

Brain functional connectivity density and individual fluid reasoning capacity in healthy young adults

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Functional connectivity density (FCD) is a newly developed data-driven method to measure the number of functional connections of each voxel, possibly providing new insight into the neural correlates of fluid reasoning. Here, we recruited 211 healthy young adults (91 men and 120 women) to investigate associations between the global FCD and fluid reasoning capacity as measured by the Raven's Standard Progressive Matrices. Raven's Standard Progressive Matrices scores were correlated negatively with the global FCD in multiple brain regions of the frontal, parietal, occipital, and temporal cortices in male participants. No significant correlation was found in female participants. Our findings confirmed the association between fluid reasoning and functional connectivity of multiple cognitive-related brain regions. The positive correlation with the functional connectivity strength and the negative correlation between fluid reasoning and FCD suggest that individuals with superior fluid reasoning capacity may possess a small number of strong functional

connections. The sex dichotomy of this association indicates that the fluid reasoning capacity of men and women may have different neural substrates. *NeuroReport* 26:17–21 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Fluid reasoning reflects the capacity of relational reasoning, which is used to identify relationships, comprehend implications, and draw inferences in a novel situation. Fluid reasoning roughly corresponds to fluid intelligence, which is not only a central component of general intelligence but also interacts with educational and cultural experience to determine crystallized intelligence [1]. Individual fluid reasoning capacity influences how fast and how much an individual learns and affects his/her ability to manipulate information during the reasoning process [2]. In humans, this capacity can be measured by the Raven's Progressive Matrices (RPM), which is a widely used, culture-fair, nonverbal index [3].

The neural mechanisms of intelligence have been investigated extensively by neuroimaging techniques and have been summarized in a parietofrontal integration theory (P-FIT) [4]. However, most of these studies have focused on general intelligence and do not exclusively reflect the neural substrate of fluid reasoning capacity. Thus, several studies have investigated correlations between brain activation and individual RPM scores and shown correlations in the lateral prefrontal and parietal cortices [5]. Voxel-based morphometry analysis has shown a positive correlation between gray matter volume (GMV) of the medial prefrontal cortex (MPFC) and fluid

intelligence [6]. In addition, fluid reasoning capacity has been associated with GMV and regional homogeneity (ReHo) of spontaneous activity in multiple brain regions, especially those of the salience network [7].

Recently, graph theory/network approaches have been applied to linking connectivity and intelligence; these studies have shown that network efficiency is correlated closely with intelligence [8]. As a network analysis, functional connectivity density (FCD) mapping is a newly developed data-driven method used to identify the number of functional connections of each voxel of the brain [9]. This ultrafast technique allows the identification of voxels that play more important roles in information processing [9] and may provide a full picture of the functional organization of intelligence.

Although there is no direct evidence to support a sex difference in correlations between graph theory indices and intelligence, sex-related differences have been reported in graph theory indices [10] and FCD [11]. Moreover, sex differences have been found in correlations between intelligence and GMV [12], resting-state functional connectivity [13], and anatomical connectivity [14]. These findings suggest that men and women may have different neural substrates for intelligence. In this study, we aimed to investigate the sex-specific neural correlates of fluid reasoning capacity using FCD analysis.

Materials and methods

Participants

This study was approved by the ethics committee of the Tianjin Medical University General Hospital, and written informed consent was obtained from each participant. A total of 324 right-handed healthy young adults were recruited through advertisements. All participants had no history of psychiatric or neurological disorders and did not have any contraindications to MRI scans. Conventional brain MRI scans did not indicate visible lesions in any individual. In all, 42 participants were excluded for the following reasons: lack of behavioral data (16 cases), structural anomalies (two cases), excessive head motion (15 cases), and the Raven's Standard Progressive Matrices (RSPM) score was within the lowest 5% of the Chinese norm (nine cases). In addition, 71 participants were excluded because their mean global FCD value of the whole brain was not within the range of 0.25–1.75 of the median global FCD value of the remaining 282 participants. A total of 211 participants (91 men and 120 women) were included in the statistical analysis.

Behavioral examination

The RSPM battery was used to test the capacity of fluid reasoning [3]. The RSPM battery includes 60 matrix-reasoning problems, which are further categorized into five levels of increasing complexity and difficulty. Participants must identify relevant features on the basis of the spatial organization of an array of visual stimuli and then select one of several possible answers that matches the identified features. In our examination, all participants were instructed to study each problem until they had determined the best answer, and no explicit time limit was imposed. The RSPM score of each participant included the number of correct items out of 60 possible items; however, it is not a scaled score.

MRI acquisition

Within a week after the RSPM test, MRI scans were performed on a 3.0 T scanner (Signa Excite HDx; GE Healthcare, Milwaukee, Wisconsin, USA). Tight but comfortable foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. Resting-state functional MRI (fMRI) scans were performed using an echo planar imaging sequence with scan parameters of repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, matrix = 64 × 64, field of view (FOV) = 240 × 240 mm², slice thickness = 4 mm without gap. Each brain volume was comprised of 40 axial slices and each functional run contained 180 volumes. During fMRI scans, participants were instructed to keep their eyes closed, to remain as motionless as possible, to think of nothing in particular, and to not fall asleep. Structural images were acquired using a brain volume (BRAVO) sequence with the following parameters: TR = 8.1 ms, TE = 3.1 ms, inversion time = 450 ms, FOV = 256 × 256 mm², slice thickness = 1.0 mm

without gap, FA = 13°, matrix = 256 × 256, and 176 contiguous sagittal slices.

Data preprocessing

The fMRI data were preprocessed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>). The first 10 volumes for each participant were discarded to allow the signal to reach equilibrium and the participants to adapt to the scanning noise. The remaining 170 volumes were then corrected for the acquisition time delay between slices. Because of the thresholds of head motions (translational or rotational motion parameters lower than 2 mm or 2°), 13 participants were excluded. We also calculated framewise displacement (FD), which indexes volume-to-volume changes in head position. These changes were obtained from the derivatives of the rigid-body realignment estimates that were used to realign fMRI data. Two participants were excluded because they had an FD higher than 0.3. The approach used to normalize these functional images included the following steps: (a) individual structural images were linearly coregistered to the functional images after motion correction; (b) the transformed structural images were segmented into gray matter, white matter, and cerebrospinal fluid, and then gray matter was nonlinearly coregistered to the Montreal Neurological Institute (MNI) space; and (c) the motion-corrected functional images were spatially normalized to the MNI space using the parameters estimated during the nonlinear coregistration. The functional images were then resampled into a voxel size of 2 × 2 × 2 mm³. Several nuisance covariates (six motion parameters and average BOLD signals of the ventricular and white matter) were regressed out from the data, and the datasets were band-pass filtered within a frequency from 0.01 to 0.1 Hz.

FCD calculation

We calculated the global FCD of each voxel using an in-house script that was written in a Linux platform according to a previously described method [9,11]. The global FCD calculation was restricted to gray matter voxels with a signal-to-noise ratio of greater than 50%. We first calculated the Pearson correlation coefficient between each pair of voxels within the gray matter mask. If the Pearson correlation coefficient between a pair of voxels was higher than 0.6, the two voxels were considered functionally connected. To determine whether the selection of correlation thresholds could affect our results, we also used three other thresholds (0.3, 0.4, and 0.5) to calculate the FCD. The global FCD of a given voxel (x_0) was calculated as the number of voxels that were functionally connected with x_0 . Finally, the global FCDs were spatially smoothed with an 8 × 8 × 8 mm³ Gaussian kernel.

Statistical analysis

A two-sample *t*-test was used to investigate the sex differences of global FCD. Then, a general linear model

was used to assess correlations between the FCD and RSPM scores in either men or women, and the sex differences in these correlations. In the general linear model, sex and RSPM score were treated as two independent variables, and their interaction was also considered. In the analysis, age, educational years, and FD values were treated as covariates of no interest. Multiple comparisons were corrected using the false discovery rate (FDR) method ($q < 0.05$ and cluster size > 50 voxels).

Results

Behavioral and demographic data

A total of 211 participants were included in the final FCD analysis, including 91 men (mean age: 22.2 ± 2.5 years; years of education: 15.1 ± 2.3) and 120 women (mean age: 23.3 ± 2.2 years; years of education: 16.3 ± 1.8). The average RSPM score was 53.8 ± 5.3 (ranging from 34 to 60) for men and 53.7 ± 5.6 for women (ranging from 35 to 60). There was no statistical difference in the RSPM scores between male and female participants ($t = 0.145$, $P = 0.885$).

Sex differences in global FCD

Brain regions with significant sex differences in global FCD are shown in Fig. 1. They included the bilateral precuneus (Pcu), the anterior cingulate cortex, the superior parietal lobule, the superior occipital gyrus, the superior temporal gyrus, the middle frontal gyrus (MFG), the inferior frontal gyrus, and the supramarginal gyrus (SMG) (Fig. 1). The distribution of brain regions with sex differences was similar to that reported previously [11].

Correlation between the RSPM score and global FCD

After adjusting for the effects of age, educational years, and FD values, the male participants showed negative correlations between RSPM scores and global FCD ($q < 0.05$, FDR corrected) in the MPFC; bilateral superior frontal gyrus (SFG), MFG, middle temporal gyrus (MTG), calcarine sulcus (CalS), lingual gyrus (LG), Pcu and precentral gyrus (PreCG), right parahippocampal gyrus (PHG), and left SMG (Fig. 2a). No brain area showed a positive correlation between global FCD and the RSPM score in men. In addition, no brain area showed a statistical correlation between global FCD and

RSPM score in women. When the FCD was calculated using other connectivity thresholds (0.3, 0.4, and 0.5), similar results were obtained (Fig. 2b–d).

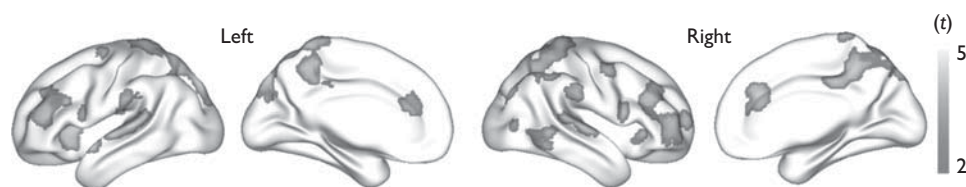
Sex differences in correlations between global FCD and the RSPM score

Compared with female participants, male participants showed increased negative correlations ($q < 0.05$, FDR corrected) in several brain regions including the bilateral MPFC, MTG, CalS, LG, cuneus, and Pcu; left MFG, SFG, and SMG; and the right PreCG (Fig. 2e). When the FCD was calculated using other connectivity thresholds (0.3, 0.4, and 0.5), similar results were obtained (Fig. 2f–h).

Discussion

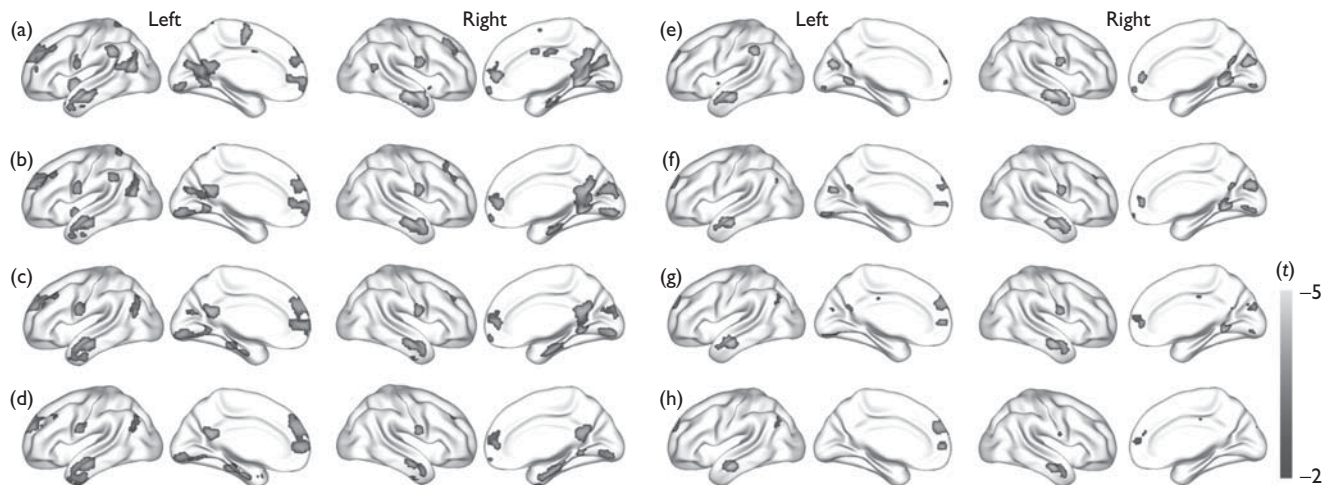
This is the first study to explore the neural mechanisms of fluid reasoning capacity using an FCD mapping method. We found that RSPM scores were negatively correlated with the global FCD in the bilateral MPFC, SFG, MFG, MTG, CalS, LG, Pcu and PreCG, right PHG, and left SMG in men, but not in women. The MPFC, Pcu, SMG, PHG, and MTG are nodes of the default-mode network (DMN) that is involved in self-referential and cognitive processing. Damage to the posterior DMN, such as in the Pcu region, has been consistently associated with Alzheimer's disease [15], which is characterized by episodic memory deficits. Our finding of a negative correlation between the global FCD of the DMN and RSPM scores supports the established association between the DMN and cognitive performance. We also found that the global FCD in the prefrontal cortex (SFG and MFG) was correlated negatively with RSPM scores, which is consistent with the central role of the prefrontal cortex in cognitive processing. For example, the prefrontal cortex is activated by reasoning tasks [2] and the activation of this region is correlated positively with RPM scores [5]. Moreover, the functional connectivity of the dorsolateral prefrontal cortex has been associated with intelligence [16]. Jung and Haier proposed the P-FIT model to explain the neural basis of intelligence. In this theory, the prefrontal cortex is considered to be critical for intelligence [4]. We also found that the global FCD in the visual cortex (CalS and LG)

Fig. 1



Brain regions with significant differences in global FCD between male and female participants ($q < 0.05$, FDR corrected). FCD, functional connectivity density; FDR, false discovery rate.

Fig. 2



Correlations between RSPM scores and global FCD in male participants and sex differences in these correlations. (a–d) Brain regions with significant correlations between RSPM scores and global FCD in male participants with different connectivity thresholds consisting of 0.6 (a), 0.5 (b), 0.4 (c), and 0.3 (d). A uniform uncorrected threshold of $P=0.0028$ is used for all correlation analyses, which is equal to $q=0.05$ (FDR corrected) for the FCD data with $r=0.6$. (e–h) Brain regions with significant sex differences in correlations between RSPM scores and global FCD with different connectivity thresholds consisting of 0.6 (e), 0.5 (f), 0.4 (g), and 0.3 (h). A uniform uncorrected threshold of $P=0.0012$ is used for all comparisons, which is equal to $q=0.05$ (FDR corrected) for the FCD data with $r=0.6$. The statistical t map is projected onto the brain surface with CARET software (Washington University School of Medicine in Saint Louis, Missouri, USA). FCD, functional connectivity density; FDR, false discovery rate; RSPM, Raven's Standard Progressive Matrices.

was correlated negatively with the RSPM scores. The visual cortex is involved in updating information in working memory by making comparisons among visual images and modulating visual attention. These functions are critically important for dealing with fluid reasoning tasks. Our finding is consistent with previous studies that have shown a positive correlation between the GMV of the visual cortex and RSPM scores [7] and that the visual cortex is activated by a variety of cognitive tasks, particularly RPM relational reasoning [2]. The global FCD of the PreCG also showed a negative correlation with RSPM scores, which is in agreement with previous findings that reported positive correlations between the GMV of this region and visuospatial cognition processing [17]. Moreover, the PreCG was frequently activated during cognitive tasks associated with relational reasoning [18]. In the P-FIT model of intelligence, the sensorimotor areas are engaged in generating appropriate responses in the final processing of intelligence [4].

Two seemingly contradictory hypotheses of the neural mechanisms of intelligence exist. One hypothesis is that the larger is the smarter. This theory is supported by studies that report positive correlations between intelligence and multiple measures such as brain size [19], efficiency of the brain network [8], GMV [4], white matter integrity [20], activation [4], ReHo [7], and functional connectivity [16] of the whole brain or certain regions. The other hypothesis is the neural efficiency hypothesis of intelligence, postulating that more intelligent individuals are more likely to focus their activation

on task-relevant areas, whereas less intelligent individuals activate their brains in a more distributed manner. This hypothesis was proposed and validated in several task-based studies that showed a negative relationship between cognitive functioning and activation over the whole brain [21]. The hypothesis has been extended to other structural and functional characteristics of the brain. For example, hippocampal volumes were significantly and inversely correlated with intelligence [22] and RSPM scores were negatively correlated with ReHo in the DMN [7]. Consistent with the neural efficiency hypothesis, we found a negative correlation between global FCD and fluid intelligence. Considering the positive relationship between functional connectivity strength and intelligence, our finding may be interpreted as meaning that an individual with higher intelligence needs a smaller number of stronger connections to meet the demand for efficient processing of information.

In the present study, we found that fluid reasoning capacity was negatively correlated with global FCD in men, but not in women. Although no significant sex difference has been found in intelligence levels, we hypothesize that men and women may have different neural mechanisms of intelligence. This hypothesis is supported by the previously described sex-dependent differences in the structural and functional organization of the brain [11], correlations between intelligence and brain volume [12], and behavior abilities [23]. For example, the positive correlation between intelligence and GMV was more significant in men, whereas the

positive correlation between intelligence and white matter volume was more significant in women [12]. Another example indicated that men showed superior performance in spatial cognitive tasks, but were less efficient in verbal cognitive tasks than women [23]. Moreover, an electroencephalographic study relating intelligence with brain activity under cognitive load showed that men were more likely to produce cortical activation patterns that are in line with the neural efficiency hypothesis (i.e. less activation in more intelligent individuals), whereas in women, no significant differences were observed [24]. In addition, a resting electroencephalographic study has also shown that the brain activity of men decreases with the level of general intelligence, whereas an opposite pattern of brain activity was observed in women [25]. These findings suggest that men and women may recruit different neural pathways or adopt different cognitive strategies to accomplish the same cognitive task. Moreover, our finding of the sex-dependent association between global FCD and fluid reasoning ability may be related to other factors; for example, the RSPM battery may have a bias for spatial capacity [23] and sex differences exist in the global FCD of the brain [11].

Conclusion

Our study showed that fluid reasoning ability was correlated negatively with the global FCD of multiple brain regions only in men. These findings support the neural efficiency hypothesis of intelligence and the sex-dependent neural mechanisms of intelligence.

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Conflicts of interest

There are no conflicts of interest.

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