Neuroscience Letters 629 (2016) 1–8

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research article

Regional homogeneity changes in amnestic mild cognitive impairment patients

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HIGHLIGHTS

- The aMCI patients showed abnormal ReHo values in temporal, parietal and occipital lobes by examining spontaneous brain activity during rest state.
- Regional brain atrophy may act as a necessary consideration during the functional imaging studies of aMCI patients.
- ReHo measurement could be a biomarker for the early diagnosis of aMCI.

ARTICLE INFO

Article history:
Received 21 April 2016
Received in revised form 19 June 2016
Accepted 23 June 2016
Available online 23 June 2016

Keywords:
Regional homogeneity
Mild cognitive impairment
Functional magnetic resonance imaging
Default mode network

ABSTRACT

Objective: Regional Homogeneity (ReHo) measures the local coherence of spontaneous brain activity, and it is sensitive to detect aberrant local functional connectivity of brain region. We tried to explore the activity of brain network by ReHo method in amnestic mild cognitive impairment (aMCI) patients and examine the impact of regional brain atrophy on the functional results.
Methods: Data of both structural magnetic resonance images (MRI) and resting-state functional MRI scans were collected from 36 aMCI patients and 46 age-matched healthy controls.
Results: Compared with the HC subjects, the aMCI patients showed significant decreased ReHo areas in the right inferior parietal lobule (IPL), left posterior cingulate cortex/precuneus (PCC/PCu), left inferior temporal gyrus (ITG), right supramarginal gyrus (SMG), right fusiform gyrus (FG), bilateral lentiform nucleus (LN) and right cerebellum posterior lobe, with the right IPL being the most significant area. In addition, the aMCI group also had some significant increased ReHo areas in the right medial frontal gyrus (MFG), bilateral postcentral gyrus (PoCG), left cuneus and right lingual gyrus (LG), possibly reflective of some underlining compensatory mechanism. Furthermore, in the aMCI patients, we found the ReHo index of the left PCC was positively correlated with the AVLT-Immediate Recall scores, while the ReHo index of the left cuneus was negatively correlated with the MMSE scores. In addition, we found that after regressing out the identified regional brain atrophy, the significant correlations between fitted ReHo index and clinical variables still remained.
Conclusions: Our study indicated that aMCI patients showed significant abnormal local coherence of biological activity in resting state and ReHo could serve as a sensitive biomarker in functional imaging studies of aMCI.

1. Introduction

People with amnestic mild cognitive impairment (aMCI), are conceptualized as the transitional prodromal state between normal aging and Alzheimer's disease (AD) [1] and are at an increased risk of progressing to AD [2]. Identifying distinctive neuroimaging based features in aMCI might provide great opportunities for early diagnosis and prevent the onset of the clinical manifestations of AD [1].

Among the neuroimaging modalities, resting-state functional magnetic resonance imaging (rs-fMRI) is a promising technique to measure the spontaneous activity of human brain *in vivo* [3], and has been widely used to investigate the functional brain activity

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http://dx.doi.org/10.1016/j.neulet.2016.06.047
0304-3940/

abnormality in patients with aMCI [2,4–8]. For instance, compared with the healthy controls (HCs), the aMCI group was revealed to exhibit both disrupted resting-state functional connectivity [3,6] and abnormal amplitude of low frequency fluctuations [7] in the precuneus (PCu) and posterior cingulate cortex (PCC).

Regional homogeneity (ReHo) measures the local coherence of spontaneous brain activity, and is sensitive to detect aberrant local functional connectivity of brain regions. It has been used in the studies of neurological and psychiatric diseases, including migraine [9], stroke [10], epilepsy [11], neuromyelitis optica [12], Parkinson's Disease [13], attention-deficit hyperactivity disorder [14], AD [4,15], aMCI [3], social anxiety disorder [16], panic disorder [17], blindness [18], depression [19] and schizophrenia [20].

Bai et al. [5] found significant regional coherence decreases in most areas of the default mode network (DMN), especially in the PCC/PCu. After controlling the regional grey matter (GM) atrophy and age, significant reduction in ReHo values of the aMCI patients remained as compared with HCs.

Zhang et al. [4] observed MCI and AD patients had significantly decreased ReHo values in the medial prefrontal cortex (MPFC), the bilateral PCC/PCu, and the left IPL compared with the HCs. Furthermore, a positive association was found between the cognitive abilities and ReHo after controlling age, gender and GM volumes. However, such association in MCI group alone was not reported.

He et al. [15] found significant ReHo values decreased in brain regions especially PCC/PCu in AD patients. Moreover, decreased level was associated with the severity of AD regardless of correcting the regional brain atrophy.

Wang et al. [21] found decreased ReHo index in medial temporal gyrus and hippocampus and increased ReHo index in paracentral lobe, precuneus, and postcentral gyrus in early MCI patients, and there was a positive correlation between ReHo index in precuneus and MMSE scores.

In current study, we employed the rs-fMRI data to confirm the previously reported whole-brain ReHo differences between aMCI patients and HC group. And more importantly, we studied the relationship between ReHo values and cognitive performances in aMCI patients *alone*, which was different from the previous studies. Then, we examined the effect of regional GM atrophy on the local brain connectivity coherence in a voxel-wise fashion, and observed the relationships again between the ReHo values and cognitive performances after regressing out the regional atrophy.

2. Methods and materials

2.1. Participants

36 aMCI patients and 46 healthy control (HC) participants were recruited from the memory clinic of the neurology department of Xuanwu Hospital, Capital Medical University, Beijing, China. The Medical Research Ethics Committee and Institutional Review Board of Xuanwu Hospital approved this study and informed consent was obtained from each participant.

The diagnosis of the aMCI patients was made by experienced neurologists according to the Petersen's criteria [2,22]. Every participant received a standard set of neuropsychological assessments including Mini Mental State Examination (MMSE) [23], Clock Drawing Test (CDT) [24], Auditory Verbal Learning Test (AVLT), and Clinical Dementia Rating (CDR) Scale [25]. The detailed demographic and clinical data for all the participants were presented in Table 1. The dataset in this study was used to investigate frequency-dependent topological disruption of the functional brain network in a former study [26].

Table 1
Demographic and neuropsychological data in HCs and aMCI patients.

	aMCI (n = 36)	*HC (n = 46)*	*p value*
Gender (F/M)	19/17	27/19	0.29[b]
Age	66.8 ± 9.5	64.3 ± 7.8	0.20[a]
Education	10.0 ± 4.1	11.4 ± 5.1	0.19[a]
MMSE	24.9 ± 3.4	28.5 ± 2.0	$<10^{-7}$[a]
CDT	2.1 ± 0.8	2.8 ± 0.6	$<10^{-4}$[a]
CDR	0.5	0	–
AVLT-Immediate recall	5.7 ± 1.9	8.8 ± 2.0	$<10^{-9}$[a]
AVLT-Delayed recall	5.3 ± 3.4	9.8 ± 2.8	$<10^{-8}$[a]
AVLT-Recognition	8.8 ± 3.3	11.8 ± 2.4	$<10^{-5}$[a]

MMSE, Mini-Mental state Examination; CDT, Clock Drawing Task; CDR, Clinical Dementia Rating; AVLT, auditory verbal learning test.
Plus-minus values are mean ± S.D.
[a] the p value was obtained using a two-sample two-tailed *t*-test.
[b] the p value was obtained using a two-tailed Pearson Chi-square test.

2.2. Data acquisition

All the participants were scanned on a 3.0 T Siemens Trio scanner (Erlangen, Germany) at Xuanwu Hospital, Capital Medical University. Resting-state functional images were collected by using an echo-planar imaging (EPI) sequence, with scan parameters of repetition time (TR) = 2000 ms, echo time (TE) = 40 ms, flip angle = 90°, slice number = 28, slice thickness = 4 mm, gap = 1 mm, voxel size = $4 \times 4 \times 4\,mm^3$, matrix size = 64×64.3D T1-weighted magnetization-prepared rapid gradient echo sagittal images were collected for each participant with scan parameters of TR = 1900 ms, TE = 2.2 ms, inversion time = 900 ms, flip angle = 9°, slice number = 176, slice thickness = 1 mm, matrix size = 256×256.

2.3. Data preprocessing

Resting-state fMRI data were preprocessed by using the Data Processing Assistant for Resting-State fMRI (DPARSF) which was based on Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm). The first 5 vol were removed because of magnetization instability and participants' adaption. The remaining 234 vol were firstly corrected for time offset between slices and then corrected for translation and rotation displacement due to head motion. No participants had excessive head motions of translation >3 mm or rotation > 3°. No significant difference on head motion was observed between the aMCI and HC groups ($p > 0.11$ in any of 6 directions and $p = 0.35$ for FD Jenkinson index) [27]. The motion-corrected data were then normalized to the standard EPI template in Montreal Neurological Institute space and resampled to $3 \times 3 \times 3\,mm^3$ resolution. Furthermore, the linear trend was removed and a band-pass filtering (0.01–0.08 Hz) was performed to reduce the low-frequency drifts and the high-frequency uninteresting signals. Finally, several spurious variables were regressed out, including 6 head motion parameters, the mean signal of white matter (WM) and cerebrospinal fluid (CSF). The global signal was not regressed out due to its controversial biological interpretations [28,29]. Nevertheless, to validate our findings, we additionally performed analysis with the global signal regressed out. Notably, we did not perform spatial smoothing before ReHo analysis because it enhances ReHo intensity and influences its reliability [30,31].

2.4. Regional homogeneity (ReHo) analyses

We used ReHo to measure the regional brain activity coherence [32]. It is defined by exploring the degree of regional coherence of time series voxel-by-voxel based on Kendall's coefficient of concor-