Evaluation of the default-mode network by quantitative $^{15}$O-PET: comparative study between cerebral blood flow and oxygen consumption

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Received: 25 December 2017 / Accepted: 19 June 2018 / Published online: 22 June 2018 © The Author(s) 2018

Abstract

Objective Resting-state functional MRI (rs-fMRI) has revealed the existence of a default-mode network (DMN) based on spontaneous oscillations of the blood oxygenation level-dependent (BOLD) signal. The BOLD signal reflects the deoxyhemoglobin concentration, which depends on the relationship between the regional cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen (CMRO$_2$). However, these two factors cannot be separated in BOLD rs-fMRI. In this study, we attempted to estimate the functional correlations in the DMN by means of quantitative $^{15}$O-labeled gases and water PET, and to compare the contribution of the CBF and CMRO$_2$ to the DMN.

Methods Nine healthy volunteers (5 men and 4 women; mean age, 47.0 ± 1.2 years) were studied by means of $^{15}$O-O$_2$, $^{15}$O-CO gases and $^{15}$O-water PET. Quantitative CBF and CMRO$_2$ images were generated by an autoradiographic method and transformed into MNI standardized brain template. Regions of interest were placed on normalized PET images according to the previous rs-fMRI study. For the functional correlation analysis, the intersubject Pearson’s correlation coefficients ($r$) were calculated for all pairs in the brain regions and correlation matrices were obtained for CBF and CMRO$_2$, respectively. We defined $r > 0.7$ as a significant positive correlation and compared the correlation matrices of CBF and CMRO$_2$.

Results Significant positive correlations ($r > 0.7$) were observed in 24 pairs of brain regions for the CBF and 22 pairs of brain regions for the CMRO$_2$. Among them, 12 overlapping networks were observed between CBF and CMRO$_2$. Correlation analysis of CBF led to the detection of more brain networks as compared to that of CMRO$_2$, indicating that the CBF can capture the state of the spontaneous activity with a higher sensitivity.

Conclusions We estimated the functional correlations in the DMN by means of quantitative PET using $^{15}$O-labeled gases and water. The correlation matrix derived from the CBF revealed a larger number of brain networks as compared to that derived from the CMRO$_2$, indicating that contribution to the functional correlation in the DMN is higher in the blood flow more than the oxygen consumption.

Keywords Default-mode network · Functional correlation · $^{15}$O PET · Cerebral blood flow · Cerebral metabolic rate of oxygen

Introduction

The default-mode network (DMN) was discovered by Raichle et al., as a set of brain regions that typically deactivate during performance of cognitive tasks by perfusion PET [1, 2]. Since DMN is active in the resting state, it is reported to have a relationship with our consciousness and has drawn much attention from researchers. Until now, researchers have mainly investigated the DMN by resting state functional MRI (rs-fMRI) based on functional connectivities using the blood oxygenation level dependent (BOLD)
signal [3]. For example, Fox et al. discovered 13 foci of DMN using rs-fMRI by calculating functional connectivity between voxels and three seed regions: the medial prefrontal cortex (ventral), the posterior cingulate cortex, and the left lateral parietal cortex [4]. The BOLD signal reflects the deoxyhemoglobin concentration, which depends on the relationship between the regional cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO₂). However, these two factors cannot be separated in BOLD rs-fMRI. In this study, we attempted to estimate the functional correlations in the DMN by means of quantitative ¹⁵O-labeled gases and water PET, and to compare the contribution of CBF and CMRO₂ to the DMN. While a similar study has been conducted previously using FDG-PET [5], there is still no report of analysis of the CBF and CMRO₂ to identify DMN correlations. The purpose of this study was to evaluate the functional correlations in the DMN by means of quantitative ¹⁵O-labeled gases and water PET, and to compare the contribution of the CBF and CMRO₂ to the DMN.

Materials and methods

Participants

¹⁵O-PET was performed in nine normal volunteers (4 men and 5 women; mean age ± SD = 50.9 ± 0.4 years). The criteria for defining “normal” volunteers were as follows: (1) no past history of neurological and psychiatric disorders, heart failure, liver or renal dysfunction, respiratory diseases, acute inflammatory disease, autoimmune diseases, or cancer, (2) no smoking or alcohol habit, (3) no significant abnormality on MR imaging or MR angiography of the brain, and (4) no history of medication within the previous 3 months [6]. This study was conducted with the approval of the Ethics Committee of Osaka University Hospital. Written informed consent was obtained from all participants.

PET measurements

PET images were obtained in 3-D mode using the SET-3000 GCT/X scanner (Shimadzu Corp., Kyoto, Japan). The intrinsic spatial resolution was 3.5-mm full-width at half maximum (FWHM) in-plane and 4.2-mm FWHM axially. Subjects were placed lying on the bed of the PET system in a resting state but awake condition with the head fixed. Transmission scanning with a ¹³⁷Cs point source was performed for attenuation correction. The PET images were reconstructed by a filtered-back projection method after 3D Gaussian smoothing with a 6-mm FWHM. Scattered radiation was corrected by the hybrid dual-energy window method combined with a convolution-subtraction method, and estimation of the true scatter-free component of the standard photo peak window was performed on a sonographic basis [7, 8]. The cerebral blood volume (CBV), CMRO₂, oxygen extraction fraction (OEF), and CBF were measured by means of C¹⁵O and ¹⁵O₂ gas inhalation, and H₂¹⁵O injection [8]. A series of ¹⁵O-gases and ¹⁵O-water PET scans were performed once per subject. A cannula was inserted into the radial artery for arterial input. CBV measurement was performed with 4-min static scanning after 1 min of continuous inhalation of C¹⁵O gas (3.0 GBq/min) followed by a 3-min interval [9]. Arterial blood was collected three times during the scanning to measure the whole-blood radioactivity. OEF was measured by 3-min scanning starting simultaneously with 1.5-min ¹⁵O₂ gas bolus inhalation (1.0 GBq/min). Continuous arterial blood sampling was performed using a β-detector system to determine the whole-arterial blood radioactivity. CMRO₂ and OEF were calculated by an autoradiographic method [9–12]. The CBV data were used to correct for intravascular hemoglobin-bound ¹⁵O₂ [13]. CBF was measured by 3 min of scanning started simultaneously with the intravenous bolus injection of H₂¹⁵O (370 MBq) [10, 14]. Continuous arterial blood sampling was also performed with a β-detector system (Continuous Blood radioactivity sampling System, Shimadzu Corp., Kyoto, Japan). Delay and dispersion occurring in the β-detector system were corrected by the methods described previously [15]. Quantitation of the reconstructed PET images by the 3-D mode PET scanner has been validated in a previous report [8].

Data analysis

We normalized the CBF images to the Montreal Neurological Institute (MNI) standardized brain by applying affine transformation, using International Consortium for Brain Mapping (ICBM) space template, and nonlinear transformations, using the built-in water PET template, by SPM8 (Wellcome Trust Centre for Neuroimaging). For normalization of the CMRO₂ images, we applied the same transformations as those for the CBF. To calculate the ROI value, we used the PMOD3.6 software (PMOD Technologies LLC). For the ROI of the DMN, we used the same 12-mm spherical ROI as those in the previous rs-fMRI study of the DMN in the MNI coordinates (Fig. 1) [4, 16]. Center locations of the ROIs are shown in Table 1. CBF and CMRO₂ values of each brain regions were compared by paired t-test with Bonferroni correction and probability values of less than 0.05 divided by the number of pairs (13 combinations of 2) were considered to denote statistical significance.

For each ROI pair, we calculated the intersubject Pearson’s correlation coefficient (r) by plotting the quantitative values of each ROI (nine data points for each pair of brain regions) and obtained a correlation matrix (Fig. 2). r > 0.7 was defined as a significant positive correlation. When the number of data is 9, the 95% confidence interval is

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0.06703–0.9312 for $r = 0.7$. Therefore, $r = 0.7$ is regarded as a reasonable threshold for determining a significant positive correlation.

We assumed that two brain regions were functionally correlated when there was a significant positive intersubject Pearson’s correlation between them according to the previous study [17]. Calculated functional correlations were visualized using the BrainNet Viewer (Xia et al. [18], http://www.nitrc.org/projects/bnv/) [18].

Table 1  Center location of ROIs of DMN used in this study

| Regions                        | Talairach coordinates (x, y, z) | MNI coordinates (x, y, z) |
|-------------------------------|---------------------------------|---------------------------|
| Medial prefrontal cortex (ventral) | ($-3, 39, -2$)                | ($-3, 44, -2$)            |
| Medial prefrontal cortex (anterior) | ($1, 54, 21$)                 | ($2, 57, 24$)             |
| Posterior cingulate cortex     | ($-2, -36, 37$)                | ($-3, -39, 39$)           |
| Left lateral parietal cortex   | ($-47, -67, 36$)               | ($-47, -70, 37$)          |
| Right lateral parietal cortex  | ($53, -67, 36$)                | ($52, -71, 38$)           |
| Left superior frontal cortex   | ($-14, 38, 52$)                | ($-15, 35, 58$)           |
| Right superior frontal cortex  | ($17, 37, 52$)                | ($17, 34, 57$)            |
| Left inferior temporal cortex  | ($-61, -33, -15$)              | ($-65, -31, -22$)         |
| Right inferior temporal cortex | ($65, -17, -15$)               | ($69, -14, -23$)          |
| Left parahippocampal gyrus     | ($-22, -26, -16$)              | ($-23, -25, -24$)         |
| Right parahippocampal gyrus    | ($25, -26, -14$)               | ($26, -25, -21$)          |
| Cerebellar tonsils             | ($7, -52, -44$)                | ($7, -50, -55$)           |
| Retro-splenial                 | ($3, -51, 8$)                 | ($3, -52, 5$)             |

Fig. 1  Setting of ROIs using a 12-mm sphere (note that the center of the sphere is located in the specific MNI coordinate point)

Fig. 2  Correlation analysis between pairs of brain regions and correlation matrices. Above example calculated the intersubject Pearson’s correlation coefficient between a pair of brain regions showing a significant positive correlation. Each plot in the left graph represents the data for one subject.
Results

The quantitative values of the CBF and CMRO₂ in various brain regions are summarized in Table 2. The CBF and CMRO₂ values were 50.4 ± 5.9 mL/100 mL/min and 3.6 ± 0.5 mL/100 mL/min in the medial prefrontal cortex (ventral), 47.8 ± 7.6 mL/100 mL/min and 3.7 ± 0.8 mL/100 mL/min in the posterior cingulate cortex, and 40.2 ± 6.6 mL/100 mL/min and 3.3 ± 0.5 mL/100 mL/min in the left lateral parietal cortex.

The correlation matrices for pairs of DMN ROIs are shown in Fig. 3. In the correlation matrix based on the CBF, the PCC showed significant positive correlations with the left lateral parietal cortex, right lateral parietal cortex, right superior frontal cortex, right inferior temporal cortex, and cerebellar tonsils. The correlation matrix based on the CMRO₂ showed fewer correlations as compared to that of the CBF. In Fig. 4, 24 pairs of significant positive correlations were observed for the CBF, while 22 pairs were observed for the CMRO₂. There were 12 overlapping significant positive correlations between the CBF and CMRO₂. Thus, analysis based on the CBF led to the detection of more brain networks as compared to that based on the CMRO₂. The significant positive correlations are anatomically illustrated in Fig. 5.

Discussion

We evaluated the functional correlations of the DMN based on analyses of the CBF and CMRO₂. More brain networks were found in the analysis based on CBF, and about a half of them overlapped with those identified by analysis of the CMRO₂. When the local brain activity increases because of physiological fluctuations in the resting state or in response

Table 2 Quantitative values for various brain regions in the nine subjects

|                  | CBF (mL/100 mL/min) | CMRO₂ (mL/100 mL/min) |
|------------------|---------------------|------------------------|
| vMPFC            | 50.4 ± 5.9<sup>a,c,g,l</sup> | 3.6 ± 0.5<sup>g,k</sup> |
| aMPFC<sup>a</sup> | 35.8 ± 7.5<sup>d,e,g,k</sup> | 2.6 ± 0.5<sup>e,k</sup> |
| PCC<sup>b</sup>  | 47.8 ± 7.6<sup>d,l,k</sup> | 3.7 ± 0.8<sup>c,h</sup> |
| L.LatP<sup>c</sup> | 40.2 ± 6.6<sup>d,l,j</sup> | 3.3 ± 0.5<sup>d,l</sup> |
| R.LatP<sup>d</sup> | 33.8 ± 6.1<sup>e,l</sup> | 2.7 ± 0.5<sup>e,k</sup> |
| L.Sup.F<sup>e</sup> | 23.5 ± 3.5<sup>k</sup> | 1.6 ± 0.3<sup>e,k</sup> |
| R.Sup.F<sup>f</sup> | 29.3 ± 5.3<sup>i</sup> | 2.2 ± 0.4<sup>i</sup> |
| L.IT<sup>g</sup>  | 39.1 ± 7.9<sup>i</sup> | 3.0 ± 0.5<sup>i</sup> |
| R.IT<sup>h</sup>  | 37.6 ± 6.7<sup>i</sup> | 2.9 ± 0.5<sup>i</sup> |
| L.PHC<sup>i</sup> | 36.3 ± 2.8<sup>i</sup> | 2.4 ± 0.4<sup>i</sup> |
| R.PHC<sup>j</sup> | 38.8 ± 4.3<sup>j</sup> | 2.4 ± 0.4<sup>j</sup> |
| Cereb<sup>k</sup> | 52.2 ± 9.6<sup>i</sup> | 3.6 ± 0.7<sup>i</sup> |
| Retro-splenia<sup;l</sup> | 29.7 ± 7.0<sup>i</sup> | 2.0 ± 0.5<sup>i</sup> |

<sup>a</sup> anterior, <sup>v</sup> ventral, <sup>L</sup> left, <sup>R</sup> right, <sup>MPFC</sup> medial prefrontal cortex, <sup>Sup.F</sup> superior frontal cortex, <sup>IT</sup> inferior temporal cortex, <sup>PHC</sup> para-hippocampal gyrus, <sup>PCC</sup> posterior cingulate cortex, <sup>LatP</sup> lateral parietal cortex, <sup>Cereb</sup> cerebellar tonsils

<sup>a–l</sup> There is a significant difference between the two regions (p < 0.05 with Bonferroni correction)
to some stimulation, the local CMRO2 increases first, reflecting the increased energy metabolism. Then, the local CBF also increases following the increase of the local CMRO2. The extent of increase of the local CBF is usually much larger than that of the local CMRO2 [1, 19], which is the main reason for the detection of more brain networks by analysis of the CBF than by analysis of the CMRO2. Paulson et al. also reported that CBF and glucose metabolism remain coupled as they increase in proportion during functional activation, whereas oxygen metabolism only increases to a minor degree [20]. Moreover, the CMRO2 image is calculated from three scans of \( \text{H}_2\text{O}^{15}\text{O}, \text{H}_2\text{O}^{15}\text{O}^2 \), and \( \text{C}_1\text{H}_2\text{O}^{15}\text{O} \), and the long study time for the three scans may blur the regional changes in CMRO2, leading to the fewer detection of networks.

We assumed that two brain regions were functionally correlated when there was a significant positive intersubject Pearson’s correlation between them. The underlying idea is that if changes of quantitative CBF or CMRO2 values of each subject fluctuate in a similar pattern between the same regions of the brain, we can capture the several different phases of resting state network with significant correlation using the all subject data. A similar method of analysis was also used in the previous study [17].

We used quantitative value itself for the correlation analyses without performing global normalization. Global normalization is used for masking the global fluctuation of blood flow or oxygen metabolism, usually to detect the specific brain region with activation. Since our correlation analysis should include the physiological global fluctuation, we used the quantitative value of CBF and CMRO2 directly for the analyses. Nevertheless, future studies should consider global normalization to eliminate the effects of inevitable variations of quantitative values.

We did not compare our results directly with results from rs-fMRI because the number of data and the time scale are significantly different. The rs-fMRI measurement obtained 150 data per each subject, because data were acquired every 2 s over a period of 5 min. On the other hand, our PET measurement obtained one data per each subject because evaluation of the temporal changes...
was impossible, as every single of the CBF and CMRO₂ measurements was the average value of 3 min of measurement. In terms of the time scale, rs-fMRI detects changes on the seconds’ scale, whereas PET detects changes on the minutes’ scale, and both data might reflect different brain functions. To evaluate physiological fluctuations in the resting state, we need several repeated scans per subject. Performing several PET scans per subject should be considered in the future study to assess physiological fluctuations for a comparison to the rs-fMRI studies. ¹⁵O-water PET has several advantages compared to BOLD fMRI, being quantifiable, less deteriorated by movement, and allowing for longitudinal studies [21].

Significant differences were observed between right and left sides in some brain regions (Table 2). Previous study reported the asymmetries in CBF and CMRO₂, but not in CBV and OEF [22]. In this study, the ratios of CMRO₂ to CBF were similar between right and left regions, which were consistent with the previous report about OEF.

This study had the limitation of a small number of subjects, so the results could include false-positive signals. Therefore, a further multi-modality study with a sufficient number of subjects should be performed to accurately evaluate the relationships among the CBF, CMRO₂ and rs-fMRI BOLD signals.

Conclusions

We estimated the functional correlations in the DMN by means of quantitative PET using ¹⁵O-labeled gases and water. The correlation matrix derived from the CBF revealed a larger number of brain networks as compared to that derived from the CMRO₂, indicating that contribution to the functional correlation in the DMN is higher in the blood flow more than the oxygen consumption. A multi-modality study is warranted in the future to evaluate the relationships among the CBF, CMRO₂ and BOLD signals and establish an integrated system for detection of brain networks.

Acknowledgements This study was supported in part by the Molecular Imaging Program, a Grant (no. 21591561) from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) and the Japan Science and Technology Agency (JST), Japan, by the Research Promotion Program on Health from the National Institute of Biomedical Innovation, Japan, and a Grant-in-Aid (H21-019 and H21-5) from the Ministry of Health, Welfare, and Labour, Japan. The authors declare no conflict of interest.

Sources of funding This study was funded by Ministry of Education, Culture, Sports, Science, and Technology (MEXT) and Ministry of Health, Welfare, and Labour, Japan.

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