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Cognitive enhancement of healthy young adults with hyperbaric oxygen: A preliminary resting-state fMRI study

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HIGHLIGHTS

- Hyperbaric oxygen (HBO) caused increases in spatial working memory and memory quotient.
- The alternation of regional homogeneity (ReHo) induced by HBO is related to the cognitive performance.
- HBO administration affects the functional connectivity of several subcortical regions.

ABSTRACT

Objective: To date, no study has examined the effect of hyperbaric oxygen (HBO) on the cognitive performance and spontaneous brain activity in healthy adults using resting-state functional magnetic resonance imaging (rsfMRI). Our aim was to reveal the neural mechanism underlying the change in cognitive performance caused by increased oxygen.
Methods: In this study, we acquired fMRI data from 20 healthy young adults and used placebo-controlled (PBO) rsfMRI to identify the effect of HBO on the cognitive measures and the regional homogeneity (ReHo) in healthy adults.
Results: Compared to the PBO group, the HBO group showed the following: (1) the scores of the spatial working memory and memory quotient were significantly increased after HBO administration; (2) the ReHo value was significantly increased in three clusters, the left hippocampus, right inferior frontal, and lingual gyri, and for these three clusters, their functional connectivity with the subcortical brain system was significantly increased after HBO administration; and (3) the changes of ReHo values in these clusters generated by HBO administration were correlated with several aspects of cognitive performance, clarifying the cognitive locus of the effect.
Conclusion: Our results suggested that the increased availability of oxygen can, to some extent, improve memory performance.
Significant: Our findings may improve our understanding of the role of HBO in clinical and practical applications.

1. Introduction

Humans have long used cognitive enhancement methods to reduce suffering and improve the quality of life, which has attracted a surge of interest in their effects on cognitive functions in health and diseases in recent years (Kennedy, 2004; Anon, 2007; Normann and Berger, 2008; Husain and Mehta, 2011; Clark and Parasuraman, 2014; Graf et al., 2013; Lane, 2013). A growing body of evidence suggests that some kinds of cognitive-enhancing drugs

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could improve the proficiency and the range of various mental activities that they engage in, including working memory, attention, and emotion, to achieve better performance in many aspects of daily life (Mehta et al., 2000; Zaninotto et al., 2009; Eickenhorst et al., 2012; McKendrick et al., 2014). The potential opportunities, limitations, and ethical problems of neuroenhancement have also been widely discussed in society (Partridge et al., 2011; Graf et al., 2013; Heinz et al., 2014).

The human brain is the most metabolically active organ in the body. Oxygen supply is essential for mental activities in the brain. Although the adult brain does not grow, divide, or move, it consumes up to 25% of the blood oxygen supply (Roland, 1993; Raichle, 2010). During brain neural activity, the energy used for information processing and transiting originates from the breakdown of glucose, which ultimately depends on the abundant supply of oxygen. Therefore, oxygen supply is regarded as a neurocognitive enhancer, and it is widely used in various brain diseases and healthy subjects. Moss and Scholey (1996) demonstrated that increased availability of cerebral oxygen can improve performance on cognition measures, such as memory consolidation in healthy young adults, but the effect appeared to be specific to consolidation. Likewise, Scholey et al. (1998) showed a significant effect of oxygen administration on word recall, but not forward or backward digit span by a double-blind design, which suggested that oxygen administration could selectively enhance several aspects of cognitive performance. In addition, Moss et al. (1998) showed that oxygen administration can improve performance of attention and vigilance, and the oxygen-induced cognitive enhancement changes with the duration of the oxygen administration.

Recently, some functional magnetic resonance imaging (fMRI) studies have reported the neural mechanism of oxygen-induced cognitive enhancement. Several studies demonstrated that the improvement of visuospatial task performance in the condition of higher oxygen concentration was related to increased brain activation in several brain regions, such as the cingulate gyrus, thalamus, and superior parietal regions (Chung et al., 2004; Choi et al., 2010). In addition, Chung et al. (2006) also found increased activation in the right frontal gyrus, left temporal gyrus, and left fusiform gyrus when subjects were exposed to higher oxygen concentration compared to air administration during verbal tasks. These findings revealed the positive effects of highly concentrated oxygen on brain function and cognitive performance.

Based on the positive effect of higher oxygen concentration on brain cognitive performance, an increasing number of people, especially some students under the stress of examination in China, have been exposed to HBO administration for improving cognitive performance. Previous studies have revealed that HBO, 100% oxygen at two to three times the standard atmospheric pressure, can result in arterial oxygen tension in tissues and have a number of beneficial biochemical, cellular, and physiologic effects (Tibbles and Edelsberg, 1996). In clinics, hyperbaric oxygen therapy (HBOT) is widely used to treat the long-term sequelae of a variety of neurological diseases, for example, chemic stroke (Efrati et al., 2013), subarachnoid hemorrhage (Griessenauer et al., 2012), and traumatic brain injury (TBI) (Wolf et al., 2012; Boussi-Gross et al., 2013). Most importantly, these studies demonstrated that HBOT can improve the memory quotient (MQ) and intelligence of patients and can help recover brain function by promoting the reanimation of brain cells (Veltkamp et al., 2005). In an animal experiment, Harch et al. (2007) demonstrated that HBO therapy can improve spatial learning and memory in a rat model of TBI using the Morris water navigation task, and they observed the improvement in spatial learning to be strongly associated with the increased vascular density. However, to the best of our knowledge, no study to date has examined the neurocognitive enhancement of HBO administration in healthy adults.

Resting-state fMRI (rsfMRI) has been used to measure low-frequency spontaneous neural activity of human brain in vivo, and it is a crucial technique for uncovering the intrinsic brain functional architecture under both normal and pathological conditions (Fox and Raichle, 2007; Fox and Greicius, 2010; Zhang and Raichle, 2010). Regional homogeneity (ReHo), which measures the similarity of fMRI time courses of a given voxel with its nearest voxels, provides useful information about the degree of signal coherence (Zang et al., 2004). ReHo is a voxel-wise data-driven approach that takes into account the spontaneous neural activity across the entire brain in the resting state. Compared to model-driven methods, ReHo appears more sensitive in the detection of unpredictable hemodynamic responses that model-driven methods fail to identify (Zhang et al., 2014). Because ReHo measures the similarity of neural activity for a specific voxel with its nearest neighboring voxels, it can be widely used as a complementary tool to describe local brain spontaneous activity and regional stability. Previous studies have shown that ReHo is a valuable index to reflect the abnormality involved in cognitive function impairments, including depression (Yao et al., 2009), Parkinson's disease (Wu et al., 2009), Alzheimer's dementia (He et al., 2007), and schizophrenia (Liu et al., 2006). Several recent studies also used ReHo to estimate the effect of cognitive task training on the modulation of local spontaneous neural activity in healthy subjects (Zang et al., 2004; Lv et al., 2013). They demonstrated that the higher ReHo of BOLD signal may indicate higher synchronization of local neuronal activity in the human brain, and an evoked activity by the task may be associated with increased ReHo (Zang et al., 2004; Lv et al., 2013).

In this study, we used a placebo (PBO)-controlled parallel group design. The aim was to explore the effect of HBO administration on cognitive measures and ReHo values of the human brain in the resting state, and to reveal their relationship. We hypothesized that HBO administration could enhance the cognitive performance, such as memory and attention in healthy adults; correspondingly, the values of ReHo in the regions associated with memory and attention may be changed.

2. Materials and methods

2.1. Subjects

We recruited 20 healthy undergraduates/postgraduates (nine males and 11 females, aged 18–20 years) from the campus of the South China Normal University. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Each subject was randomly assigned to receive either hyperbaric oxygen (HBO) or hyperbaric-air administration. No one had a history of neurological or psychiatric disease or head injury. The protocols were approved by the Research Ethics Committee of the Guangzhou Liuhuaqiao Hospital. Written consent was obtained from each subject prior to the experiment.

2.2. Experimental procedure

According to the subject receiving either the HBO or hyperbaric-air administration during the experiment, 20 subjects were divided into two groups, with 10 subjects in the HBO group and the other 10 subjects in the placebo (PBO)-controlled group. Each subject of the HBO group inhaled 100% oxygen in a chamber under 2.0 absolute atmospheric pressure (ATA) for 80 min every day (excluding the time for the subject to adapt to the HBO administration and the resting time). Conversely, each subject in the PBO group received 2.0 ATA air in the same chamber for 80 min every day. The HBO and PBO groups were given the same instruction before

the experiment and then treated with repeated HBO or PBO administration for five consecutive days, respectively. In clinical application, 5 consecutive days of HBO administration is usually used as one course of treatment. The whole experiment was performed by a professional technician and lasted about 2 h. Measures of a wide range of cognitive tests and the rsfMRI data were collected from each subject before the experiment, and again after the completion of the experiment. The schematic experimental procedure was shown in Supplementary Fig. S1.

2.3. Cognitive measures

The day before and after the HBO or PBO administration, each subject took the following cognitive measures, the Wechsler Memory Scale – Chinese Revision (WMS-RC), the working memory span test, and the attention test. The WMS-RC includes the long-term memory (LTM) test, the short-term memory (STM) test, and the immediate memory (IM) test. The MQ and each factor score of the WMS-RC were measured pre- and post-experiment using two versions (version A and version B) of WMS-RS, respectively. The working memory was evaluated using two computerized working memory span tests: the digital working memory span test (DST) (Salthouse and Babcock, 1991) and the spatial working memory span test (SST) (Casey et al., 1998). The attention performance was examined with four types of pencil-and-paper tests: (i) the shape discrimination test (SDT) (Corbetta et al., 1991), selecting the defined shape from 300 approximate shapes in 3 min; (ii) the four-circles test (FCT), selecting the pictures that include four circles from 650 pictures in 3 min; (iii) the visual tracking test (VTT) (Yantis, 1992), tracking the lines from the origin to the end in 2 min and labeling the number of lines at the end; and (iv) the addition and subtraction test (AST) (Chung et al., 2008), performing the addition and subtraction task alternately in 3 min. The order of all cognitive measures was randomized and counterbalanced across subjects. In about 1.5 h for each subject, we obtained the following 10 items of cognitive measures: MQ, LTM, STM, IM, DST, SST, SDT, FCT, VTT, and AST.

2.4. Image acquisition

Each subject was scanned pre- and post-HBO or PBO administration to acquire the rsfMRI datasets and brain structural images. To rule out the effect of the extra oxygen content in the brain on the measure of the brain activity, we acquired the rsfMRI datasets after 1 day of the experiment for both the HBO and PBO groups. All MRI data were obtained on a 3T GE MR scanner with an eight-channel phased-array head coil at the Guangzhou Liuhuaqiao Hospital. The rsfMRI datasets were acquired using a gradient-echo echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2400 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FOV) = 240 × 240 mm, data matrix = 64 × 64, thickness = 4 mm without gap, 36 axial slices covering the whole brain, and 240 volumes acquired in approximately 10 min. During the rsfMRI scan, each subject was asked to keep their eyes open, to relax their minds, and not to think of anything in particular. In addition, we also acquired 3D high-resolution brain structural images for each subject using a T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence. The sequence parameters were as follows: TR/TE = 8.852 ms/3.516 ms, inversion time (TI) = 450 ms, slice thickness = 1 mm, FA = 20°, FOV = 240 × 240 mm, data matrix = 256 × 256, BW = 190 Hz/pixel, and 176 sagittal slices.

In this study, two subjects dropped out of the experiment owing to conflicting schedules. Furthermore, the fMRI data of two subjects were excluded because of their excessive head motion after checking images in either rsfMRI dataset corresponding to pre- or post-experiment. Thus, 16 subjects were left for further analysis, eight in the HBO group (five males and three females, aged 18–20 years, mean ± SD = 19.63 ± 1.06 years) and eight in the PBO group (five males and three females, aged 18–20 years, mean ± SD = 19.38 ± 0.92 years).

2.5. Data processing

We preprocessed the rsfMRI data using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and DPARSF (http://www.restfmri.net/) (Zang et al., 2004; Chao-Gan and Yu-Feng, 2010). For each subject, we discarded the first 10 volumes of the rsfMRI dataset to avoid instability of the initial MRI signal, leaving 230 volumes for further analysis. The remaining images were first corrected for the acquisition time delay between slices within the same TR, and then they were realigned to the first volume for correcting the inter-TR head motions. This realignment calculation provided a record of head motions within the rsfMRI scan. The corrected rsfMRI data were spatially normalized to the standard EPI template, and resampled to 3-mm cubic voxels. We excluded the subject whose head motion was larger than 2 mm of displacement or 2° of rotation in any direction in either the pre- or post-experiment fMRI dataset for further analysis. After linear detrending, the rsfMRI dataset was filtered using a typical temporal band pass (0.01–0.08 Hz) in order to reduce low-frequency drift and high-frequency physiological noise. We regressed out the influence of head motions, global mean signal, signals of cerebrospinal fluid (CSF), and white matter (WM), for removing the effects of head motion and non-neuronal BOLD fluctuations on brain spontaneous activity (Kelly et al., 2008).

The ReHo map was calculated in a voxel-wise way to indicate the degree of regional synchronization of fMRI time courses. In the calculations, we generated individual ReHo maps using Kendall's coefficient of concordance (KCC) (Kendall, 1948) of the time series of a voxel with those of its nearest neighbor's voxels. Given a voxel, its KCC value will tend to be 0 if no similarity (desynchronized) exists between this voxel with its neighboring voxels, whereas it will tend to be 1 if the time series of the given voxel was identical to those of its neighboring voxels (synchronization). For a given voxel, the Kendall's coefficient value is calculated by

$$W = \frac{\sum_{i=1}^{n}(R_i)^2 - n(\overline{R})^2}{\frac{1}{12}K^2(n^3 - n)}, \quad (1)$$

where W is Kendall's coefficient of concordance of the K voxels, ranging from 0 to 1 (here, $K = 27$, the central voxel plus its 26 neighbors). $R_i = \sum_{j=1}^{k} r_{ij}$ and r_{ij} is the rank of the i th time point in the j voxel; $\overline{R} = (n+1)K/2$ is the mean of R_i; and n is the number of time points of the time series (here, $n = 230$). The Kendall's coefficient value was calculated at every voxel, and an individual Kendall's coefficient map or ReHo map was obtained for each subject. To reduce the global effects of variability across subjects, we divided the ReHo of each voxel by the individual global mean ReHo value within a brain mask provided in the REST software (http://resting-fmri.sourceforge.net). Thus, we obtained the normalized ReHo map for each subject.

2.6. Functional connectivity analysis

Functional connectivity (FC) analysis was performed to determine the cortical connectivity patterns between seed regions of interest (ROI) and all of the voxels in the whole brain. Three ROIs (HIP.L, SFGdor.R, and LING.R; see the "Results" section) were used according to the analysis of variance (ANOVA) results, which showed an increase in ReHo after the HBO administration in the HBO group, but not in the PBO group. For each subject, the FC

correlation map was calculated for each ROI by a voxel-wise multiple regression. To reduce the effects of head motion or the physiological processes, we computed the additional covariates, such as the global signal, WM, CSF, and motion parameters for head movement, and used them in the general linear model. We first acquired the time course for each ROI by averaging the time series of all voxels within the ROI. Then we calculated the correlation between the time series of ROI and all voxels in the whole brain, which was taken as the ROI-based functional connections. Finally, we transformed the ROI-based functional connections into Z values (zFC map) using Fisher's transformation to improve normality.

2.7. Statistical analysis

First, we performed a mixed-effects ANOVA on the scores of cognitive measures to determine whether the HBO administration had a significant effect on cognitive measures. In the calculations, we took Group (HBO group and PBO group) as a between-subject variable and Time (pre- and post-experiment) as a within-subject variable. Then, using paired t-tests, we performed post hoc comparisons to test the changes of cognitive measures after HBO or PBO administration if the null hypothesis is rejected. Considering our limited sample size, we also compared changes of cognitive measures after the HBO or PBO administration with the baseline scores (before the HBO or PBO administration) as a covariate. Statistical power and effect size analysis of ANOVA were carried out on the cognitive measures with significant changes between pre- and post-experiment (Supplementary Table S2) according to Cohen's criterion (Cohen, 1992). A nonparametric permutation test was used in the post hoc comparison (5000 permutations) to determine the significant changes of cognitive measures between the pre- and post-experiment for the HBO or PBO group, respectively (paired t-test). We set $p < 0.05$ as the significance level for all statistical tests.

Then, we performed the ANOVA analysis to explore the effect of HBO administration based on the ReHo values of the two groups. The post hoc comparisons were conducted on the normalized ReHo maps voxel-wise using paired sample t-tests between the pre- and post-administration in each group ($p < 0.05$ with Alphasim correction). To explore the differences in functional connectivity between the pre- and post-HBO administration, the zFC maps of brain regions were compared using paired sample t-tests between the pre- and post-HBO administration ($p < 0.01$ with Alphasim corrected). All coordinates are reported in the MNI coordinates, as given by SPM.

We also analyzed the relationship between the changed cognitive measures and ReHo value resulting from the HBO administration, and we assessed which cognitive measures were associated with the changed ReHo value. In the calculations, we applied an exploratory stepwise hierarchical multiple regression analysis (Keller and Just, 2009) (which took the different baseline scores into account) for all subjects. The cluster regions showing significant interaction on the ReHo values were determined and extracted, and the mean ReHo value for all voxels in each cluster was calculated. For each cluster, we carried out multiple regression analyses to detect correlations between the changed ReHo value after HBO or PBO administration and the changes of cognitive scores.

3. Results

3.1. Demographic comparison between two groups

No significant difference was found in the age between the HBO and PBO groups (age: $p = 0.62$, two-tailed two-sample t-test). In addition, the gender is completely matched between two groups (three females and five males in each group).

3.2. Cognitive measures

For each subject, we recorded the scores of the following 10 cognitive measures: MQ, LTM, STM, IM, DST, SST, SDT, FCT, VTT, and AST. Using two-sample t-test, we found no significant difference in each of the cognitive measures between the HBO and the PBO groups before the experiment (Table 1).

Two-factor ANOVA (two groups × two times) was conducted to assess the effect of HBO on the cognitive measures (Table 2). We found that the SST showed a significant Group × Time interaction ($F_{(1,\ 14)} = 11.485$, $p = 0.004$). Further analysis revealed that the HBO group showed significant improvement in SST after HBO administration ($p = 0.003$), indicating an HBO effect on the cognitive function, while the PBO group failed to improve the score in SST ($p = 0.815$) after PBO administration (Figs. 1 and 2). As for the MQ score, we found that the HBO group showed a reasonably significant improvement after HBO administration ($p = 0.001$), while only a marginally significant change was observed in the PBO group ($p = 0.063$) after PBO administration (Figs. 1 and 2), which were indicated by the marginal Group × Time interaction effect ($F_{(1,\ 14)} = 3.608$, $p = 0.078$). Furthermore, we detected that all other cognitive measures except for the IM and DST showed significant main effect of time (Table 2 and Supplementary Fig. S2).

With the baseline as a covariate, we also explored the difference of changes in cognitive measures between the two subject groups after the experiment. Compared to the PBO group, the HBO group showed a significant increase in the score of SST (please see Supplementary Table S4). A nonparametric permutation test was also applied in the post hoc comparison to test the changes of cognitive measures after the experiment for the two groups (5000 permutations). The results are listed in Supplementary Table S5, which are consistent with those of the parametric t-test.

3.3. ReHo changes induced by HBO administration

Fig. 3 shows the brain clusters with significant interactions between Group and Time ($p < 0.05$, Alphasim correction). One cluster was located in the left hemisphere, including the left hippocampus (HIP.L) and left inferior temporal gyrus (ITG.L), and four clusters in the right hemisphere, including the right lingual gyrus (LING.R), right orbital part of inferior frontal gyrus (ORBinf.R), right dorsolateral superior frontal gyrus (SFGdor.R), and right precuneus gyrus (PCNU.R). The details are listed in Table 3. The post hoc

Table 1
Score of each cognitive measure collected before the subjects attended hyperbaric oxygen (HBO) or hyperbaric-air (placebo-controlled, PBO) administration.

Measures	Groups		Between-group comparison
	HBO (Mean ± SD)	PBO (Mean ± SD)	HBO vs PBO P (15)
MQ	119.63 ± 8.65	123.75 ± 6.94	0.31
LTM	43.00 ± 4.04	43.38 ± 3.20	0.84
STM	69.25 ± 4.62	71.25 ± 4.71	0.41
IM	13.88 ± 4.12	15.00 ± 3.46	0.56
DST	8.00 ± 1.60	8.50 ± 0.76	0.44
SST	3.38 ± 0.92	3.75 ± 1.04	0.46
SDT	23.57 ± 6.21	24.29 ± 6.32	0.83
FCT	92.38 ± 16.60	93.13 ± 13.71	0.92
VTT	16.00 ± 3.51	17.50 ± 1.07	0.27
AST	123.75 ± 20.52	148.38 ± 34.99	0.11

Note: MQ – memory quotient, LTM – long-term memory test, STM – short-term memory test, IM – immediate memory test, DST – digital working memory span test, SST – spatial working memory span test, SDT – shape discrimination test, FCT – four-circles test, VTT – visual tracking test, AST – addition and subtraction test.

Table 2
Comparison of cognitive measures by using a two-factor ANOVA for each of cognitive measures. We took group (HBO group and PBO group) as a between-subject variable and time (before and after experiment) as a within-subject variable.

Measures	ANOVA (group × time)					
	Main effect of group		Main effect of time		Interaction effect	
	F	*p*-value	*F*	*p*-value	*F* (1,14)	*p*-value
MQ	0.191	0.669	35.566	<0.001***	3.608	0.078[a]
LTM	0.039	0.847	14.501	0.002**	0.006	0.939
STM	0.147	0.708	30.729	<0.001***	1.487	0.243
IM	0.689	0.420	2.245	0.156	0.120	0.735
DST	0.792	0.388	0.038	0.856	0.118	0.737
SST	0.988	0.337	8.223	0.012*	11.485	0.004**
SDT	0.004	0.954	18.403	0.001***	0.451	0.514
FCT	0.009	0.927	13.618	0.002**	0.022	0.970
VTT	0.528	0.479	6.422	0.024*	0.997	0.335
AST	5.040	0.041*	20.095	0.001***	0.057	0.815

Note: *$p \leqslant 0.05$; **$p \leqslant 0.01$; ***$p \leqslant 0.001$; [a]denotes the marginal significance ($0.05 < p < 0.1$).
MQ – memory quotient, LTM – long-term memory test, STM – short-term memory test, IM – immediate memory test, DST – digital working memory span test, SST – spatial working memory span test, SDT – shape discrimination test, FCT – four-circles test, VTT – visual tracking test, AST – addition and subtraction test.

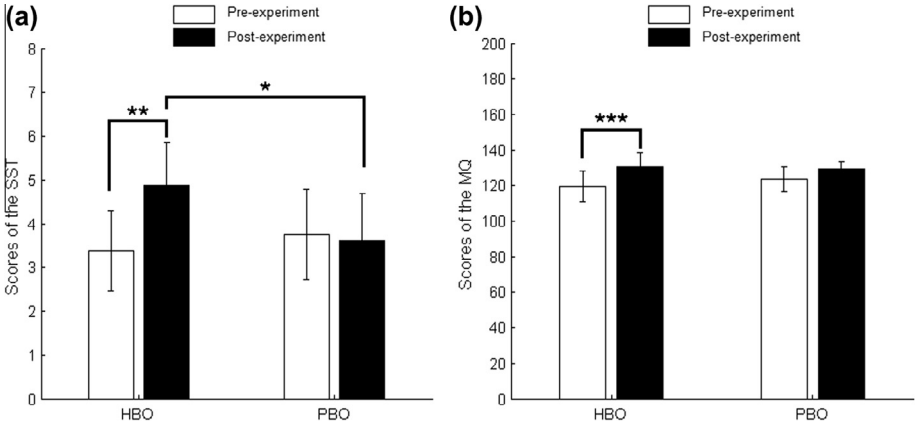

Fig. 1. Comparison of cognitive measures between the pre- and post-experiment for the HBO and PBO groups, respectively. (a) Spatial working memory span test (SST) and (b) memory quotient (MQ). The SST revealed a significant Group and Time interaction. The HBO group improved their SST scores in cognitive performance after HBO administration, while no significant improvement was found in the PBO group. Similarly, the HBO group showed significant increased MQ, while no significant change in MQ was shown in the PBO group.

voxel-wise analysis in these clusters indicated that the HBO group showed a reliable increase in ReHo after HBO administration, with a peak difference at HIP.L, ORBinf.R, and LING.R. On the other hand, the PBO group showed no significant change in ReHo in any of these regions ($p < 0.05$, voxel size > 10). The corresponding comparisons showed that the ReHo value at PCNU.R was significantly increased in the PBO group, but significantly decreased in the HBO group, after the experiment. As for the ReHo in the cluster of SFGdor.R, we did not find a significant change in either the HBO group or the PBO group after the experiment ($p < 0.05$, voxel size > 10).

3.4. Relationship between ReHo and cognitive measures

Our findings of the increased cognitive performance and increased ReHo suggest that HBO administration may bring about a change in both variables, but they say little about the relationship between them. Therefore, we performed a multiple linear regression analysis to model the relationship between the changes of cognitive measures and the ReHo change by fitting a linear equation. For each of the five clusters listed in Table 3, we took the change in ReHo as the dependent variable and the changes of cognitive scores as independent predictor variables, and we used the multiple correlation coefficients to indicate how well the changes of cognitive measures for every subject could account for the ReHo change. We found that the changes of scores on two items, SST and MQ, can provide the best fit to the change in ReHo in the HIP.L ($R^2 = 0.600$, $F = 9.748$, $p = 0.003$). The change of ReHo in HIP.L was significantly positively correlated with the scores of SST ($r = 0.658$, $p = 0.006$) and MQ ($r = 0.513$, $p = 0.042$) (Fig. 4a). Detailed information on the multiple regressions can be found in Supplementary Table S1.

Similarly, for the cluster in SFGdor.R, we found that two items, SST and AST, can provide the best fit to the change in ReHo ($R^2 = 0.507$, $F = 6.697$, $p = 0.010$) for the HBO group. In SFGdor.R, the change in ReHo was significantly negatively correlated with the change in the SST score ($r = -0.510$, $p = 0.044$), but significantly positively correlated with the change in the AST score ($r = 0.312$, $p = 0.239$) (Fig. 4b).

In addition, we found that the change in SST had a significant effect on the change of ReHo in LING.R ($R^2 = 0.646$, $F = 25.561$, $p = 1.75 \times 10^{-4}$), and the change in SST was significantly positively correlated with the ReHo in LING.R ($r = 0.804$, $p = 2.0 \times 10^{-4}$, Fig. 4c). Unfortunately, in ORBinf.R and PCNU.R, we found that no change in any cognitive measure had a significant effect on the change in ReHo. The coefficients of multiple linear regression analyses for each predictor that entered into the linear equation are listed in Supplementary Table S2.

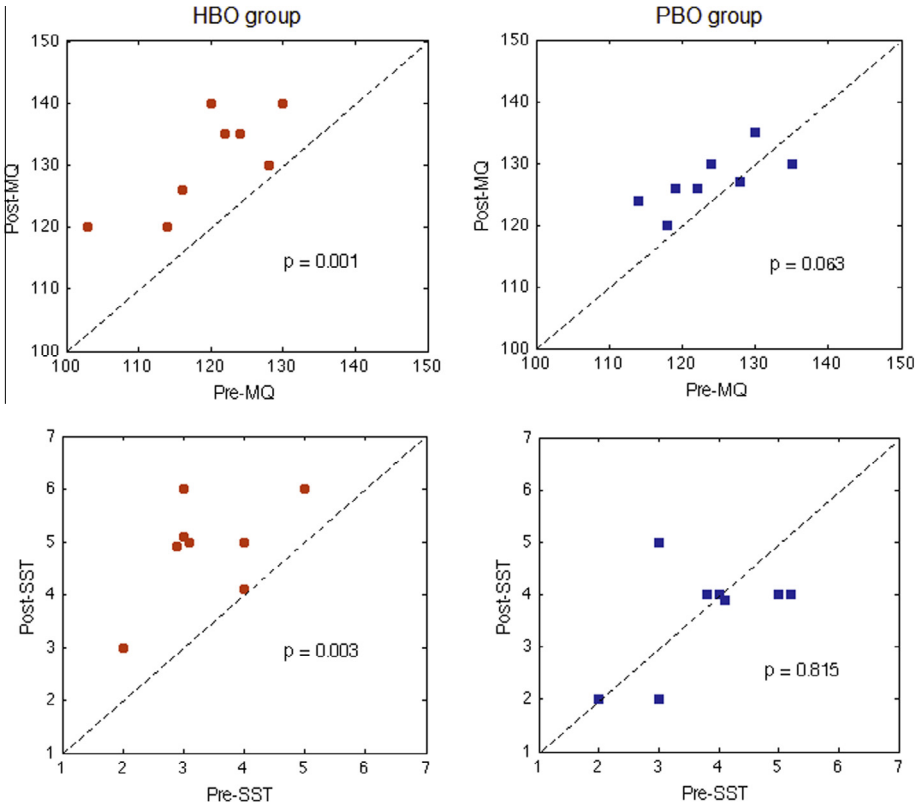

Fig. 2. Scatter plot of cognitive measures with significant changes in the HBO group (MQ and SST), while no changes were observed in the PBO group. Each point represents a subject. We note that the lines indicate the diagonal. Abbreviation: SST – spatial working memory span test, MQ – memory quotient.

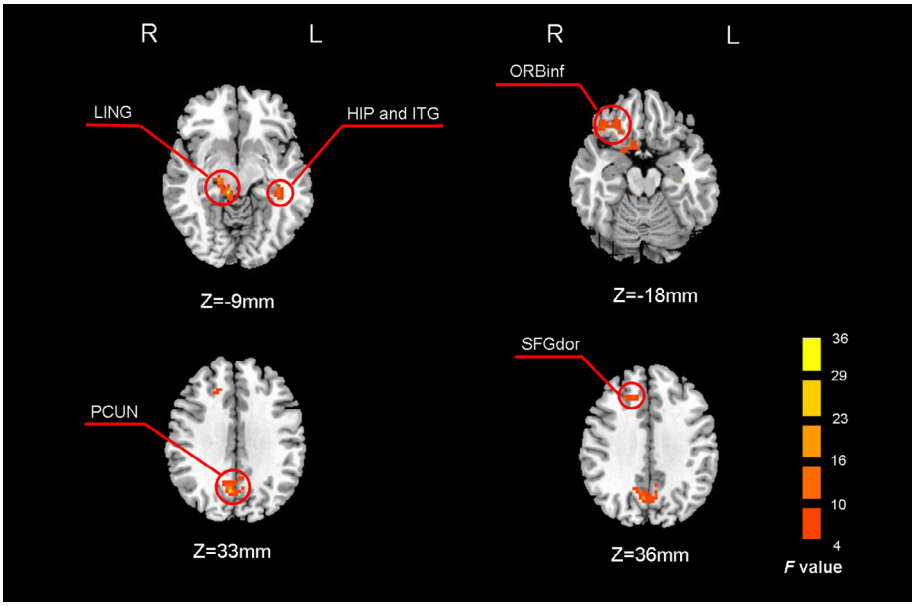

Fig. 3. Cluster regions showing significant interaction between Group and Time on ReHo value. Abbreviations: HIP – hippocampus, ITG – inferior temporal gyrus, ORBinf – orbital part of inferior frontal gyrus, LING – lingual gyrus, SFGdor – dorsolateral superior frontal gyrus, and PCNU – precuneus. Color bar indicates the *F* values.

3.5. Increased functional connectivity after HBO administration

According to the ReHo analysis, we selected three ROIs, HIP.L, SFGdor.R, and LING.R, which showed significantly increased ReHo values in the HBO group instead of the PBO group after HBO or PBO administration, to perform an ROI-based connectivity calculation. We found that the functional connections between the SFGdor.R and bilateral median cingulate gyri (MCG) were significantly increased in the HBO group after HBO administration (Fig. 5). Furthermore, HIP.L showed significantly increased functional connectivity with the bilateral MCG, left thalamus (THA.L), and left caudate (CAU.L) in the HBO group after HBO administration (Fig. 5). Detailed information on the clusters is provided in Supplementary Table S6. As for the LING.R, we found no significant

Table 3
Brain regions showing statistically significant interaction between group and time on ReHo value derived from a two-way repeated measure ANOVA.

Clusters	Brain regions	Peak coordinate in MNI space			Cluster size in No. of voxels (volume, mm^3)
		x (mm)	*y* (mm)	*z* (mm)	
1	HIP_L & ITG _L	−39	−36	−9	61 (3431)
2	LING_R	9	−33	−9	84 (4725)
3	ORBinf_R	39	30	−18	65 (3656)
4	SFGdor_R	15	30	36	72 (4050)
5	PCNU_R	6	−66	33	174 (9788)

Note: HIP – hippocampus gyrus; ITG – inferior temporal gyrus; LING – lingual gyrus; ORBinf – orbital part of inferior frontal gyrus; SFGdor – dorsolateral superior frontal gyrus; PCNU – precuneus gyrus.

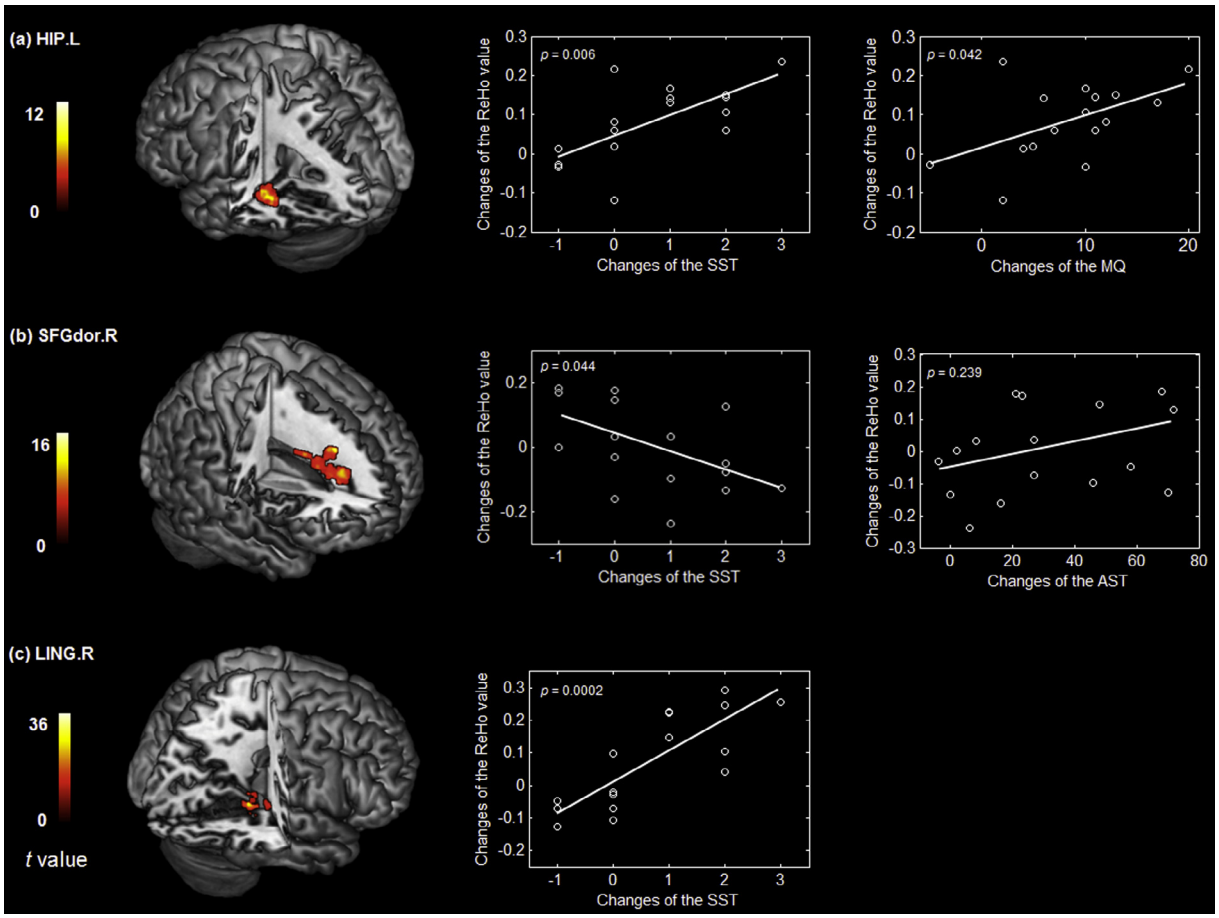

Fig. 4. Brain cluster regions showing significant changes in cognitive measures in the HBO group after HBO administration. The correlations between the changed ReHo and cognitive measures were also plotted at the detected clusters, left HIP, right SFGdor, and right LING. Color bar indicates the *F* values.

change in connectivity between pre- and post-experience for the HBO group ($p < 0.01$, Alphasim correction).

4. Discussion

4.1. Changes in cognitive performance induced by HBO administration

In this study, the HBO group showed a significantly increased SST and MQ after HBO administration, but the subjects of the PBO group showed no improvement in these two measures (Figs. 1 and 2). This indicates that the HBO administration can affect memory performance. These results were consistent with several previous studies (Moss and Scholey, 1996; Scholey et al., 1998; Chung et al., 2004; Choi et al., 2010). An earlier behavioral study (Moss and Scholey, 1996) demonstrated that increased availability of cerebral oxygen can improve performance on tests of cognition, including memory consolidation in healthy young adults. Likewise, Scholey et al. (1998) detected a significant effect of oxygen administration on word recall, but not on forward or backward digit span test based on a double-blind design study, which suggested that oxygen administration could selectively enhance some aspects of cognitive performance. Two recent studies (Chung et al., 2004; Choi et al., 2010) showed that higher oxygen concentration can contribute to the improvement of visuospatial task performance, and they suggested that oxygen administration can contribute to the consolidation of memory and visuospatial abilities. Taken together, this study indicates that oxygen administration can enhance the performance of memory function, mainly in terms of spatial working memory.

However, we found no significant effect of HBO administration on the score of attention-related cognitive measures. Actually, Moss et al. (1998) reported that oxygen administration could

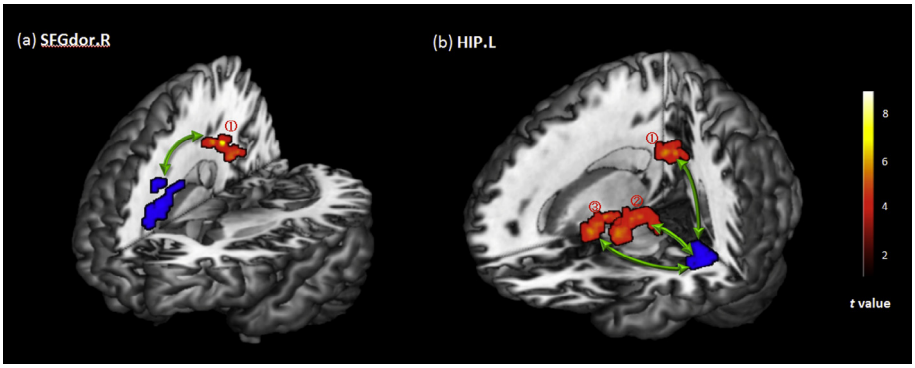

Fig. 5. Rendering plot of the significantly increased brain functional connections in the HBO group post HBO administration. Three clusters were detected with significantly changed ReHo post HBO administration at $p < 0.01$: ① bilateral median cingulate gyri (MCG), ② left thalamus (THA.L), and ③ left caudate (CAU.L). The arrows are only used to indicate the connectivity, not for indicating the direction information, between two clusters.

significantly affect a number of measures related to attentional processes. Because the attention performance can be measured using different aspects of attention tests, we cannot rule out the possibility that other attentional tests may be sensitive to appropriate durations of oxygen administration thus not being examined. Clearly, more precise assessments are required to eliminate the HBO effect on attentional performance.

4.2. Relationship between changes of ReHo and cognitive measures

Some recent studies examined the effect of HBO therapy on TBI and suggested that the common mechanisms of HBO therapy may relate to the metabolic change by supplying the missing energy/oxygen needed for the regeneration processes, which leads to increased neuronal activity and connectivity (Boussi-Gross et al., 2013). In our study, we found an increase in ReHo in HIP.L after HBO administration, which is in line with several previous studies (Harch et al., 1996, 2007; Choi et al., 2010). Using a rat model, Harch et al. (1996, 2007) found that the rat with unilateral cortical contusion could improve spatial learning performance after low-pressure HBO therapy, and they detected simultaneously increased vascular density in the affected hippocampus compared to the control group. With a visuospatial task-based fMRI, Choi et al. (2010) studied the effect of oxygen concentration on the cognitive performance in college students. They observed increased brain activation in the limbic system under air administration with 30% O_2 during the task compared to the condition under normal air, and they found that the improvement in the task performance under 30% O_2 was related to the increase in brain activation in the limbic system, including hippocampus, parahippocampal, and cingulate gyri. The hippocampus has been widely proven to be involved in long-term memory, short-term memory, and spatial working memory (Baddeley et al., 2011; Mustroph et al., 2012; von Allmen et al., 2013). Our finding of increased ReHo value in the hippocampus may reflect the improvement of memory resulting from the HBO administration. In addition, we detected that the changes of the SST and MQ were significantly positively correlated with the change of ReHo in the hippocampus region (Fig. 4). This result demonstrated not only the improvement of simple memory-related cognitive performance but also the increase of ReHo in the hippocampus along with improved memory performance.

We also observed an increase in ReHo in ORBinf.R after HBO administration (Table 3 and Fig. 4). With air administration of different oxygen levels, Chung et al. (2004) studied brain activation when subjects performed a visuospatial task, and they found greater activation in the left precuneus, right inferior frontal gyrus, and superior frontal gyrus with 30% oxygen concentration compared to 21% O_2 concentration. Later, Chung et al. (2006) used a verbal task and demonstrated that brain activations were increased in the right inferior frontal gyrus, superior frontal gyrus, and cingulate gyrus under air administration with 30% O_2 concentration compared to the normal air administration. The correlations between the increased ReHo in ORBinf.R and the cognitive scores have been tested. Unfortunately, we found that the change in ReHo did not correlate with the change in any cognitive measure. As the inferior frontal gyrus (IFG) is believed to be associated with the visuospatial perception and the control of attention (Fink et al., 2001; Klingberg et al., 2002; Takahashi and Ikegami, 2008), we may infer that the HBO administration contributes to a higher ReHo in ORBinf and facilitates cognitive performance.

In addition, we also found increased ReHo in LING.R after HBO administration, which has not been reported in previous studies. The LING is believed to play an important role in visual memory (Bogousslavsky et al., 1987). A clinical study (Bogousslavsky et al., 1987) has shown that visual memory dysfunction and visuo-limbic disconnection were related to the damage of LING in patients with stroke or TBI. Furthermore, the activation of LING has been shown in selective attention studies (Mangun et al., 1998). Our result of the increased ReHo in LING.R after HBO administration may provide new evidence to reveal the wide effect of HBO on the diverse aspects of the memory performance.

4.3. Enhanced functional connectivity with the subcortical system after HBO administration

Our study revealed the effect of HBO not only on the increased brain spontaneous activity but also on the connectivity between the ROIs with increased ReHo value and subcortical brain system in the HBO group after HBO administration. The limbic system of the subcortical areas includes the thalamus, cingulate, and hippocampus, and it relates to emotions, memory, learning, and visuospatial skills (Gitelman et al., 1999; Choi, 2004). In fact, previous studies have also adopted the event-related potential (ERP) technique to test the roles of subcortical regions in the generation of electrical brain activity due to high temporal resolution of electrophysiological recordings. The caudate nucleus, a part of basal ganglia, has been demonstrated to be involved in generating contingent negative variation (CNV) potential related to the processing of sensory information (Bares and Rektor, 2001). Furthermore, previous studies suggested the posterior thalamus to be one of the intracranial sources of auditory oddball P3 and CNV, and involved in the processing of afferent information and in cognitive operations (Rektor et al., 2001). In an fMRI study, Choi et al. (2010) studied the activation of limbic system during visuospatial tasks under concentrated O_2, and they found that the improvement in visuospatial task performance was related to the increase of

neural activation in the thalamus and cingulated gyrus. This indicated the necessity of considering the roles of the brain subcortical system in higher-order function when examining the effect of highly concentrated O_2 on the cognitive performance. In the present study, the increased functional connectivity of subcortical regions after HBO administration was in line with the previous results. It is meaningful that increased functional connectivity was observed between the ROIs with increased ReHo and the cingulate gyrus, thalamus, and caudate, which plays an integrative role in the processing of visuospatial, cognitive, and sensory information. Our results also provide further evidence on the importance of oxygen in subcortical regions from the resting-state perspective.

4.4. Considerations

Some considerations in this preliminary study need to be mentioned. First, the precise neurochemical substrates affected by oxygen enrichment are still not known entirely. Considering that the specific neuronal mechanism responding to HBO administration is complex, we should be careful to interpret and expand this study to the clinical application. Second, there are still debates surrounding the effect of placebo on healthy controls. Several previous studies illustrated significant effects of HBO on the brain activity even due to small increases in air pressure (Boussi-Gross et al., 2013; Mychaskiw and Stephens, 2013). In addition, a less expensive and simple treatment with mild hyperbaric air (1.3 ATA) can also lead to a meaningful effect for patients with mild traumatic brain injury (mTBI) (Boussi-Gross et al., 2013). In this study, the healthy subjects or the PBO group also showed some changes in behavioral measurements, but fewer changes in the ReHo value and functional connectivity, compared to the HBO group. We cannot separate the placebo and oxygen effects because we used the 2.0 ATA air for the PBO group. In our study, the only between-group difference in environment was the oxygen condition. We may infer to some extent the specific effect of oxygen on the brain activity in the HBO group. Additionally, the crossover study is useful in ruling out the individual variation when compared to a longitudinal study in which the subjects can receive a sequence of different treatments. However, the main problem is "carryover" between two trials, which confounds the estimates of HBO effects on human cognitions. For the healthy subjects, we used a randomized placebo (PBO)-controlled parallel group design that is more economical and effective. Lastly, the limited sample size has to be taken into account when interpreting to what extent the results can be generalized, especially for use of HBO in patients. The small sample size may result in decreased sensitivity and increased false-negative rate, but it is indicative of larger effect sizes for positive findings. The presence of significant changes of cognitive measures points to a large effect size, which has also been demonstrated by the non-parametric permutation test. In addition, we did not test the effect of HBO duration on cognitive functions. In this study, all subjects were tested with repeated HBO or PBO administration in only five consecutive days. This duration is usually used as one course of treatment in clinical applications.

5. Conclusion

In summary, we identified the effect of HBO on the cognitive functions and on the ReHo values in healthy young adults by using a placebo-controlled resting-state fMRI study. We found that the scores of cognitive measures in both the spatial working memory span test and MQ were significantly increased, and the ReHo values in HIP.L, ORBinf.R, and LING.R were significantly increased in the HBO group after HBO administration compared to the PBO group. Importantly, we found that the changes of ReHo in these clusters were associated with the changes of cognitive measures in MQ, SST, and AST. Moreover, the functional connectivity analysis revealed increased connectivity between the defined ROIs and bilateral MCG, left THA, and left CAU after HBO administration in the HBO group. Our results suggest that increased availability of cerebral oxygen may improve memory performance and activity of the related brain system. The findings may improve our understanding to the role of HBO in clinical and practical applications.

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The authors declare no competing financial interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2015.01.010.

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