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Altered effective connectivity patterns of the default mode network in Alzheimer's disease: An fMRI study

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HIGHLIGHTS

- The DMN interactions in AD patients were decreased compared with NC.
- PCC was significantly active and had to be the convergence center.
- Region of the rITC exhibited stronger interactions in normal controls.
- Some interactions in the NC were weaker than those in AD patients.

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ABSTRACT

The aim of this work is to investigate the differences of effective connectivity of the default mode network (DMN) in Alzheimer's disease (AD) patients and normal controls (NC). The technique of independent component analysis (ICA) was applied to identify DMN components and multivariate Granger causality analysis (mGCA) was used to explore an effective connectivity pattern. We found that: (i) connections in AD were decreased than those in NC, in terms of intensity and quantity. Posterior cingulated cortex (PCC) exhibited significant activity in NC as it connected with most of the other regions within the DMN. Besides, the PCC was the convergence center which only received interactions from other regions; (ii) right inferior temporal cortex (rITC) in the NC exhibited stronger interactions with other regions within the DMN compared with AD patients; and (iii) interactions between medial prefrontal cortex (MPFC) and bilateral inferior parietal cortex (IPC) in the NC were weaker than those in AD patients. These findings may implicate a brain dysfunction in AD patients and reveal more pathophysiological characteristics of AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder which is mainly characterized by significant impairments in a global cognitive decline [2]. It is estimated that half of the population above 80 years old may have symptomatic AD and this number will grow to approximately 81 million by the year 2040 [9]. AD is a widespread epidemic disease threatening social health. However, there is no current effective treatment for this disease [25]. The principal cause of the formation of such a situation is that the pathological mechanism of AD still remains unknown. It would be quite worthwhile to explore the brain activity characteristics from a network perspective.

A number of functional magnetic resonance imaging (fMRI) studies have reported the existence of the default mode network (DMN) and its core regions which mainly include the posterior cingulated cortex (PCC), medial prefrontal cortex (MPFC), inferior parietal cortex (IPC), inferior temporal cortex (ITC) and (para)hippocampus (HC) [3,8]. Viewed as an integrated system, the DMN plays a critical role in monitoring the external environment and supporting internal mentation [10,19]. However, the DMN was frequently found to be abnormal due to AD [1,13,27]. It is totally necessary to investigate how these DMN brain regions interact with

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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each other and the altered causal interaction pattern in relation to AD.

This study combined independent component analysis (ICA) and multivariate Granger causality analysis (mGCA) to investigate the issue of effective connectivity within the DMN in AD patients and normal controls (NC). ICA was successfully used to identify DMN components and mGCA was applied to explore effective connectivity. It is worth noting that our approach of mGCA is quite different from previous implements which were based on the decrease of residual F to evaluate the causal effect [23,24]. Since the residual-based F approximately obeys chi-square distribution, it is a little troublesome in subsequent statistical analysis for group level inference. Our approach applied signed-path coefficients to evaluate the causal effects among brain DMN regions. The signed-path coefficients are considered to be normally distributed and could be used in a parametric statistical analysis at the group level [7]. The use of this model greatly simplifies the subsequent statistical analysis procedure.

2. Materials

2.1. ADNI

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu/). ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians in developing new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date, these three protocols have recruited over 1500 adults, ages 55–90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

2.2. Subjects

We downloaded 3 T functional MRI data and corresponding clinical data from baseline and follow-up scans from the ADNI publically available database (http://adni.loni.usc.edu/). Thirty-five AD patients (range 63–83 years) and 30 NC (range 65–83 years) were used in this study. The main characteristics of the subjects are reported in Table 1, which presents the baseline clinical and demographic variables of the two groups.

Table 1
Demographics and neuropsychological characteristics.

	Age (mean ± SD)	Female/male	MMSE (mean ± SD)	CDR
NC (n = 30)	74.9 ± 5.80	15/15	29.0 ± 1.15	0
AD (n = 35)	72.7 ± 6.76	17/18	21.0 ± 3.52	1

No significant differences ($p < 0.05$) were observed in age or gender between the two groups. Significant differences were noted in MMSE scores between the two groups ($p < 0.0001$).
AD, patients with Alzheimer's disease; NC, normal controls; MMSE, Mini Mental State Examination; CDR, Clinical Dementia Rate.

2.3. Data acquisition

The fMRI data were collected by a 3.0-Tesla Philips MRI scanner. Resting-state functional images were obtained using an echo-planar imaging (EPI) sequence and the parameters included repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle = 80°, number of slices = 48, slice thickness = 3.3 mm, voxel size = 3 mm × 3 mm × 3 mm, voxel matrix = 64 × 64 and total volume = 140. All original image files are available to the general scientific community.

2.4. Data processing

All preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF, Yan and Zang, 2010, http://www.restfmri.net), which is based on Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (REST, Song et al., 2011, http://www.restfmri.net). The first ten time points from each functional image were discarded to allow for equilibration of the magnetic field. All remaining volume slices were corrected for different signal acquisition times. Then, the time series of images for each subject was realigned using a six-parameter (rigid body) linear transformation. Participants with head motion exceeding 1.0 mm in any dimension of x, y and z or 1.0° in any angular motion were excluded for further analysis. The resulting images were then spatial normalized to the standard EPI template with 3 × 3 × 3 resolution. The normalized images were further spatially smoothed with a Gaussian kernel of 6 mm full width at half maximum (FWHM). In order to reduce the effects of confounding factors, the linear trends of time courses were removed using REST. Finally, we applied temporal filtering (0.01 Hz < f < 0.08 Hz) to the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency noise such as respiratory and cardiac rhythms.

3. Methods

3.1. ICA

The preprocessed data for all subjects were analyzed with independent component analysis (ICA) for the fMRI toolbox (GIFT, http://icatb.sourceforge.net/) which includes twice principal component analysis (PCA) reduction, ICA separation, and back-reconstruction [5]. Prior to PCA, the optimal number of components was set to 25/30 for NC and AD patients, which was estimated based on minimum description length (MDL). In the first step, data from each subject were temporally reduced to the optimal number. Then, the reduction step was once again achieved by PCA according to the optimal numbers. In the second step, the data were separated by ICA using the Infomax algorithm [16]. Finally, independent components (ICs) and time courses for each subject were back-reconstructed. The IC that best matched DMN component was selected with a standard DMN template [13]. After the conversion of the intensity values in each IC spatial map to Z-scores, a one sample t-test (height threshold: false discovery rate (FDR), $p = 0.05$, extent