BRAIN RESEARCH 1348 (2010) 21–29

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BRAIN RESEARCH

Research Report

Cerebral and functional adaptation with chronic hypoxia exposure: A multi-modal MRI study

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ARTICLE INFO

Article history:
Accepted 9 June 2010
Available online 17 June 2010

Keywords:
Hypoxia
VBM
DTI
ReHo
Resting state
BOLD fMRI
Plasticity

ABSTRACT

The current study obtained multi-modal MRI data from 28 immigrant high altitude (HA) young adults who were born and grew up at Qinghai-Tibetan plateau matched with 28 matched sea level (SL) controls. We compared their regional gray matter volumes (VBM) and white matter quality (DAI FA values) as well as resting state brain activity (Regional Homogeneity (ReHo) of BOLD-fMRI). We found that HA residents showed decreased gray matter volume at bilateral anterior insula, bilateral prefrontal cortex, the left precentral, the left cingulate and the right lingual cortex; accompanied by changed FA and ReHo values in relevant and other regions. The resting state activity at the hippocampus and the right insula were increasing with SL relocation. The HA subjects performed worse on a series of working memory tasks, with the ReHo values of several regions as significant predictors of their performance. This study demonstrated the cerebral and functional modifications with chronic high altitude hypoxia.

1. Introduction

In recent years more and more people are travelling or working at high altitude (HA, (West and Readhead, 2004)). New comers to HA usually experience series of symptoms of mountain sickness, such as headache, lightheadedness, fatigue, insomnia or anorexia (Hackett and Roach, 2001; Basnyat and Murdoch, 2003), even with pulmonary (Hultgren, 1996) or cerebral edema (Hackett and Roach, 2004). In contrast, indigenous high altitude residents have been found to have several adaptive mechanisms in peripheral physiology to increase pulmonary ventilation and facilitate blood oxygen transportation (Chiodi, 1957; Hultgren and Grover, 1968; Frisancho et al., 1973; Frisancho, 1975; Moore et al., 1998; Beall, 2000; Moore, 2000; Beall et al., 2002; Wu and Kayser, 2006; Beall, 2007). These mechanisms will help to maintain oxygen supply to the brain, but it is not yet clear whether they are sufficient to compensate for the hypoxic risk to the central neural system.

Neuroimaging studies on indigenous high altitude residents have reported conflicting results. The earliest neuroimaging study found reduced $rCMR_{(glc)}$ in the brain of the Andean dwellers (Quechua) (Hochachka et al., 1994), especially at the frontal and parietal cortex, the angular gyrus and the

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doi:10.1016/j.brainres.2010.06.024

thalamus, thus hypometabolism was proposed as a defense against chronic hypoxia. However when a similar study was conducted on Tibet dwellers (Sherpa), such differences did not show up (Hochachka et al., 1996). Impaired cerebral autoregulation was also repeatedly observed in Himalaya dwellers (Jansen et al., 2000) and Sherpa (Jansen et al., 2007), suggesting the adaptation capability of human brain was limited, even after the natural selection of millions of years.

The current study examined the brain morphological and functional modifications of young adult HA immigrant residents compared to age-matched controls who had been sea level (SL) residents. Using immigrant residents as subjects allows us to exclude the factor of natural selection (Moore, 2001) and focus on the development problems. We acquired multi-modal MRI data from the subjects, including anatomical high-resolution T1-weighted MRI which were used for Voxel Based Morphology (VBM) analysis (Ashburner and Friston, 2000), in order to explore possible regional changes in the volume of gray matter, white matter and cerebrospinal fluid (CSF); and diffusion tensor imaging (DTI) to explore changes in white matter quality (Basser et al., 1994); besides the structural modification, we also examined changes in the baseline function with resting state fMRI (Gusnard and Raichle, 2001; Morcom and Fletcher, 2007). Based on previous studies on indigenous high altitude residents, laboratory rodents under prolonged hypoxia, as well as reports from acute hypoxia (Mórocz et al., 2001; Hackett and Roach, 2004), we expected changes in the gray matter of frontal cortex, the motor cortex, as well as hippocampus, possibly with changes on the corpus callosum. Since working memory decline was frequently reported with high altitude hypoxia exposure (Virues-Ortega et al., 2004; West, 2004), we also administered a series of working memory behavioral tests to examine the possible changes in working memory.

We found that the HA subjects had globally decreased volume at CSF and gray matter, as well as regionally decreased gray matter volumes, accompanied by regional increases as well as decreases in terms of fractional anisotropy (FA) from DTI and regional homogeneity (ReHo) from resting state fMRI. HA subjects showed recovery at a few regional MRI measurements with SL relocation time. The HA subjects also had poorer working memory capacity, which was correlated with their ReHo values at certain regions. In conclusion, prolonged chronic hypoxia exposure indeed impacts cerebral morphology and functionality.

2. Results

2.1. *Physical and physiological assessments*

There were no significant differences in hemoglobin levels, circulating red blood cell count, blood pressure, and pulse rate between HA residents and SL controls. Body height of both males ($p<0.01$) and females ($p<0.05$) in HA residents were significantly larger than that of SL controls. HA females had a higher diastolic pressure ($p<0.01$), HA males had a lower inspiratory reserve volume ($p<0.05$). No significant differences in cardiovascular functions were found between HA residents and SL subjects (see supplementary material).

2.2. *MRI measurements*

No subject from either group showed visible abnormalities on T1-weighted structural images. With the gender factor controlled, the HA subjects showed lower volume of gray matter and CSF than SL controls (Table 1).

2.2.1. *VBM*

VBM analysis showed that the HA residents had decreased gray matter volume compared to the SL controls at bilateral anterior insula, bilateral prefrontal cortex, the left precentral, the left cingulate and the right lingual cortex (two-sample *t*-test, $|t|>2.70$, $p<0.01$, FWE corrected) (Fig. 1, Table 2).

2.2.2. *DTI*

Voxel-by-voxel analysis revealed a significant decrease of the FA value in the right posterior cingulum and the right precentral cortex ($|t|>2.72$, $p<0.01$, FWE corrected) in HA subjects compared with SL controls (Fig. 1, Table 2). ROI analysis revealed significant increase of FA values at both the right and left anterior limb of internal capsule (ALIC) and a significant decrease of FA value at the right posterior cingulum in HA residents compared with SL controls. No significant differences were detected in other areas.

2.2.3. *ReHo*

Two-sample *t*-test found significantly increased ReHo values at the left middle frontal cortex, the right inferior frontal cortex, the right posterior insula, the left hippocampus, the right lingual cortex, and the dorsal middle pon, and decreased ReHo values at the right cingulate cortex, the right superior frontal cortex and both sides of the precuneus in HA residents compared with that of SL controls (Fig. 1, Table 2, $|t|>2.67$, $p<0.01$, FWE corrected).

2.3. *Behavioral experiments of working memory*

HA subjects showed longer reaction time in the verbal and spatial working memory tasks, they also reproduced fewer items in the Rey–Osterrieth Complex Figure Test (ROCF) either immediately after presentation or 20 min later; they also performed worse on the count forward and count backward tasks (Table 3).

2.4. *Correlation and regression analysis*

Correlation analysis revealed significant correlations between the SL relocation time and the gray matter volume at the left prefrontal cortex, and the ReHo value at the left hippocampus, as well as the ReHo value at the right insula (see Fig. 2). There were also significant correlations between the performances on the *count backward* task and the ReHo values from the left and the right sides of the lingual cortex, the pon, the right inferior frontal cortex, as well as the right middle frontal cortex (see Fig. 3), the latter four of which were found to be significant predictors of the performance (see Table 4).

3. Discussion

With multimodal MRI techniques, the current study found that childhood exposure to high altitude hypoxia was