al. 2006; Forster et al. 2007; Garg et al. 2007; Stevens et al. 2007);

124   (3) the blind subjects have increased functional couplings between the attention and

125   visual networks for they show increased occipital activation evoked by non-visual

126   attention-demanding tasks (Gougoux et al. 2005; Stevens et al. 2007; Renier et al.

127   2010); and (4) the onset and/or duration of blindness may impact the intrinsic

128   functional organisation of the attention networks in the blind as the CB/EB and LB

129   show different reorganisation patterns in the occipital cortex (Jiang et al. 2009; Park et

130   al. 2009; Collignon et al. 2013; Qin et al. 2015).

Materials and methods

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Subjects

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133   This study recruited 90 right-handed blind subjects and thirty sighted controls (22

134   males, age range 20-44 years). Blind subjects included thirty CB (onset since birth, 22

135   males, age range 18-39 years), thirty EB (onset from 0.5 to 12 years old, 22 males,

136   age range 20-45 years), and thirty LB (onset from 13 to 28 years old, 22 males, age

137   range 20-38 years). The samples size, age and gender of the four groups were well

138   matched (Table 1). The protocol was approved by the Medical Research Ethics

139   Committee of Tianjin Medical University, and written informed consent was obtained

140   from all participants prior to the experiment.

MRI data acquisition

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142   MRI data were obtained using a 3.0 Tesla MR scanner (Trio Tim system; Siemens,

143   Erlangen, Germany) with a 12-channel head coil. The resting-state fMRI data were

144   acquired using a gradient-echo echo-planar imaging sequence with the following

145   parameters: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, matrix =

146   64×64, field of view = 220 mm $\times$ 220 mm, 32 axial slices with a thickness of 3 mm

147   and a gap of 1 mm. During scans, all subjects were instructed to keep eyes closed and

148   awake, stay motionless, and think of nothing in particular. The three-dimensional

149   structural images were acquired using a magnetization-prepared rapid-acquisition

150   gradient echo sequence: repetition time = 2000 ms, echo time = 2.6 ms, inversion time

151   = 900 ms, flip angle = 9°, matrix = 256 × 224, field of view = 256 mm × 224 mm, 176

152   continuous sagittal slices with a thickness of 1 mm.

153   **The fMRI data preprocessing**

154   The resting-state fMRI data were preprocessed using Statistical Parametric Mapping

155   (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes were removed

156   because of incomplete T1 relaxation, and to allow the participants to adapt to the

157   scanning environment. The remaining 170 volumes were corrected for the acquisition

158   time delay between slices and were realigned to the first volume to estimate and

159   correct rigid head motion. All subjects were within the predefined head motion

160   thresholds of translation < 2 mm and rotation < 2°. We also calculated the frame-wise

161   displacement (FD) (Power et al. 2012) and percent of spike motion (defined as FD >

162   0.5) in each subject. The mean FD was included as an additional nuisance variable

163   during all fMRI-related statistical analyses to further exclude out the effect of head

164   motion. Then fMRI dataset were affinely corregistered with the structural volume,

165   and the structural images were segmented and nonlinearly normalized into the

166   Montreal Neurological Institute (MNI) space. Finally, the fMRI volumes were written

167   to the MNI space and resampled into 3-mm^3 voxels using the deformation parameters

168   derived from structural images. Several spurious variances, including the motion

169   parameters (six parameters and their first time derivatives), and average BOLD

170   signals of the whole brain, ventricular and white matter were removed from the

171   normalized fMRI data through linear regression. After band-pass frequency filtering

172   (0.01-0.08 Hz), the functional images were spatially smoothed with a Gaussian kernel

173   of 6 mm full width at half maximum.

174 **Attention network extraction**

175 The attention networks were extracted based on a meta-analysis of attention-evoked

176 coactivation. BrainMap Sleuth 2.0.3 (http://www.brainmap.org/) was used to search

177 papers reporting brain activation evoked by visual attention tasks in right-handed

178 healthy adults using either positron emission tomography or fMRI. We excluded

179 conditions aimed to investigate the effects of diseases, handedness, gender or drugs on

180 task-evoked activation. All retrieved foci were transformed into MNI space and

181 manually checked to exclude those out of the MNI grey matter mask. A total of 128

182 papers that included 360 experiments, 4793 subjects, and 3470 foci were finally

183 included in the meta-analysis.

184 The meta-analysis was performed using the revised version of Activation

185 Likelihood Estimation (ALE) technique (Eickhoff et al. 2009; Turkeltaub et al. 2012)

186 implemented in GingerALE 2.3.6 (http://www.brainmap.org/). This algorithm aims to

187 identify regions showing convergent activation across experiments if the merged

188 activation is higher than the expectation under a random spatial association. For a

189 given experiment, all activation coordinates are modelled as independent Gaussian

190 probability distributions and combined to generate a modelled activation (MA) map

191 for this experiment. To minimize within-experiment foci number and proximity on the

192 ALE calculation, the maximum probability of each voxel in a given experiment was

193 considered as the MA value (Turkeltaub et al. 2012). Then, the ALE score of each

194 voxel was calculated by summing individual MA values of all experiments. A

195 random-effect non-parametric permutation test was used to identify voxels with

196 significant ALE differences against the null-hypothesis. Multiple comparisons were

197 corrected using a false discovery rate (FDR) method ($q < 0.05$ and cluster size > 1000

198 mm^3). The task-evoked spatial activation pattern in the attention network was shown

199 in Supplementary Fig. 1.

DAN and VAN extraction

As performed in a prior study (Fox et al. 2006), we used rsFC-based conjunction analysis to define the DAN and VAN. The right FEF [28 -6 52] and IPS [30 -58 46] were used to identify the DAN, and the right aINS [38 26 -6] and TPJ [58 -42 30] were used to identify the VAN. These peak MNI coordinates were defined based on the ALE map (Supplementary Fig. 1). A 6mm-radius sphere centered on each coordinate was drawn and the overlap voxels between the sphere and ALE map were taken as the seed. Pearson correlation coefficients between the mean time series of each seed and that of each voxel of the whole brain were computed and transformed into z-values using Fisher's transform. In each group, individuals' z-values were entered into a one-sample t-test to identify brain regions with significant positive correlations with each seed. The conjunction analysis was then applied to identify the DAN regions that exhibit positive rsFC with both the FEF and IPS and the VAN regions that show positive rsFC with both the aINS and TPJ ($q < 0.05$, FDR corrected; cluster size > 30 voxels). The spatial distributions of the DAN and VAN of each group are shown in Supplementary Figs 2 and 3, respectively. We used a leave-one-out (LOO) method to verify if the inter-subject variability would impact the spatial distribution pattern of the DAN and VAN of each group. In each LOO experiment, we performed conjunction analysis using the same method as the original one after excluding one subject's rsFC data. The spatial overlapping ratio (SOR) and spatial correlation coefficient (SCC) of the DAN/VAN between each LOO experiment and original one were calculated. The SOR and SCC of the DAN/VAN between each pair of groups were also calculated to evaluate the spatial similarity of the attention networks among the groups.

To increase the functional specificity of the DAN and VAN, we further redefined the two attention networks within brain regions that showed both high functional connectivity with the hubs of this network and high activation by visual attention tasks, which was computed by multiplying the rsFC-based DAN and VAN with the

228   ALE-based coactivation map. Because we aimed to investigate if the intrinsic

229   functional couplings of brain regions that originally serve visual attention in the SC

230   would change after visual deprivation, the redefined DAN and VAN were only

231   calculated from the SC subjects.

232   **NB-FCSM**

233   A NB-FCSM method was proposed to voxel-wisely compare intergroup FCS

234   differences within (DAN and VAN) and between networks (DAN-VAN, DAN-VN

235   and VAN-VN). Similar to the FCD mapping that measures the degree distribution of

236   the intrinsic functional networks at the voxel-level (Tomasi and Volkow 2012),

237   NB_FCSM measures the weighted degree distribution, namely the FCS (Liang et al.

238   2013). As an extension of the original whole-brain FCS analysis (Liang et al. 2013),

239   this method can not only measure FCS distribution within a network, but also map the

240   FCS between each pair of networks, which can provide information about

241   inter-network functional coupling. The preprocessing steps were the same as the rsFC

242   analysis. The pipeline of NB-FCSM is shown in Fig. 1. For within-network FCS, we

243   first calculated the rsFC between each pair of voxels within a given network to

244   construct a voxel-wise correlation matrix. Then a threshold ($P < 0.05$, uncorrected) of

245   the positive rsFC was used to sparsify the correlation matrix. Within-network FCS of

246   a given voxel was calculated as the average rsFC between this voxel and all other

247   survived voxels within the sparse matrix, and this step was iterated for each remaining

248   voxel. Similarly, between-network FCS was calculated except that the rsFC was

249   calculated from each pair of voxels from two different networks (e.g., A and B). We

250   obtained two between-network FCS measures: $FCS_{A\&B}$ represents the average rsFC of

251   one voxel in network A with all survived voxels in network B, and vice versa for FCS

252     $_{B\&A}$. To test the effect of connectivity thresholding on our results, we also calculated

253   FCS using four different thresholds (r > 0, 0.1, 0.2 and 0.3) and compared the

254   intergroup differences.

255 **Statistical analyses**

256 A fixed-effect general linear model (GLM) was used to voxel-wisely compare

257 intergroup differences in FCS within each attention network, between the DAN and

258 VAN, and between the DAN/VAN and VN ($q < 0.05$, FDR corrected), controlling for

259 the effects of age, gender and mean FD. Brain regions with significant FCS

260 differences were extracted as regions-of-interest (ROIs) and entered into *post-hoc*

261 comparisons to test pair-wise differences among the four groups ($q < 0.05$, FDR

262 corrected). To clarify which functional connectivities contributed to the FCS changes

263 in blind subjects, the rsFC between each identified ROI and each voxels of the whole

264 brain were calculated, and intergroup differences in rsFC were compared using the

265 same statistical model as the FCS analyses ($q < 0.05$, FDR corrected). Finally, partial

266 correlation analyses controlling for the effects of gender and mean FD were

267 performed to test possible correlations of regional FCS with onset age and duration of

268 blindness ($q < 0.05$, FDR corrected).

269 # Results

270 **Demographic data**

271 The demographic data of these subjects are shown in Table 1. A total of thirty CB,

272 thirty EB, thirty LB and thirty SC were included in this study. There were no

273 significant differences in gender ($\chi^2 = 0$, $P = 1$), age ($F = 1.95$, $P = 0.125$), mean FD (F

274 $= 0.21$, $P = 0.888$) and percentage of motion spikes ($\chi^2 = 2.33$, $P = 0.508$) among the four

275 groups. The age of onset of blindness was 0 year in the CB, 7.7 ± 3.2 years in the EB,

276 and 18.0 ± 4.4 years in the LB; and the duration of blindness was 25.7 ± 4.6 years in

277 the CB, 20.8 ± 7.9 years in the EB, and 10.2 ± 4.2 years in the LB.

278 **The spatial distribution of the attention network**

279 The spatial distribution of the attention network identified by coordinated-based ALE

280   meta-analysis ($q < 0.05$, FDR corrected) is shown in Supplementary Fig. 1. Visual

281   attention-evoked activation was located in the bilateral FEF, IPS, middle (MFG) and

282   inferior (IFG) frontal gyrus, superior parietal lobule (SPL), dorsal anterior cingulate

283   cortex (dACC), aINS, and the right TPJ. The spatial distributions of the DAN and

284   VAN in each group identified by rsFC-based conjunction analyses ($q < 0.05$, FDR

285   corrected) are shown in Fig. 2A-C, and Supplementary Figs. 2 and 3. The spatial

286   distribution maps of these two networks were similar among the CB, EB, LB and SC

287   (SOR: $56.3 \pm 4.7\%$ for the DAN and $55.2 \pm 2.2\%$ for the VAN; SCC: 0.693 ± 0.038

288   for the DAN and 0.524 ± 0.048 for the VAN). The overlapped regions of the DAN for

289   all groups included the bilateral FEF, IFG, IPS and SPL, whereas the overlapped

290   regions of the VAN included the right-lateralized TPJ, aINS, IFG, MFG, dACC and

291   superior frontal gyrus (SFG). LOO methods demonstrated that the spatial distributions

292   of the rsFC-based DAN/VAN were highly consistent in each group (SOR = $91.7 \pm$

293   1.6%, SCC = 0.991 ± 0.004), indicating a highly reproducibility of the resting-state

294   DAN and VAN (Fig. 2D). The spatial distributions of the redefined DAN and VAN

295   with both positive rsFC and high activation probability in the SC are shown in Fig. 3.

296   The DAN was composed of the bilateral FEF, posterior IFG (pIFG), IPS and SPL; and

297   the VAN was a right-lateralized network and included the aINS, TPJ, pIFG, MFG, and

298   dACC. The right pIFG was the only region shared by the DAN and VAN.

299   **FCS changes within the attention network in the blind**

300   Within the DAN, GLM analysis showed significant intergroup FCS differences ($q <$

301   0.05, FDR corrected) in the bilateral SPL/IPS and the right FEF and pIFG (Fig. 4A).

302   The blind groups generally had increased FCS than the SC group, but they did not

303   differ from each other. There were no significant FCS differences within the VAN

304   among the four groups.

305   Significant between-network FCS differences ($q < 0.05$, FDR corrected) were

306   found between the bilateral FEF and SPL/IPS (DAN components) and the VAN (Fig.

307 3B), and between the bilateral aINS, dACC, the right pIFG and TPJ (VAN

308 components) and the DAN (Fig. 3C). Generally, the FCS in each region was increased

309 in the blind than in the SC, but there were no significant differences among the blind

310 groups. The only exception was that the CB had a higher FCS between the right FEF

311 and the VAN than the EB, and a higher FCS between the left FEF and the VAN than

312 the LB ($q < 0.05$, FDR corrected).

313   In the validation analysis, we recalculated FCS using four different connectivity

314 thresholds (r > 0, 0.1, 0.2 and 0.3, respectively) and repeated these intergroup

315 comparisons. The intergroup FCS differences were highly consistent across the four

316 thresholds and very similar with the original ones (Supplementary Figs 4 and 5).

317 **FCS changes between the attention and visual networks in the blind**

318 The GLM showed significant intergroup FCS differences ($q < 0.05$, FDR corrected)

319 between the DAN and VN (Fig. 5A and B). Generally speaking, compared to the SC,

320 the blind subjects showed increased FCS between hubs (the bilateral FEF, IPL and

321 pIFG) of the DAN and the VN and between higher-level visual hubs (the bilateral

322 superior [SOG] and inferior [IOG] occipital gyri, the left lingual gyrus [LG] and the

323 right middle occipital gyrus [MOG]) and the DAN, and decreased FCS between the

324 primary visual areas (the bilateral calcarine sulcus [CalS]) and the DAN (most of

325 them can pass FDR correction). Among the blind subjects, the CB had a lower FCS

326 between the left IOG and the DAN compared to the EB and LB, while higher FCS

327 between the right pIFG and the VN relative to the LB ($q < 0.05$, FDR corrected) (Fig.

328 5A and B).

329   GLM analysis also revealed significant intergroup FCS differences ($q < 0.05$,

330 FDR corrected) between the VAN and VN (Fig. 5C and D). Compared to the SC, the

331 blind subjects showed increased FCS between hubs (the right pIFG, MFG, TPJ, and

332 the bilateral aINS and dACC) of the VAN and the VN and between hubs (most of the

333 right visual areas, the left middle temporal visual area [MT] and SOG) of the VN and

334 the VAN ($q < 0.05$, FDR corrected). No significantly decreased FCS between the

335 VAN and VN were found in any blind groups. In the blind groups, the CB showed a

336 higher FCS between the right aINS and the VN than the LB ($q < 0.05$, FDR corrected),

337 and a higher FCS between the right pIFG and the VN than the EB and LB ($q < 0.05$,

338 FDR corrected) (Fig. 5C and D). As shown in Supplementary Figs 4-6, the intergroup

339 FCS differences between the attention and visual networks were highly consistent

340 across rsFC thresholds and very similar with the original ones.

341 **The rsFC changes within the attention network in the blind**

342 Treating all regions with significant FCS differences as seeds, voxel-wise rsFC

343 analyses ($q < 0.05$, FDR corrected) demonstrated: within the DAN, the blind subjects

344 generally had increased rsFC between the left SPL and the left IPS and pIFG, and

345 between the right SPL and the right FEF, pIFG and IPS compared to the SC. Blind

346 subjects also had increased rsFC between most hubs (such as the bilateral FEF and

347 SPL) of the DAN and those (such as the bilateral aINS and dACC, and right pIFG and

348 TPJ) of the VAN. However, there were no significant differences in rsFC within the

349 attention network among blind subjects (Supplementary Fig. S7).

350 **The rsFC changes between the attention and visual networks in the blind**

351 Voxel-wise rsFC analyses ($q < 0.05$, FDR corrected) demonstrated that most hubs

352 (including bilateral FEF, IPL and pIFG) of the DAN had increased rsFC with

353 higher-level visual areas in the blind compared with the SC, while the primary visual

354 areas (bilateral CalS) showed decreased rsFC with most DAN hubs (Supplementary

355 Fig. S8). Blind subjects also had increased rsFC between most hubs (such as the

356 bilateral dACC and aINS, and right MFG, pIFG, and TPJ) of the VAN and those (such

357 as the bilateral MT and SOG) of the VN (Supplementary Fig. S9). There were no

358 significant differences in rsFC of DAN-VN and VAN-VN among blind subjects.

359 **Correlations between connectivity changes and blindness chronometry**

360 While controlling for gender and head motion effects, partial correlation analyses ($q <$

361 0.05, FDR corrected) showed that duration of blindness was positively correlated with

362 the FCS between the right pIFG of both the VAN ($pr = 0.346$, $P < 0.001$) and DAN

363 ($pr = 0.311$, $P = 0.003$) and the VN, and negatively correlated with the FCS between

364 the left IOG of the VN and the DAN ($pr = -0.326$, $P = 0.002$) (Fig. 9). Furthermore,

365 after additionally controlling for the onset of blindness, the correlations between the

366 right pIFG of the VAN and the VN and between the left IOG of the VN and the DAN

367 were still significant. There were no significant correlations between the FCS of each

368 ROI and the age of onset of blindness ($q < 0.05$, FDR corrected).

369 # Discussion

370 In this study, we found that the blind had similar spatial pattern of the attention

371 network with the SC, suggesting that the intrinsic functional organisation of the

372 attention network is preserved in the blind. The blind subjects showed increased

373 functional connectivity within the DAN, between the DAN and VAN, and between

374 the attention and visual networks, indicating increased information communication

375 within and between these attention-related networks in the blind. The lack of

376 connectivity differences between the blind groups and the lack of correlations

377 between connectivity and onset age of blindness suggest that the intrinsic functional

378 organisation of the attention network is not influenced by its developmental maturity

379 degree at the time of onset of blindness. Our study provided systematic knowledge of

380 the intrinsic functional reorganisation of the attention networks by blindness with

381 different onset age, and can improved our understanding about the interactions

382 between higher-level attention network and visual areas in compensating for visual

383 loss..

Methodological consideration

In light of the FCD that voxel-wisely measure the unweighted degree distribution of the whole brain network (Tomasi and Volkow 2012), the FCS is proposed to voxel-wisely measure the weighted degree distribution of the network (Liang et al. 2013). In contrast to the FCD that is sensitive to connection thresholds, the FCS is insensitive to connection thresholds because of the weighting property, which is supported by our findings of different connection thresholds resulting in similar intergroup FCS differences. Here, we extended the traditional whole-brain-level FCS analysis to voxel-wisely assess the FCS within and between networks, namely the NB-FCSM. Compared with the independent component analysis (ICA) that is typically used to measure the global between-network functional connectivity (Allen et al. 2014; Wang et al. 2014), our voxel-wise between-network FCS analysis can identify the specific brain regions with between-network connectivity differences between groups. A prerequisite for robust application of NB-FCSM is accurate definition of networks of interest. Here, we combined the coordinated-based ALE meta-analysis and the rsFC-based conjunction analysis to more accurately define the DAN and VAN. Thus, each voxel of the redefined attention networks possess both high functional connectivity and coactivation, which was used for NB-FCSM.

Preserved intrinsic functional organisation in the attention network in the blind

The human attention system closely interacts with the sensory systems. For example, the VAN controls stimulus-driven reorienting from sensory modalities and the DAN generates top-down signals to bias the response of the sensory cortex (Astafiev et al. 2003; Kincade et al. 2005) (Astafiev et al. 2006; Indovina and Macaluso 2007). As the main information input of the human brain, visual experience plays an important role in establishing and reshaping the functional organisation of the attention network. For example, visual attention training can reshape the attention network in normal subjects (Rueda et al., 2005; Rueda et al., 2012). In this study, we found that the

411   attention networks showed similar spatial distribution in the blind and the SC,

412   suggesting that the intrinsic functional organisation of the attention networks is

413   preserved in the blind. This finding also indicates that the functional organisation of

414   the attention network can be normally established in the blind by receiving inputs

415   from non-visual sensory modalities because there are dense connections between the

416   attentional regions and the thalamus (Behrens et al. 2003) and non-visual sensory

417   cortices (Umarova et al. 2010). The preserved functional organisation of the attention

418   network in the blind may provide new evidence for the supramodal nature of the

419   attention regions, which is supported by the sensory modality-independent functional

420   specialization of the attention network. For example, a certain attentional region is

421   functionally specialized for processing a specific type of attention despite of the

422   inputs from what sensory modalities (Downar et al. 2000; Smith et al. 2010; Ptak

423   2012).

424   **Enhanced intrinsic functional coupling of the attention network in the blind**

425   Superior auditory/tactile attention performance has been frequently reported in the

426   blind (Roder et al. 1999; Collignon et al. 2006; Forster et al. 2007; Collignon and De

427   Volder 2009). Enhanced activation in the FEF and IPS is also observed in the CB/EB

428   compared the SC when performing attention-demanding tasks (Burton et al. 2004;

429   Garg et al. 2007; Stevens et al. 2007; Burton et al. 2010). In this study, we found

430   increased functional couplings within and between the attention networks in the blind,

431   which may provide an explanation for the superior attention performance from a new

432   perspective of functional integration. We found increased connectivity in the DAN but

433   not in the VAN in the blind, which is consistent with previous studies reporting

434   enhanced activation only in the DAN regions in the CB/EB than the SC during

435   attention-demanding tasks (Burton et al. 2004; Garg et al. 2007; Stevens et al. 2007;

436   Burton et al. 2010). This finding suggests that the DAN and VAN respond differently

437   to visual deprivation, reflecting different dependencies of the development of the

438   functional organisation of the DAN and VAN on visual experience.

439   The DAN and VAN do not work independently, instead, they closely interact to

440   determine which aspects of sensory information will be attended to (Buschman and

441   Miller 2007; McMains and Kastner 2011). In consistent with a previous study (Fox et

442   al. 2006), we found that the right posterior IFG/MFG was the region shared by the

443   DAN and VAN, which may be the anatomical substrate for information

444   communication between the two attention networks. In the theory of reorienting

445   (Corbetta et al. 2008), when one focuses on an object, the DAN sends sustained

446   top-down inhibition signals to the right TPJ to prevent unimportant and low-relevant

447   stimuli from transferring to the VAN; when the stimuli are important and relevant

448   enough to break the inhibition by the TPJ, the VAN is activated and sends the

449   reorienting salient signals to the DAN. The increased intrinsic functional coupling

450   between the DAN and VAN suggests that the information transfer efficiency or the

451   functional integration of the attention networks is enhanced after visual deprivation,

452   which may facilitate the switching between top-down attention and stimulus-driven

453   reorienting. This finding may explain why the blind subjects have superior attention

454   performance (Roder et al. 1999; Collignon et al. 2006; Forster et al. 2007; Collignon

455   and De Volder 2009).

456   **Enhanced intrinsic functional coupling between the attention and visual**

457   **networks in the blind**

458   In the SC, the DAN strongly interacts with the visual areas to bias the visual

459   perception (Buchel et al. 1998a; Tootell et al. 1998; Jack et al. 2006; Silver et al. 2007;

460   Cate et al. 2009; Bressler and Silver 2010). In the blind, the deprived visual

461   perception of the V1 may cause reduced functional coupling between the DAN and

462   the V1. In contrast, the V1 of the blind involves in attention-demanding nonvisual

463   tasks (Bavelier and Neville 2002; Collignon et al. 2009; Sathian and Stilla 2010),

464   which may cause an increased functional coupling between the DAN and the V1.

465   Thus, the reduced functional coupling between the DAN and the V1 in the blind may

466   be a combined consequence of these two mechanisms. The same mechanisms can also

467   be applied to explain for the increased functional coupling between the VAN and the

468   V1 in the blind. In contrast to the V1, the functional specialization of the higher-level

469   visual areas has found to be preserved to process non-visual stimuli in the blind

470   (Amedi et al. 2007; Renier et al. 2010; Collignon et al. 2011; Reich et al. 2011;

471   Wolbers et al. 2011). They can interact with the attention networks to process

472   non-visual attention tasks after visual deprivation (Buchel et al. 1998a; Tootell et al.

473   1998; Jack et al. 2006; Silver et al. 2007; Cate et al. 2009; Bressler and Silver 2010).

474   Thus, our findings of the increased functional coupling between the attention and

475   higher-level visual areas in the blind may reflect an increased interaction between

476   them, which may provide an explanation for the increased attention task-evoked

477   activation (Garg et al. 2007; Stevens et al. 2007) and baseline brain activity and

478   metabolism (Wanet-Defalque et al. 1988; Veraart et al. 1990; Jiang et al. 2015) in

479   these regions, and superior attention performance (Roder et al. 1999; Collignon et al.

480   2006; Forster et al. 2007; Collignon and De Volder 2009) in the blind.

481   **Functional reorganisation of the attention-related networks and brain maturity**

482   In the blind, the structural and functional reorganisation of the visual cortex has been

483   found to be dependent on the development maturity degree of the visual cortex at the

484   time of onset of blindness. Before or within the critical developmental period, visual

485   deprivation results in more significant reorganisation in the occipital cortex than that

486   occurs after the period. Compared to the LB, the CB/EB have more significant

487   changes in cortical thickness (Jiang et al. 2009; Park et al. 2009; Kupers et al. 2011),

488   glucose metabolism (Wanet-Defalque et al. 1988; Veraart et al. 1990), task-evoked

489   activation (Buchel et al. 1998b), and FCD (Qin et al. 2015) in the occipital cortex.

490   Unexpectedly, we found that the functional reorganisation of the attention-related

491   networks was quite similar among the three blind groups and was not correlated with

492 onset age of blindness, indicating that the functional reorganisation of the

493 attention-related networks is not dependent on their development maturity degree at

494 the time of onset of blindness. That is, the non-visual sensory experience is enough

495 for driving the development of the functional organisation of the attention networks.

496 The increased functional coupling may be related to enhancing or unmasking

497 connections of the attention-related networks (Kupers et al. 2011; Qin and Yu 2013).

498   In contrast, although the blind people similarly demonstrated increased intrinsic

499 functional coupling between the attention and visual networks, some hubs and

500 connections between the two networks can also impacted by blindness duration. The

501 most vulnerable attention area is the posterior IFG, the conjunction hub of DAN and

502 VAN (Fox et al. 2006), whose functional coupling with the VN was affected by

503 duration of visual deprivation, indicating the experience-dependent factors may

504 reshape the intrinsic functional connectivity.

Conclusions

506   In summary, our findings demonstrated that long-term visual deprivation can

507 reshape the intrinsic functional coupling within the attention network, and between

508 the attention and visual networks; furthermore, the functional reorganisation of the

509 attention-related networks is not dependent on their development maturity degree at

510 the time of onset of blindness. These compensatory changes may help blind people to

511 more effectively allocate the remaining sensory resources to be aware of the

512 surrounding environment.

513

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519

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676

Table 1: Demographic information of blind and sighted subjects

Measures	CB	EB	LB	SC	Statistics	P value
Gender (male/female)	22 / 8	22 / 8	22 / 8	22 / 8	$\chi^2 = 0$ [a]	1
Age (mean ± SD), years	25.7 ± 4.6	28.5 ± 6.6	28.2 ± 4.1	28.6 ± 5.9	$F = 1.95$	0.125
Onset age of blindness (mean ± SD), years	0	7.7 ± 3.2	18.0 ± 4.4	/	/	/
Duration of blindness (mean ± SD), years	25.7 ± 4.6	20.8 ± 7.9	10.2 ± 4.2	/	/	/
Mean FD (mean ± SD)	0.15 ± 0.07	0.16 ± 0.05	0.15 ± 0.07	0.14 ± 0.05	$F = 0.21$	0.888
Motion spikes (mean ± SD), %	1.69 ± 2.54	1.59 ± 2.35	2.31 ± 4.35	0.94 ± 1.79	$\chi^2 = 2.33$ [b]	0.508

Note: [a] chi-square test. [b] Kruskal Wallis Test, A motion spike is defined as a time point with FD > 0.5. CB = congenitally blind, EB = early blind, FD = frame-wise displacement, SC = sighted control, SD = standard deviation.

Figure Legends

Figure 1. Pipeline of network-based functional connectivity mapping.
Abbreviations: FC = functional connectivity, FCS = functional connectivity strength. There are four main steps for NB-FCSM: A) Extracting the timecourses of each voxel for each network; B) calculating the functional correlation matrix within each network and between each pair of networks; C) calculating the functional connectivity strength of each voxel; D) generating the FCS maps of each network and between each pair of networks.

Figure 2. Spatial similarities of the dorsal and ventral attention networks derived from rsFC-based conjunction analysis. (A) and **(B)** show **s**patial overlaps of the DAN and VAN across groups, respectively. The color of each voxel indicates the number of groups (1 to 4) that share this voxel in the DAN or VAN. **(C)** represents the spatial correlation coefficients and overlapping ratio of the attention networks between each pair of groups. **(D)** shows the spatial correlation coefficients and overlapping ratio of the attention networks between each LOO iteration and the use of full data in each group.
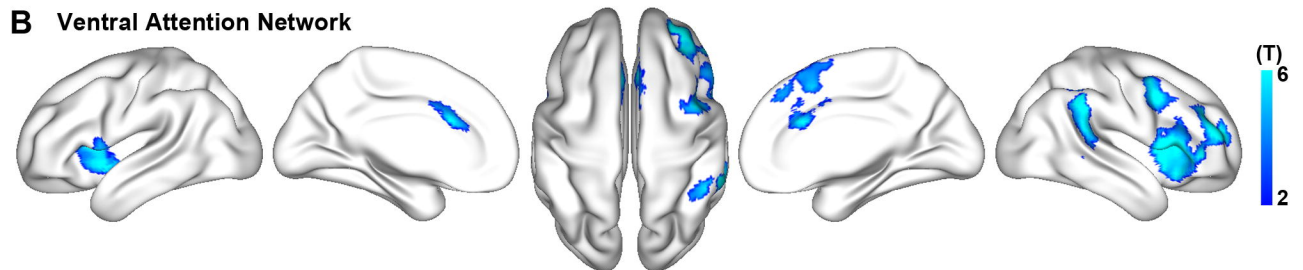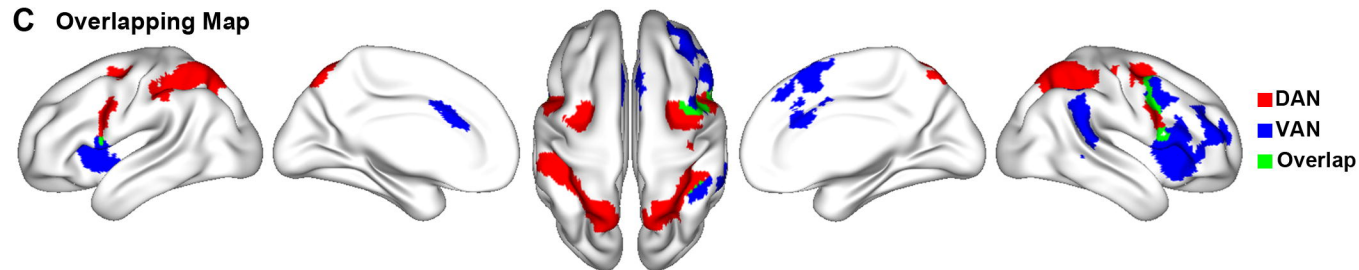
Figure 3. The refined dorsal and ventral attention networks in the sighted controls. The DAN **(A)** and VAN **(B)** were identified by combination of ALE-based coactivation and rsFC-based conjunction analyses ($q < 0.05$, FDR corrected). Each non-zero voxel of an attention network has both positive rsFC with the hubs of this network and high activation probability by visual attention tasks. The color bar represents the T value of the conjunction analysis. The DAN (red) and VAN (blue) are spatially overlapped at the right posterior IFG (green) **(C)**.

Figure 4. FCS changes within the attention networks in the blind. General linear model is used to compare FCS differences within the attention networks between the total blind subjects and the sighted controls ($q < 0.05$, FDR corrected), while controlling for the effects of age, gender, and mean FD. Color bar represents the T value. Warm and cold colors represent increased and decreased FCS in the blind, respectively. **(A)** shows the intergroup FCS differences within the DAN; **(B)** shows brain regions of the DAN that exhibit intergroup differences in FCS with the VAN; and **(C)** shows brain regions of the VAN that exhibit intergroup differences in FCS with the DAN. The lines connecting any two groups in bar graphs indicate significant differences between the two groups ($q < 0.05$, FDR corrected).

Figure 5. FCS changes between the attention and visual networks in the blind. General linear model is used to compare FCS (between the attention and visual networks) differences between the total blind subjects and the sighted controls ($q < 0.05$, FDR corrected), while controlling for the effects of age, gender, and mean FD. Color bar represents the T value. Warm and cold colors represent increased and decreased FCS in the blind, respectively. **(A)** shows brain regions of the DAN that exhibit intergroup differences in FCS with the VN; **(B)** shows brain regions of the VN that exhibit intergroup differences in FCS with the DAN; **(C)** shows brain regions of the VAN that exhibit intergroup differences in FCS with the VN; **(D)** shows brain regions of the VN that exhibit intergroup differences in FCS with the VAN. The lines connecting any two groups in bar graphs indicate significant differences between the two groups ($q < 0.05$, FDR corrected).

Figure 6. Correlations between duration of blindness and FCS in the blind. Partial correlation analyses controlling for the effects of gender and mean FD are performed to test correlations between duration of blindness and regional FCS in the blind ($q < 0.05$, FDR corrected).
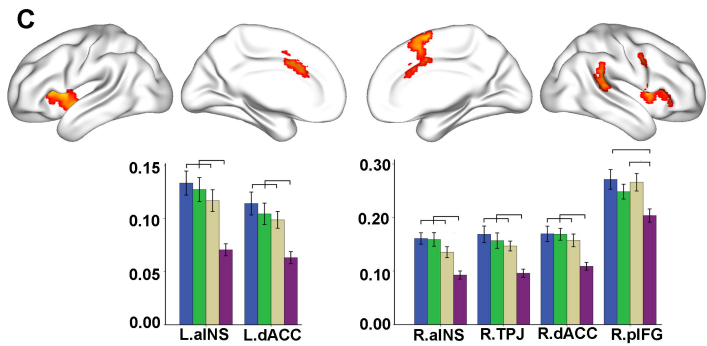
A Time Courses

Network A

Network B

B FC Matrix

C FCS of Each Node

Network A

Network B

A1

Ai

An

B1

Bi

Bn

→ FC within Network A

⇢ FC between Network A&B

⇢ FC between Network B&A

→ FC within Network B

D FCS Mapping

FCS_A

$FCS_{A\&B}$

$FCS_{B\&A}$

FCS_B
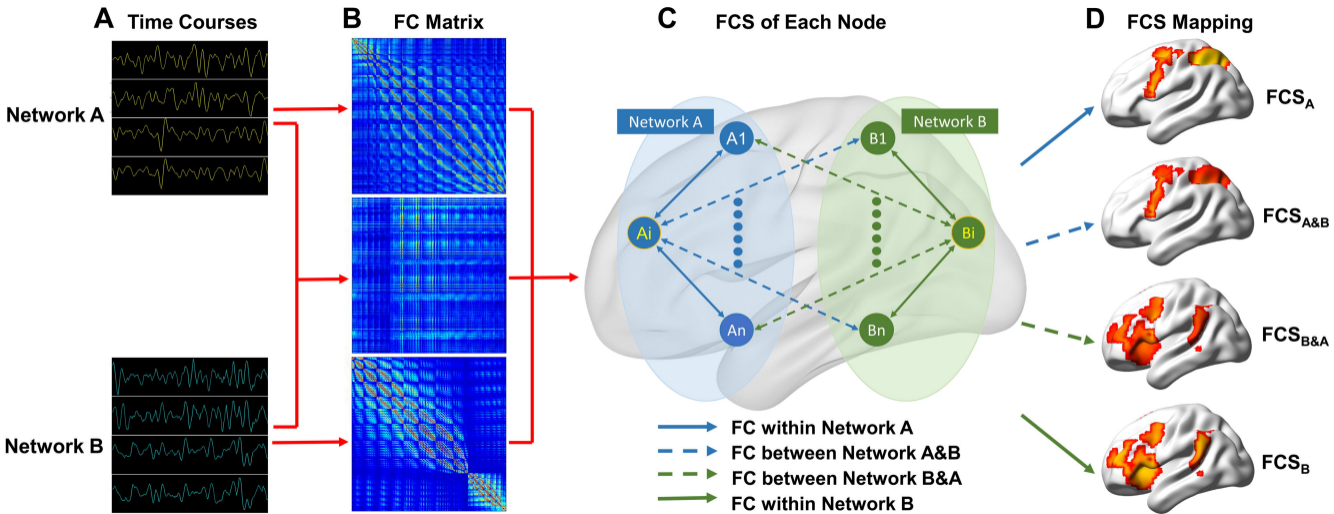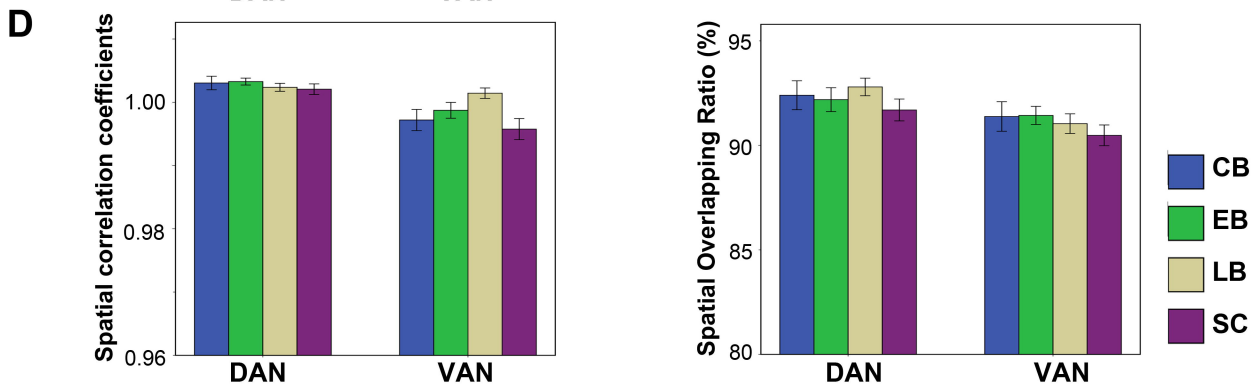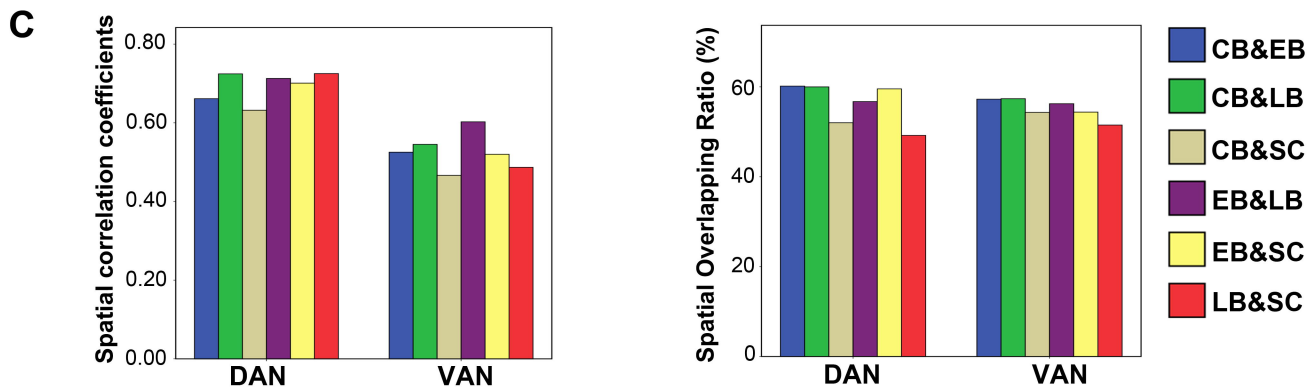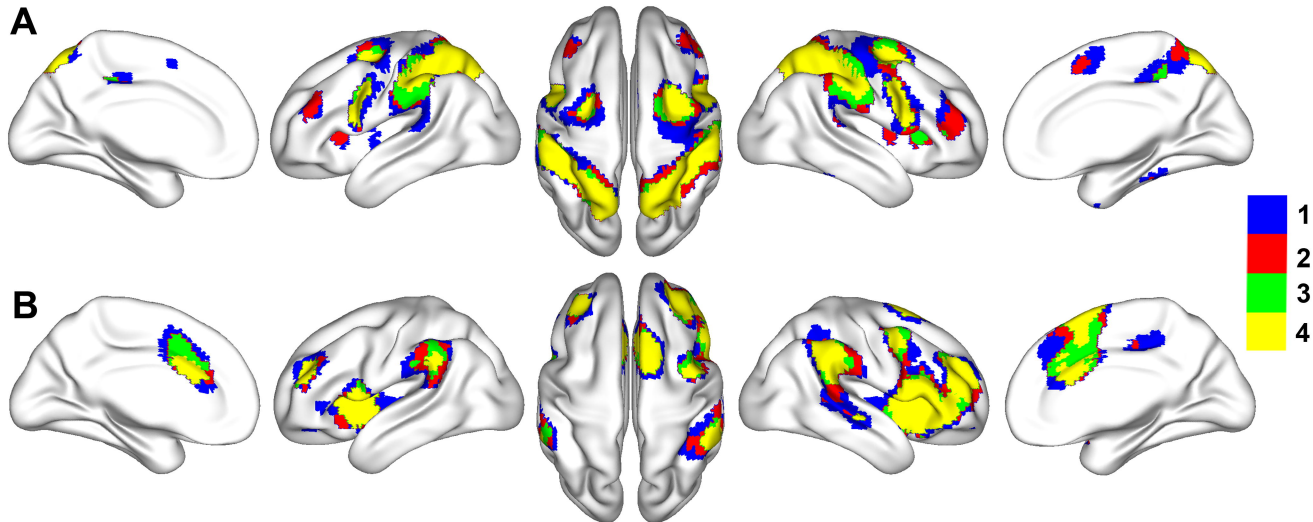
A Doral Attention Network
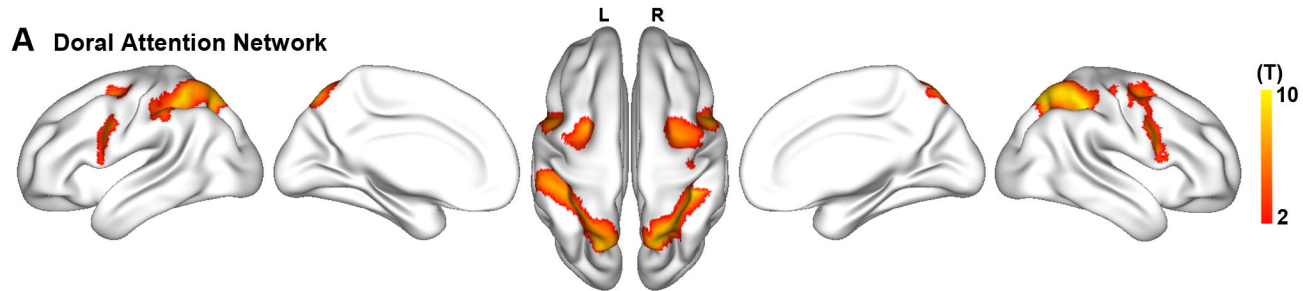
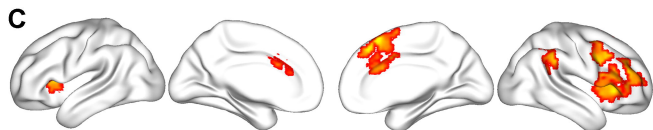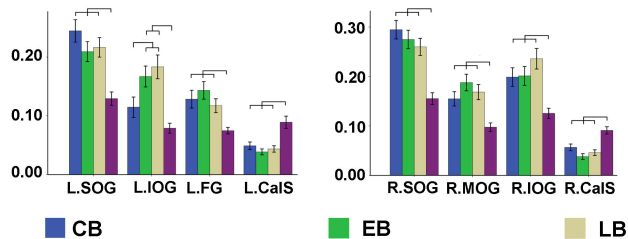**B** Ventral Attention Network

C Overlapping Map

L R

(T) 10 — 2

(T) 6 — 2

DAN
VAN
Overlap