NeuroImage 186 (2019) 510–517

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

BOLD-fMRI reveals the association between renal oxygenation and functional connectivity in the aging brain

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ARTICLE INFO

Keywords:
fMRI
Aging
Brain
Kidney
FCD
MCR

ABSTRACT

Aging is accompanied by a decline in physical and cognitive function. Vascular aging may provide a major influence on these measures. The purpose of this study was to explore the relationship between renal oxygenation and functional connectivity of the aging brain because of the anatomic and hemodynamic similarities between cerebral and renal vessels. Fifty-two healthy older adults were recruited to undergo a BOLD-fMRI scan of the brain and kidneys, and forty-four healthy younger subjects were recruited as the control group. First, cerebral functional connectivity density (FCD) was used to evaluate functional connectivity. Renal medullary and cortical R2* values were extracted respectively, and the ratio of medullary and cortical R2* values (MCR) was calculated. Then, the association between brain FCD and renal MCR was analyzed. Compared with younger adults, the elderly group showed higher renal medullary R2* and MCR, which might reflect a slight abnormality of renal oxygenation with aging. The older subjects also showed enhanced FCD in bilateral motor-related regions and decreased FCD in regions of the default mode network (DMN). The findings indicated that the functional connectivity in the DMN and motor cortices was vulnerable to aging. Moreover, the altered brain FCD values in the watershed regions, DMN and motor cortices were significantly correlated with the renal MCR value in the elderly group. The association between renal oxygenation abnormalities and spontaneous activity in the brain might reflect vascular aging and its influence on the kidney and brain during aging to some extent. This study provided a new perspective for understanding the relationship between tissue oxygenation and brain functional connectivity.

1. Introduction

Blood Oxygenation Level-Dependent (BOLD) MRI exploits the properties that deoxyhemoglobin is paramagnetic and oxyhemoglobin is diamagnetic to assess tissue oxygen bioavailability (Prasad, 2006; Pruijm et al., 2013). It provides a sensitive noninvasive and repeatable approach to detect the oxygen partial pressure (P_{O2}) in tissue when all other factors (shimming or measurement parameters) are assumed to be constant (Prasad et al., 1996; Thoeny et al., 2008). Thus, the BOLD can reflect oxygen content and vessel fundamental changes in tissue. Till now, the fMRI relied on BOLD signal (BOLD-fMRI) has been widely used to investigate the functional state of the human brain. The functional connectivity based on the BOLD signals has provided quantitative indexes to understand the brain neurophysiological and neuropathological conditions (Hu et al., 2017; Jiang et al., 2018; Zhong et al., 2018; Zhu et al., 2018).

Brain function, including cognitive, memory and motor control, changes with aging. Using functional connectivity assessed by BOLD-fMRI, elders have reorganizations of functional connectivity in the major brain networks such as the frontoparietal network and default mode network (DMN), which explain the age-related cognitive and behavioral alterations (Cao et al., 2014, 2016; Ferreira and Busatto, 2013; Sala-Llonch et al., 2015). The biological trajectory of aging, such as cell apoptosis, special protein deposition and small vessel abnormalities, contributes to the functional alterations of the brain (Damoiseaux, 2017; Sala-Llonch et al., 2015). In the meantime, BOLD-fMRI was applied to study the renal oxygenation in mid-1990s (Prasad et al., 1996). The kidney including cortex and medulla parts is considered as a high

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https://doi.org/10.1016/j.neuroimage.2018.11.030
Received 30 September 2018; Received in revised form 19 November 2018; Accepted 20 November 2018
Available online 22 November 2018

Abbreviations

FCD	Functional connectivity density
CBF	Cerebral blood flow
CR2*	Cortical R2* value
MR2*	Medullary R2* value
MCR	Ratio of medullary and cortical R2* values
DMN	Default mode network
ACC	Anterior cingulate cortex
PCC	Posterior cingulate cortex

perfusion organ in humans. The natural oxygen pressure gradient between renal cortex and medulla makes it the ideal target for BOLD-fMRI (Prasad et al., 1996). However, differing from the mechanism of BOLD in brain, the BOLD signals in kidney represent the apparent spin-spin relaxation rate R2* (1/T2*) which are related to the tissue content of deoxyhemoglobin. (Prasad et al., 1996; Thoeny et al., 2008; Yin et al., 2012). In experimental studies in pigs, the renal BOLD-fMRI was verified to depict changes in intrarenal oxygenation (Juillard et al., 2004; Pedersen et al., 2005; Thoeny et al., 2008). Moreover, the renal cortical R2* (CR2*) and medullary R2* (MR2*) are linearly associated with renal P_{O2} levels according to previous studies (Prasad, 2006; Thoeny et al., 2008). Thus, R2* can be considered a marker of renal oxygenation (Pruijm et al., 2013). However, some external factors, such as shimming or the physiologic status of the subjects, might influence the renal R2* value (Thoeny et al., 2008). To reduce these impacts, the ratio of renal medullary and cortical R2* value (MCR = MR2*/CR2*) was also analyzed. Our previous study suggested that the renal MCR would be a sensitive feature to monitor the progression and prognosis of diabetic nephropathy (Yin et al., 2012). The kidney is involved in the excretion of waste substances and the synthesis and metabolism of hormones (e.g. vitamin D3, erythropoietin, thrombopoietin, renin) (Gekle, 2017). Thus, there is no doubt that the kidney plays a crucial role in our living system and makes a great contribution to the maintenance of the milieu interieur. The declined renal function with aging has been found in previous study such as decreased glomerular filtration rate and diminished renal reserve (Musso and Oreopoulos, 2011). Previous renal BOLD-fMRI studies have shown that aging leads to altered renal function, especially for medullary oxygenation (Epstein and Prasad, 2000; Prasad and Epstein, 1999).

Interestingly, many studies have indicated that impaired renal function is associated with cerebral small vessel disease and cognitive impairment (Akoudad et al., 2015; Vemuri et al., 2017). Kim et al. observed a significant association between cerebral microbleeds and renal function in a big cohort of adults (Kim et al., 2017). It has been suggested that renal function could be a useful marker for brain function related to cerebrovascular events (Cho et al., 2009; Saji et al., 2015). Actually, there is a tight link between the brain and kidney because of vascular anatomic and hemodynamic similarities (Akoudad et al., 2015; Cho et al., 2009; O'Rourke and Safar, 2005). Both the brain and kidney are considered low resistance end-organs, and they receive continuous and passive perfusion with high-volume flow during the entire cardiac cycle (Mogi and Horiuchi, 2011; O'Rourke and Safar, 2005). In addition, both of them are also sensitive to hypoxia, such as decreased P_{O2}. These resemblances may explain why renal and cerebrovascular diseases have a shared vascular pathogenesis (Akoudad et al., 2015). In general, the aging is considered as a covariant condition with slight vascular abnormality between brain and kidney. However, it remains unknown how renal function influences brain function. Although distinct BOLD-fMRI markers are used to identify clinical and subclinical brain and kidney dysfunction, systemic research examining the association between markers from brain and kidney is lacking (Akoudad et al., 2015).

For decades, a series of features emerged from BOLD-fMRI analyses and have been developed to identify brain function. For example, the amplitude of low frequency fluctuations (ALFF)(Yang et al., 2007), regional homogeneity (ReHo)(Zang et al., 2004) and FOur-dimensional (spatiotemporal) Consistency of local neural Activities (FOCA)(Dong et al., 2015) have been used to evaluate the local neural activity in resting-state fMRI studies. Functional connectivity, which represents the covariance of the BOLD signal between brain regions, could describe the interaction both between adjacent regions (local interactions) and between distant areas (distant interactions). The functional connectivity density (FCD), as a data-driven and unbiased approach to analyze whole brain connectivity, provides sensitive evidences for the detection of brain functional interaction (Tomasi and Volkow, 2010). For a given cerebral voxel, the local FCD could be calculated in the spatially adjacent region around this voxel to reflect its local interaction (Luo et al., 2014), and the long-range FCD could also be obtained in the global brain except for adjacent region to describe its distant interaction. The recent studies have shown that the functional connectivity was associated with a local blood supply in healthy subjects (Chu et al., 2018; Qiu et al., 2017; Schmithorst et al., 2015). Liang and his colleagues suggested that functional connectivity is sensitive to changes in local oxygen consumption in the human brain (Liang et al., 2013). In the illness condition, the abnormal cerebral blood supply might cause altered functional connectivity in some particular regions. For example, the altered functional connectivity was observed in specific regions such as frontoparietal and cerebellar regions in subjects with early small vessel disease (Schaefer et al., 2014). Thus, the influence on functional connectivity caused by the changes of blood supply was inconsistent in whole brain, but presented in the brain regions prominently, which were sensitive to oxygen content.

Considering the similarities of cerebrovascular and renal hemodynamics, we hypothesize that functional connectivity in the aging brain is associated with renal oxygenation features from BOLD signals. Furthermore, the brain regions (sensitive to oxygen content), such as the watershed areas (Del Sette et al., 2000), would show a more tight association with the renal BOLD-fMRI features. Thus, in this study, we aimed to explore the association between FCD (local and long-range FCDs) in the brain and renal oxygenation features and whether the watershed area is sensitive to changes in renal features.

2. Materials and methods

2.1. Subjects

Fifty-two healthy older adults (65.4 ± 7.80 years old) and 43 younger subjects (21.8 ± 2.53 years old) were recruited in this study. The elderly group was screened using the Montreal Cognitive Assessment (MoCA) and Activity of Daily Living Scale (ADL). The inclusion criteria for the older subjects included the following: more than six years of education; absence of brain injury and neurological or psychiatric disorders; absence of diabetes or hypertension; no medication; MoCA scores greater than 25; and ADL scores less than 23. All younger subjects were also limited to those without a history of head injury or other neurological conditions. Before MRI scanning, all subjects' blood pressure was measured, and subjects with abnormal blood pressure were excluded. For the elderly group included in the experiment, systolic blood pressure was 112.3 ± 18.6 mmHg and diastolic blood pressure was 71.4 ± 19.2 mmHg; in the younger group, blood pressure was 108.8 ± 19.1 mmHg/65.9 ± 14.5 mmHg (systolic/diastolic, respectively). The blood pressure of the two groups were not significantly different (systolic blood pressure: $t = 0.907$, $p = 0.18$; diastolic blood pressure: $t = 1.576$, $p = 0.06$). All participants provided written informed consent forms, and the study protocol was approved by the local Ethics Committee of University of Electronic Science and Technology of China (UESTC).

2.2. Data acquisition

All MRI data were acquired using an MRI scanner (3.0 T, Discovery

MR750, GE, USA) in the Center of Information Medicine Research in UESTC. On the night before the MRI study, each subject was required to refrain from food and water (take nothing by mouth for approximately 12 h) overnight until scanning. The next morning, the vital signs, weight and height were measured for all participants. During scanning, the head was fixed using foam pads and ear plugs to minimize the motion and scanning noise, respectively. Resting-state brain fMRI was collected using gradient-echo EPI sequences (repetition time [TR] = 2000 ms, echo time [TE] = 30 ms, field of view [FOV] = 24 × 24 cm^2, flip angle [FA] = 90°, matrix = 64 × 64, slice thickness/gap = 4 mm/0.4 mm). The brain fMRI scanning lasted for 510 s, and a total of 255 vol were collected. The subject was instructed to close the eyes and keep the head motionless without falling asleep during the scanning. BOLD-fMRI of the kidney was obtained by a 16 echoes multigradient-recalled-echo sequence (TR = 200 ms; TE: 2.216–36.896 ms (equidistant echo time spacing 2.312 ms), bandwidth = 300 Hz per pixel, FA = 25°; matrix = 256 × 256; FOV = 38 × 38 cm^2). During the renal fMRI scanning, we asked the subject breath-hold to avoid the pseudo shadow produced by breathing. Thus, sixteen T2*-weighted images were recorded within a single breath-hold of 18 s.

2.3. Brain-fMRI data analysis

For the resting-state brain images, the first five volumes were removed for the magnetization equilibrium. The imaging data pre-processing was conducted using the SPM8 (http://www.fl.ion.ucl.ac.uk/spm/sofware/spm8/) and NIT toolboxes (Dong et al., 2018). The pre-processing steps included slice-timing, head movement correction, and spatial normalization to the Montreal Neurological Institute (MNI) template using a 12-parameter affine transformation (3 × 3 × 3 mm^3).

The voxel-based FCD maps were obtained for each subject. The processing steps are as follows. For a given voxel (X_0), we calculated Pearson's correlation between the time courses of this voxel and all other voxels in the whole brain. Any voxel with a correlation coefficient greater than 0.6 was considered significant correlation voxels (functional connection with this voxel). Any voxel, which was adjacent to X_0 by a continuously functionally connected path, was included in the neighbors of X_0. The number of voxels in the cluster of neighbors was mapped to the local FCD value of X_0. This process was repeated in each voxel of the whole brain. On the other hand, the number of significant correlation voxels in the whole brain without a neighboring cluster was defined as the long-range FCD. Thus, for a subject, local FCD and long-range FCD maps were calculated based on the normalized imaging data. The detailed calculation methods have been introduced in our previous study (Chen et al., 2015).

2.4. The renal fMRI process

In this study, the renal R2* value was used to describe renal oxygenation. R2* maps were first calculated voxel by voxel using a Levenberg-Marquardt least-squares algorithm to fit an exponential function to the signal intensities measured for echo time (Epstein and Prasad, 2000; Pruijm et al., 2013; Thoeny et al., 2008). Twenty-four square regions of interest (ROIs) with 3 × 3 pixels were placed in the medulla (12 ROIs) and cortex (12 ROIs) of both kidneys on the anatomical images (the renal ROIs are shown in Fig. 1A). To precisely distinguish the renal medulla and cortex, the image with optimal contrast between renal cortex and medulla was selected across 16-echo T2* renal images. ROIs were positioned at the upper, middle and lower poles of the kidneys in the renal medulla and cortex respectively. It required attention to avoid vessels, renal sinus and susceptibility. The ROIs were drawn manually by the same experienced investigator who was blinded to the subjects' information. Then, the R2* value was averaged for renal medullary and cortex ROIs to acquire the MR2* and CR2*, respectively. Finally, the proportion of MR2* and CR2* values was computed as MCR. This procedure was repeated for renal BOLD-fMRI images of all subjects.

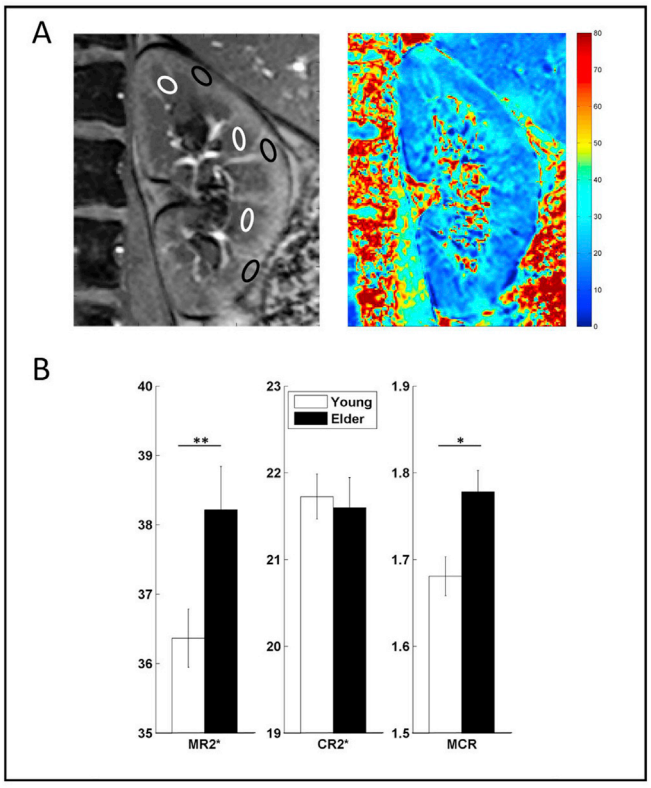

Fig. 1. A: Left side: the first image (TE = 2.216 ms) of the series of 16 renal T2* weighted images; Right side: the corresponding R2* image (right). The diagram to show the position of ROIs for computing renal oxygenation features. B: The renal CR2*, MR2* and MCR value in both groups. * represents $p < 0.05$, ** represents $p < 0.01$.

2.5. Statistical analysis

To detect the differences in renal oxygenation between older adults and younger controls, the renal MR2*, CR2*, and MCR were compared respectively using two-sample *t*-test. A two-sample *t*-test was performed to detect the brain local/long-range FCD differences between the older and younger participants. To investigate the relationship between features of brain function and renal oxygenation, the Pearson correlation between the FCD value of voxels and the MCR was calculated. For all statistical analyses, the effect of gender was controlled as an uninteresting covariate. Additionally, we also performed the same correlation analysis in the younger group, and the difference of correlation coefficients between two groups was evaluated using a nonparametric permutation test for 5000 resamples in brain regions with the significant difference of FCD resulting from the above statistical analysis.

3. Results

3.1. Renal BOLD-fMRI features

Based on the renal BOLD-fMRI analysis, the mean MR2* was 38.22 ± 4.48 in the elderly group and 36.37 ± 2.79 in the younger controls; the mean CR2* was 21.59 ± 2.49 in the older adults and 21.72 ± 1.72 in the younger subjects; and the mean MCR was 1.78 ± 0.17 in the elderly group and 1.68 ± 0.15 in the younger group. The results of two-sample *t*-test showed significantly increased MR2* values ($p = 0.016$) in the elderly group in contrast to younger group, while no difference of CR2* was observed. This result suggested that there was more hypoxia in the medulla of older adults compared to that of younger adults. In addition, the elderly group showed increased MCR values ($p = 0.005$) (Fig. 1B) relative to the younger group.

3.2. FCD analysis in brain

Compared with the younger group, the elderly group demonstrated increased local FCD in the bilateral paracentral lobule, precentral gyri, postcentral gyri, and supplementary motor area. Reduced local FCD was mainly located in the bilateral medial superior frontal gyri, bilateral precuneus, posterior cingulate cortices (PCC), inferior temporal gyrus, and right cerebellum (Fig. 2A, FDR corrected, $p < 0.05$). The details are shown in Supporting Information Table S1.

Among the long-range FCD results, significantly increased long-range FCD in the bilateral thalami, bilateral inferior temporal gyrus, paracentral lobule, left putamen, precentral gyrus, left postcentral gyrus, and inferior cerebellum were found in the elderly group compared with the younger group, while significantly decreased long-range FCD was observed in the bilateral middle temporal gyri, precuneus, superior medial frontal gyri, angular gyri, and inferior cerebellum, as shown in Fig. 2B (FDR corrected, $p < 0.05$). The details are shown in Supporting Information Table S2.

3.3. Correlation analysis between renal and brain features

In the elderly group, the local FCD value had significant positive correlations with renal MCR in the bilateral postcentral gyri, bilateral supplementary motor areas, middle cingulum, left precentral gyrus, middle occipital gyrus, inferior occipital gyrus, inferior temporal gyrus and right lingual gyrus. And significant negative correlations were found in the bilateral superior frontal gyri, medial prefrontal cortexes (MPFC), PCC, precuneus and pallidum. The areas of the cerebrovascular watershed are shown in Fig. 3, and significant correlations were found in some watershed areas (FDR corrected, $p < 0.05$). There was no significant correlation observed in younger group (FDR corrected, $p < 0.05$). While the loose threshold ($p < 0.01$ uncorrected) was used, younger adults illustrated a few regions with correlation (showed in Fig. S1A). The nonparametric permutation test illustrated a more decreased correlation with MCR at the inferior triangle frontal region and the anterior cingulate cortex (ACC) and PCC regions of the DMN, in which more reduced local FCD was observed in the elderly group compared with the younger group. In the right inferior temporal gyrus, left postcentral gyrus and precentral gyrus, the older adults showed a higher correlation between local FCD and MCR than the younger group (Fig. 4A, $p < 0.01$). The details for these regions are shown in Table 1.

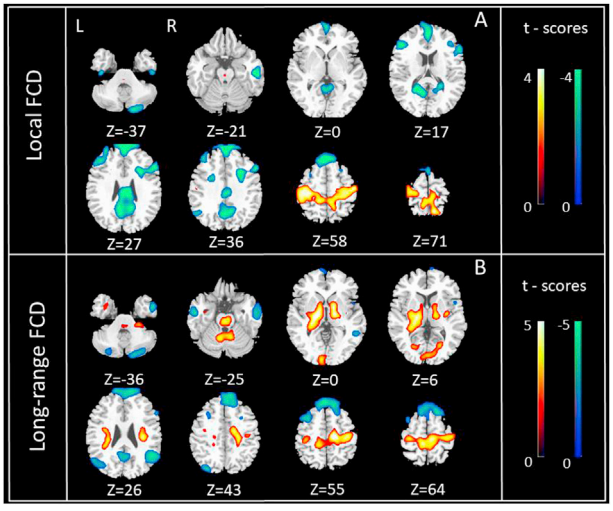

Fig. 2. The difference of the brain local and long-range FCD between older and younger adults. Section A showed the results of local FCD; section B showed the results of long-range FCD. The hot represents the increased FCD value in elderly group compared with younger adults.(FDR corrected, $p < 0.05$).

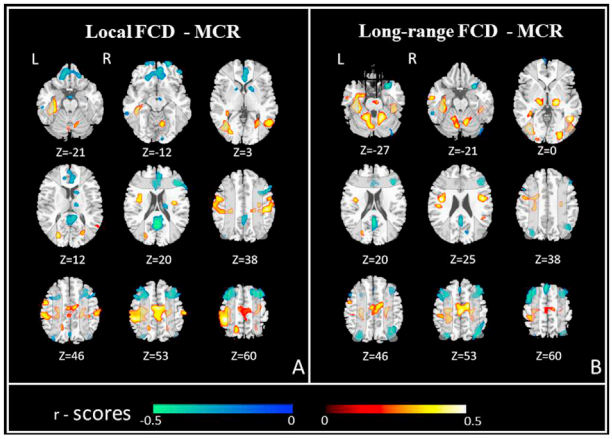

Fig. 3. The correlation between brain local/long-range FCD and renal MCR in the elderly group. The hot color represents the positive correlation, and the cold color represents the negative correlation (FDR corrected, $p < 0.05$). The dotted areas represent the area of the cerebrovascular watershed.

Similarly, there were significant positive correlations between the long-range FCD value and renal MCR located in the bilateral precentral gyri, middle cingulate gyri, thalami, middle occipital gyri, fusiform gyri, left postcentral gyrus, and left inferior temporal gyrus in the elderly group. A significant negative correlation located in the bilateral medial superior frontal gyri, middle frontal gyri, superior parietal gyri, angular gyri, PCC and precuneus, and left inferior parietal gyrus. And the significant correlations were also found in some watershed areas (Fig. 3B, FDR corrected, $p < 0.05$). However, no significant correlation (FDR corrected, $p < 0.05$) was observed in younger group. When $p < 0.01$ (uncorrected) was used, a few regions with correlation were found, such as positive correlations in bilateral postcentral gyri. Fig. S1B represented the details. Interestingly, we found that in the right middle temporal gyrus, right inferior temporal gyrus and right thalamus, the older adults

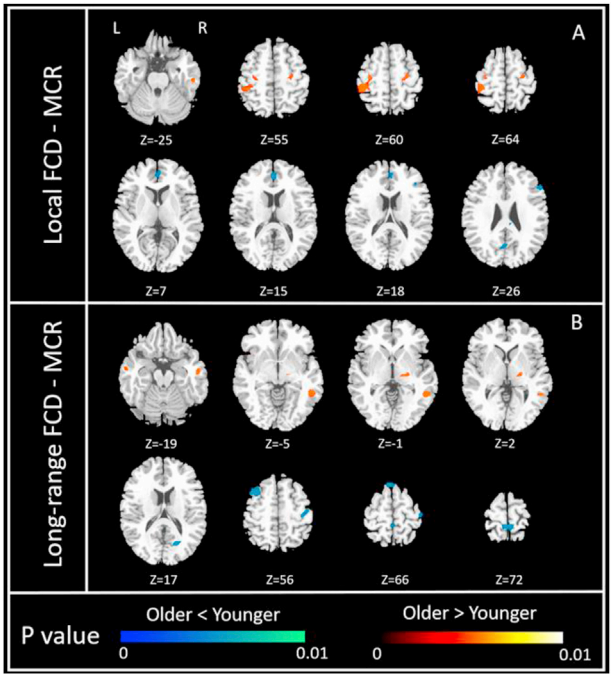

Fig. 4. The differences in correlations for both groups between (A) brain local FCD and renal MCR, and (B) between brain long-range FCD and renal MCR. The hot color represents higher correlation coefficients in older adults and the cold color represents higher correlation coefficients in younger controls.

Table 1
The differences in correlations for both groups between brain local FCD and renal MCR.

Brain region	MNI	R value		P value (peak value)	Cluster (voxels)
		Older	Younger		
Older > younger					
PoCG.L	−43 -33 56	0.495	−0.061	0.005	120
PreCG.R	25 -16 62	0.267	−0.133	0.006	57
ITG.R	52 -22 -25	−0.031	−0.366	0.006	37
Older < younger					
ACG.L	−2 46 14	−0.315	0.128	0.002	61
IFGtriang.R	50 28 21	−0.363	0.095	0.008	31

Abbreviations: PreCG, precentral gyrus; PoCG, postcentral gyrus; ITG, inferior temporal gyrus; ACG, Anterior cingulate gyri; IFGtriang, Inferior frontal gyrus, triangular part.

showed higher correlation coefficients than the younger group. In the right calcarine fissure, left middle frontal gyrus, left superior frontal gyrus, and right paracentral lobule, the correlation coefficients of older adults were lower than those of younger controls (Fig. 4B, $p < 0.01$). The details for these regions are shown in Table 2.

4. Discussion

To our knowledge, this study is the first to investigate the relationship between the features of brain functional connectivity and renal oxygenation in healthy older adults. First, higher renal MR2* and MCR were observed in older adults, which reflected a slight abnormality of renal oxygenation with aging. Then, the older adults showed increased local FCD in the motor-related regions, including the bilateral paracentral lobule, precentral gyri and postcentral gyri, compared with younger adults. Similarly, these regions also illustrated increased long-range FCD; additionally, the increase extended to sensorimotor, subcortical nuclei such as thalamus and putamen. The enhanced local FCD in the motor cortex was linked to the increased renal MCR in the elderly group, while no relationship was found in younger adults. Meanwhile, the decreased local and long-range FCD was mainly observed in the regions of the DMN and bilateral dorsal lateral frontal cortex in older adults, in contrast to younger adults. Moreover, there are FCD values of some regions have significant correlations with the renal MCR value in the elderly group, these regions mainly located in the frontoparietal and parietooccipital watershed regions, DMN and motor cortices. Furthermore, we also found differences in correlation coefficients between brain FCD and renal MCR in both groups. Compared with the young group, the older adults showed lower coefficients in ACC and higher coefficients in the postcentral gyrus, which is consistent with the results of local FCD. These findings indicated that the functional connectivity in the watershed regions, motor cortices and DMN are vulnerable to aging. Besides, the study also reflected that the oxygenation abnormalities in the kidney were associated with aging brain function.

FCD provides an unbiased fMRI feature to characterize the voxel-based functional connectivity in brain (Tomasi and Volkow, 2010). In the present study, increased local and long-range FCD were observed in older adults, predominantly in the motor cortices (precentral and postcentral gyri, paracentral lobule). In some motor task-fMRI studies, researchers had found that older subjects overactivated in some motor cortices compared to younger subjects (Mattay et al., 2002; Reuter--Lorenz et al., 2000). A previous study found that the FCD in somatosensory and motor cortices increased with age (Tomasi and Volkow, 2012). Song et al. noted that increased functional connectivity and global/local efficiency were found in the sensorimotor network in the elderly group compared with younger group (Song et al., 2014a). Our previous study using a seed-based analysis also found an increase in resting state functional connectivity with age in the motor cortex (He et al., 2016). Consistent with these studies, the findings here possibly suggested an underlying compensation mechanism, because older adults might need a higher demand to maintain the declining sensorimotor function. The DMN is considered an intrinsic property of the brain, and it is known to be involved in high-level cognitive functions. Thus, DMN play a major role in the human brain in health and disease conditions (Mevel et al., 2011; Raichle, 2015). Meanwhile, many resting-state fMRI studies have showed reduced functional connectivity in the DMN with aging (Ferreira and Busatto, 2013; Song et al., 2014b; Tomasi and Volkow, 2012), which can indicate that aging is associated with decreased connectivity in the DMN. Damoiseaux et al. (2007) found that the activity in the anterior DMN was associated with performance of cognitive tasks such as attention and processing speed. Consistent with previous studies, older adults showed decreased local and long-range FCD in the regions of DMN compared with younger controls in this study. These findings might indicate that high-level cognitive function declined with aging. It is unfortunate that the cognitive evaluation was not performed in this study. More evidence will be provided in the future.

In general, higher renal R2* values obtained with kidney BOLD-fMRI are associated with renal hypoxia (Prasad et al., 2010; Yin et al., 2012). Consistent with previous studies, the renal CR2* values were lower than MR2* here, which is due to renal medulla being more sensitive to hypoxia (Brezis et al., 1991; Brezis and Rosen, 1995; Khatir et al., 2015). We also found differences in renal MR2* and MCR

Table 2
The differences in correlations for both groups between brain long-range FCD and renal MCR.

Brain region	MNI	R value		P value (peak value)	Cluster (voxels)
		Older	Younger		
Older > younger					
MTG.R	54 -48 -6	0.288	0.010	0.001	60
ITG.R	48 -19 -33	−0.091	−0.387	0.006	35
THA.R	24 -18 0	0.188	−0.145	0.006	31
Older < younger					
MFG.L	−36 15 57	−0.297	−0.021	0.002	112
PCL.R	6 -48 69	−0.052	0.236	0.003	66
SMA.L	−4 26 63	−0.247	−0.031	0.009	37
CAL.R	18 -66 15	0.021	0.298	0.001	27

Abbreviations: ITG, inferior temporal gyrus; MTG, middle temporal gyrus; THA, thalamus; CAL, calcarine fissure and surrounding cortex; MFG, middle frontal gyrus; SMA, supplementary motor area; PCL, paracentral lobule.

between the two groups, but no difference in renal CR2*. The significantly increased renal MR2* and MCR reflected the potential abnormality of renal oxygenation in elderly group. Actually, aging is accompanied by hypofunction and organ aging (including vascular aging). Vascular aging could lead to small vessel dysregulation, which would change the blood flow and then influence renal and brain function (O'Rourke and Safar, 2005). This study also found a negative correlation between renal MCR and FCD in frontoparietal and parietooccipital watershed regions in the elderly group. First, the brain and kidney have the similar hemodynamic in the vascular beds, so the small vessel disease of the kidney may reflect the presence of small vessel alterations in the brain (Mogi and Horiuchi, 2011). Moreover, the blood supply is closely coupling with brain functional connectivity at the resting-state (Liang et al., 2013). The alteration of small vessel would change the blood supply, which further influences cerebral oxygen consumption and functional connectivity. With aging, vascular tone decreases, which may cause an insufficient blood supply to the peripheral vessels. And insufficient blood supply would cause changes in functional connectivity. In addition, watershed regions, as the vascular borderzone, are sensitive to blood supply and hemodynamic alterations. Thus, when the slight abnormality of blood supply and hemodynamics affect whole brain regions inconsistently, the regions with long-range FCD (sensitive to vascular reason) would be disrupted. The reason may include that the influence by the slight vascular abnormality is unmatched between these regions and their distant region. The decreased functional connectivity in frontoparietal and parietooccipital watershed regions with increased renal MCR would reflect a similar alteration of vascular foundation between the brain and kidney in aging.

On the contrary, a positive correlation between renal MCR and FCD was found in the motor cortices and occipitotemporal regions in elderly group, and a few motor cortices also showed similar MCR's positive correlation with long-range FCD in younger group (Fig. S1). Moreover, the higher correlation coefficients were found in the motor cortices when elderly group compared with the younger group. In recent study in adults (aged from 18 to 43 years)(Chu et al., 2018), Chu and colleagues observed that the functional connectivity features in motor and visual cortices were correlated with cerebral blood flow in the resting-state, and they also suggested that the functional connectivity in these primary cortices would be modulated by baseline blood supply. Consistent with this study, our findings also might indicate a compensatory coupling effect: the decreased blood supply associated with the increased functional connectivity in primary cortices. Moreover, the effects may be amplified by the aging conditions. Actually, the compensatory mechanism in the motor cortices was also reported in the elders widely (He et al., 2016; Sodhi et al., 2001; Ward, 2006). Taken together, aging may cause slight renal hypoxia and impact the FCD of the brain in older adults. Additionally, multiple potential physiological mechanism may lead to the various representation in brain functional connectivity.

A recent study demonstrated that the changes of the intrinsic connectivity distribution (a functional connectivity feature similar to FCD) in the DMN were related to the cerebral blood flow alteration caused by deep sedation (Qiu et al., 2017), suggesting the association between functional connectivity and blood supply in brain. Consistent with this study, the FCD in the DMN was decreased with increased renal hypoxia (MCR) within the elderly group. As mentioned above, the decreased FCD in the DMN is associated with cognitive impairment. Hypoxia is a pathophysiologic feature of chronic kidney disease (Fine and Norman, 2008; Prasad et al., 2010; Sodhi et al., 2001). The increased renal MCR indicates hypoxia, which may cause reduced kidney function. According to previous studies (Kurella Tamura et al., 2008; Mogi and Horiuchi, 2011), reduced kidney function was linked with the prevalence of cognitive impairment. The function of DMN is often degenerate in older adults (Naik et al., 2017; Tian et al., 2018). Thus, the negative relationship in DMN would reflect the synchronous change between kidney and brain. The change might be associated with cognitive decline caused by hypoxia. This speculation might contribute to explain how the hypoxia influence brain function. But it should be verified by the conjunctional study between renal and brain in kidney diseases. Moreover, the elderly group had lower correlation coefficients (local FCD and renal MCR) in the DMN regions than younger adults. This further implied that slight renal hypoxia in older adults might associate with aggravating local functional connectivity in the DMN.

4.1. Limitations

There are some limitations to the current study. First, because both groups of recruited subjects were healthy, the clinical indexes of renal function were not collected, such as the estimated glomerular filtration rate (eGFR) and creatinine clearance rate. renal function can be better depicted with these clinical indexes. Second, although R2* is a sensitive indicator of renal oxygenation, R2′ (R2' = R2*-R2) is a better index for describing renal oxygenation; the MRI data for R2, however, were not collected here. Thus, in the current study, R2* was used to describe renal oxygenation. Third, we only used the FCD to evaluate the features of brain function. However, other brain oxygen measures were also used to explore brain oxygenation, we will attempt to study the correlation between brain oxygenation and renal oxygenation in future work. Fourth, all subjects were asked to withhold food and water before scanning, which might impact the resting-state fMRI signals in the brain. In addition, the subjects' cognitive function was not measured in this study. Many previous studies have indicated that decreased functional connectivity in the DMN is associated with cognitive decline (Damoiseaux et al., 2007; Naik et al., 2017; Song et al., 2014b). Although we presumed that the decreased FCD in the DMN may be linked with cognitive impairment in aging, the speculation should be treated carefully. Lastly, this study was a preliminary study to explore the relationships between renal oxygenation and brain functional connectivity, and many conclusions are still speculative. In future work, more evidence would be offered to substantiate these speculative conclusions.

5. Conclusions

BOLD-fMRI can noninvasively reflect the tissue oxygen content. This study investigated the relationship between renal and brain tissue oxygen content simultaneously using the BOLD-fMRI tool. Older adults illustrated age-related decreased FCD in the DMN and increased FCD in the motor cortices, as well as their covariant with renal MCR. Interestingly, we also observed a significant association between altered functional connectivity in watershed regions and renal oxygen content in older adults. In consideration of vascular aging accompanied by degeneration, these findings implicated that the latent physiological mechanism coupling between kidney and brain played a crucial role in the changed functional connectivity in the certain regions of brain during aging. This study provided a new perspective for understanding the association between tissue oxygenation and brain function, especially for investigating the cognitive abnormality in the kidney illnesses.

Declarations of interest

None.

Contributors

C. Luo and H. Li designed the study and wrote the protocol. H. Li. W. Cao, B. Sun, S. Jiang, Y. Wu, W. Yin, J. Li collected the image data and clinical information. H. Li, W. Cao, C. Liu, T. Liu and X. Zhang performed data analyses. H. Li, D. Yao and C. Luo wrote and revised the manuscript. All authors contributed to and have approved the final manuscript.

Acknowledgements

This study was funded by grants from the National Nature Science Foundation of China (81771925, 81861128001, 81771822), the PCSIRT project (IRT0910), the '111' project (B12027), the Sichuan Province Science and Technology Support Project (No.2017SZ0004, 2017HH0001), the Project of Scientific Expenses of the Ministry of Education (2017PT14), Shangdong Provincial Education Department (J18KA262) and Health and Family Planning Commission of Shandong Province (2016WS0613).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2018.11.030.

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