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The Effect of Aging on Resting-State Brain Function: An fMRI Study

Background/Objective: Healthy aging may be accompanied by some types of cognitive impairment; moreover, normal aging may cause natural atrophy in the healthy human brain. The hypothesis of the healthy aging brain is the structural changes together with the functional impairment happening. The brain struggles to over-compensate for those functional age-related impairments to continue as a healthy brain in its functions. Our goal in this study was to evaluate the effects of aging on the resting-state activation network of the brain using the multi-session probabilistic independent component analysis algorithm (PICA).

Patients and Methods: We compared the resting-state brain activities between two groups of healthy aged and young subjects, so we examined 30 right-handed subjects and finally 12 healthy aging and 11 controls were enrolled in the study.

Results: Our results showed that during the resting-state, older brains benefit from larger areas of activation, while in young competent brains, higher activation occurs in terms of greater intensity. These results were obtained in prefrontal areas as regions with regard to memory function as well as the posterior cingulate cortex (PCC) as parts of the default mode network. Meanwhile, we reached the same results after normalization of activation size with total brain volume.

Conclusion: The difference in activation patterns between the two groups shows the brain's endeavor to compensate the functional impairment.

Keywords: fMRI, Resting-State, Default Mode Network, PICA, Atrophy

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Introduction

Functional magnetic resonance imaging (fMRI) is a type of MRI scan which measures the brain's haemodynamic response in reaction to neural activity. This technique uses the BOLD (Blood Oxygen Level Dependent) effect in order to show the pattern and intensity of activation in the human brain. It has some advantages including low invasiveness, lack of radiation exposure and relatively wide availability.[1] fMRI data acquisition and analysis can be done using either model-based or non model-based methods.[2] In the first method, an external stimulus is presented to the subject and the brain's haemodynamic response will be aligned to it. In the second method, we have no information about the stimulation pattern and the time series; consequently, non model-based algorithms should be used to analyze it. Independent component analysis (ICA) is one of those mathematical non model-based algorithms able to distinguish and release the components of a mixed data, which are spatially and statistically independent from each other. Spatial independency states that no two components of activation refer to the same anatomical region of the brain. This algorithm has been previously used[3] in the analysis of resting-state fMRI data to extract the brain's activation pattern.

The state of the brain, when the subjects confront no stimuli, is called the "resting-state". During resting-state the subject is not voluntarily doing any special

function and all the observed functions at the moment are caused by internal stimulations, which may be the results of passive and routine functions of the brain; such as mental functions, supervising the environment and controlling the conditions, registering the feelings and internal emotions, and other forms of interactions and undirected thoughts.[4] The network of brain functions which are activated when a subject is at the resting-state is so called "default mode network" (DMN).[4-6] DMN is of interest since it has been defined as a baseline condition of brain function and its component brain regions are believed to be abnormal in different diseases. There are different studies, which have focused on DMN to diagnose schizophrenia,[7] hepatic cirrhosis,[8] anxiety disorders[9] and mild cognitive impairment and Alzheimer's disease.[10] DMN has also been studied in functional connectivity researches which reflect structural connectivity in the brain.[11] The default mode network is mostly observable in the posterior cingulate cortex (PCC)[3] and is also considered to be related to the prefrontal areas which are known as regions of memory.[12]

The aim of this study was to evaluate the effect of aging on the brain resting-state activation pattern in default mode network. We used two groups of healthy aging subjects and young controls, and compared their activation patterns during resting-state, using the ICA algorithm. Besides, since brain volume in the healthy aging group is less than that of the controls (because of natural atrophy related to the aging process), we evaluated the brain volume for the two groups in order to normalize their activation size. In fact, our aim for normalization was to show that the effects of the aging process on the brain are not just structural changes (atrophy). We wanted to show that the aging process causes functional impairment in the brain too, which are independent from atrophy or structural changes. This may help to have a reliable comparison of the brain activation between young and old patients, and in turn between old healthy and old patient subjects in the future. The novelty of this project is that it is the first time it has been performed in Iran and that it will be continued toward mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients in the future.

Patients and Methods

A total number of 30 right-handed subjects, including 15 young subjects (8 women, 22-28 years old, mean 25±2.8), and 15 aged subjects (7 women, 60-82 years old, mean 67±7.5) were examined in this study. The inclusion criteria included right-handed non-smokers with no specific brain disease and no sign of hypertension or psychological symptoms such as depression. All subjects were examined clinically by both neurologists and psychologists and the criteria were also checked by asking subjects or their relatives. It is worth mentioning that among these 30 subjects, seven imaging data were omitted from the final analysis due to reasons such as inability of the subjects to do what was expected during the resting-state or due to technical problems such as high value of distortion in their imaging data. Therefore, the final number of subjects for analysis reduced to 12 healthy aging and 11 controls (Table 1).

Imaging

The MRI system was a 1.5-Tesla GE® Signa scanner. A T1-weighted spin-echo sequence was used to acquire high-resolution structural maps of the brain (axial; TR, 400 ms; TE, 9 ms; flip angle, 90°; voxel size, 1×1×6 mm^3). fMRI data were obtained with the same dimension and orientation of the structural images, employing a gradient echo/ echo planar imaging (EPI) protocol (axial; TE, 60.3 ms; TR, 3125 ms; field of view, 22 cm^2; NEX, 1; spatial resolution, 4.062542; flip angle, 80; number of slices, 15; slice thickness, 6mm, spacing, 0mm and bandwidth, 15.62 KHz, voxel size, 4×4×6 mm^3). Due to the hardware limitations, we had to repeat the EPI sequence to acquire the reasonable number of image volumes for data analysis. Each EPI sequence lasted for 100 seconds and resulted in 480 images of the brain. Consequently, fMRI imaging lasted as 64 fMRI scans or volumes.

During fMRI imaging, in order to create the resting-state condition, we asked the subjects to lie back relaxed in the MR scanner, with their eyes closed, their head and limbs still, not thinking about anything, with no function. That is because DMN is active during the resting-state and disappears as the subject confronts a stimulus. As we looked for activation in the default mode network, we used resting-state con-

Table 1. Demographic Information About Subjects

Subject	Control	Healthy Aging
Final number of subjects	11	12
Final subjects Male/Female	6/5	7/5
Final subjects Age mean	24 ± 2.6	68 ± 8.1

Table 2. Comparison of Statistical Parameters for PCC Region

Statistical Comparison (PCC Region)	Young Group	Old Group	P-Value
Minimum cluster intensity	3.511	3.375	---
Maximum cluster intensity	11.092	10.427	---
Cluster size (# of voxels)	564 ± 93.18	613 ± 136.71	0.045
Mean cluster intensity (Z-value)	5.93 ± 1.17	5.61 ± 0.92	0.040

Table 3. Comparison of Statistical Parameters for Prefrontal Area

Statistical Comparison (MPFC Region)	Young Group	Old Group	P-Value
Minimum cluster intensity	3.146	2.885	---
Maximum cluster intensity	8.901	6.468	---
Cluster size (# of voxels)	715 ± 118.22	1770 ± 241.53	0.001
Mean cluster intensity (Z-value)	4.49 ± 1.02	4.05 ± 0.85	0.004

ditions to see activation in this network.

Data Analysis

Data analysis consisted of both functional and structural parts. The functional analysis was performed using the independent component analysis (ICA) algorithm. Since we needed a non model-based analysis algorithm, we used ICA. We used MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) tool of FSL (fMRIB Software Library, version 4.1) software to analyze the two different groups of subjects (old and young), using multi-session temporal concatenation group PICA (probabilistic independent component analysis) algorithm. The block diagram of the data analysis is shown in Figure 1.

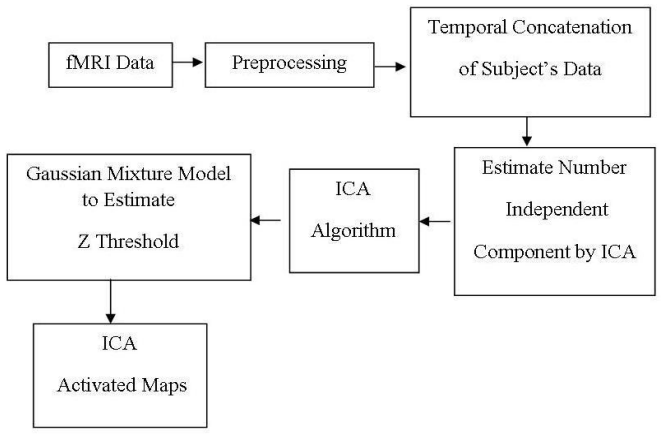

Fig. 1. The block diagram of ICA analysis.

Before ICA analysis, some preprocessing steps were necessary. The preprocessing consisted of seven stages: 1) head motion correction using motion correction with fMRIB's linear image registration tool (MCFLIRT), 2) slice-timing correction using fourier-space time-series phase-shifting, 3) mean intensity normalization of the entire 4D dataset by a single multiplicative factor, 4) spatial smoothing using a Gaussian kernel with FWHM of 5 mm, 5) brain extraction to remove non brain tissues using brain extraction tool (BET, version 1.1), 6) high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=100 s) and 7) Gaussian low-pass temporal filtering.

To estimate the number of independent components, we used the minimum description length (MDL) algorithm[13] which assumes a penalized form of likelihood function and minimizes it to estimate the number of independent sources. All extracted components have been transformed to Z-space in order to have a zero mean and unit variance. In the next step, a Gaussian mixture model[14] has been used to find a suitable threshold for each independent component. Final ICs were extracted by implementing this threshold on the probability component

Table 4. Normalized Activation Cluster Size for Both Groups and Both Regions of Interest

Normalized Activation Cluster Size	Young Group	Old Group	P-value
PCC region	354	428	0.096
MPFC region	448	1234	0.025

maps. Finally, after extracting the components of activation, all functional images were registered to their anatomical T1 images.

We used separate ICA group analysis in the form of multi-session temporal concatenation for the two groups of subjects. Of course, in this form, a standard image from FSL standard library was used to overlay the activation components on it. We have used MNI 152_T1_2mm_brain standard image for visualization of activation components in the group analysis. Nonetheless, all the analysis parameters were identical in the two groups, so the comparison of the results is valid.

The structural analysis was performed using structural image evaluation using normalization of atrophy (SIENA) tool from FSL software tools. This tool estimates the total brain, white matter and gray matter volume from a single image normalized for the skull size. It first eliminates non-brain tissue, and then uses the brain and skull images to estimate the scaling between the subject's image and standard space. It then divides the brain tissue into segments to estimate the volume and multiplies this by the estimated scaling factor, to reduce head-size-related variability between subjects.

We estimated the total brain volume in order to normalize the activation cluster size, using the following relation:

$$\text{Normalized Cluster Size} = (\text{Cluster Size}/\text{Brain Volume}) \times 10^6$$

It is worth mentioning that fMRI data analysis by MELODIC tool reveals several components of brain activation, which may be related to visual cortex, auditory cortex, default mode network, memory, or even the motor cortex. However, among all output components of brain activation, we have just selected the components, which show some parts of default mode network. In fact, in this project, the two more important regions of interest included in the DMN are the posterior cingulate cortex and the medial prefrontal area. Additionally, since all the components are spatially independent from each other, selecting PCC and MPFC (medial pre-frontal cortex) components is not a difficult task and this just needs knowledge about brain neuroanatomy.

Results

In order to compare the two young and aged subject groups, we used four statistical parameters: activation cluster size, mean intensity of activation cluster (z-value), brain volume and normalized activation cluster size.

Figure 2 shows the activated regions in both young and old groups of subjects, consisting posterior cingulate cortex and medial prefrontal areas.

The results of statistical analysis of posterior cingulate activation for both groups are shown in Table 2. A similar table is dedicated to the results from the prefrontal area (Table 3).

The tables above show that the mean z-value of the PCC region in the young group is significantly greater than that of the old group (5.93>5.61, P-value=0.04). This is also true for the prefrontal area (4.49>4.05, P-value=0.004).

On the other hand, activation cluster size in the prefrontal area was significantly larger in the old group, compared with controls (1770>715, P-value=0.001). There are also the same results for the PCC region (613>564, P-value=0.045).

As expected, the mean brain volume in the old group is less than that of the young group, and the difference is significant (1433500<1593100, P-value=0.016).

The result of normalization of activation cluster size is provided in Table 4.

As shown in this table, normalized cluster size in both regions of the PCC (824>354, P-value=0.096) and MPFC (1234>448, P-value=0.025) is greater for the old group.

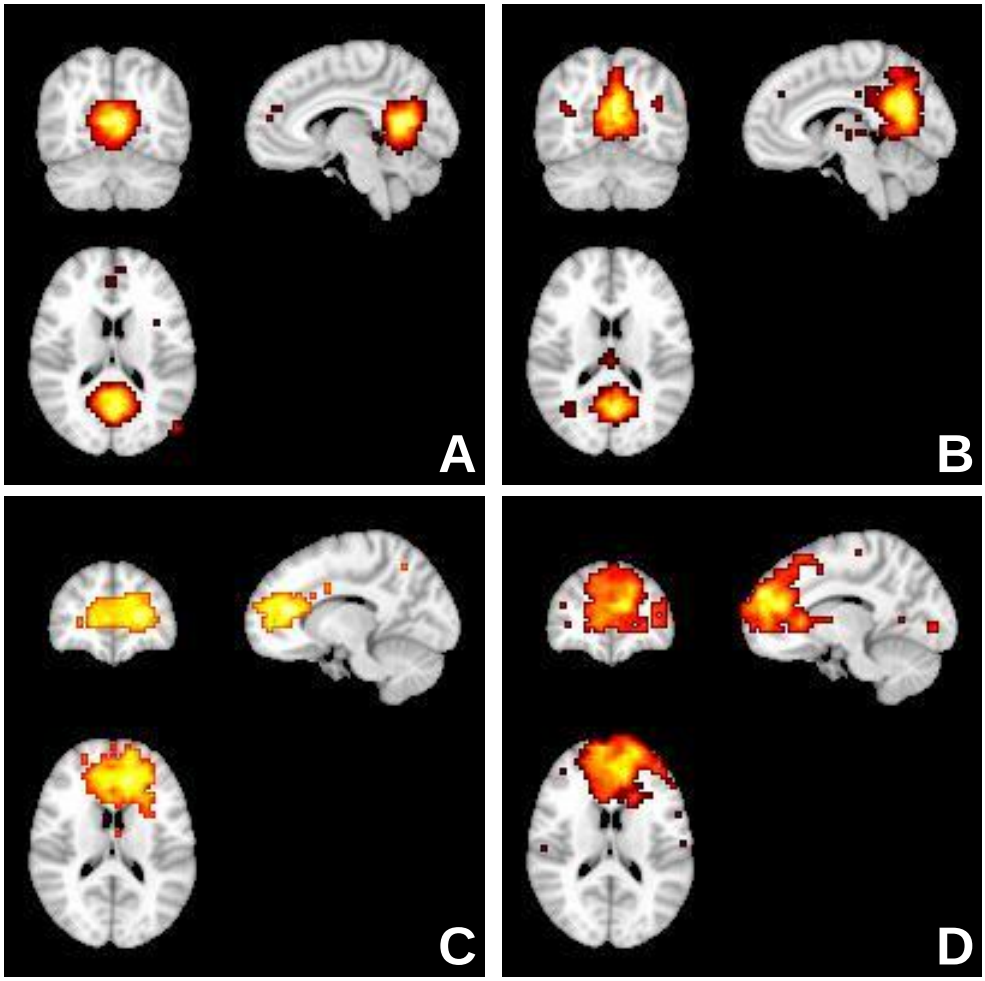

Fig. 2. fMRI of resting-state brain function (axial, coronal and sagittal views).

A. Activation of posterior cingulate cortex (young group).

B. Activation of posterior cingulate cortex (old group).

C. Activation of prefrontal area (young group).

D. Activation of prefrontal area (old group).

Discussion

This study showed different patterns of brain resting-state activation in young and old subjects in MPFC and PCC regions, as parts of the default mode network. Using the resting-state fMRI method and normalizing the activation size to the brain volume, we found that older subjects show larger clusters of activation (greater number of active voxels), but less intense activities (lower z-values). This change in the activation pattern can be used as a clue on how the old brain compensates the functional age-related impairments. Indeed, during the resting-state, the old brain benefits from larger areas of activation. These results were obtained in prefrontal areas as regions with regard to memory functions as well as PCC as the main parts of the default mode network.

Greater intensity in young subjects compared to that of the old group, proposes that weaker brain activation in old subjects is related to the brain's altering deficiency in this group. So far, reduced resting-state brain activity in the "default mode network" has been reported in normal aging.[15] This confirms the age-related alterations of brain activation intensity in the resting-state fMRI. This result is consistent with our knowledge about functional compensation in the brain. In fact,"overcompensation" for functional impairment is what we expect when age-related or structural damage is evident. In this regard, an old atrophic brain will show lower activation intensity, which is the result of those age-related deficiencies.

Alternatively, cluster size was found to be higher in old subjects when compared to young brain activation. Since brain atrophy can potentially change the cluster size of activations,[16,17] evaluation of brain activation inside the live brain tissue is essential during activation assessment. Larger clusters of activation in older subjects imply a silent struggle of the brain to compromise its weakness as a result of senile atrophy. This finding means compensation in aging impairments of an old brain could occur by activation of

larger areas.

From a clinical standpoint, these age-related alterations can occur more severely in degenerative diseases of the brain. Changes in intrinsic brain activity have previously been reported in several different medical conditions such as Alzheimer's disease,[18] schizophrenia,[19] depression[20] and autism.[21] Increasing evidence suggests that coherent intrinsic brain activity is important for healthy brain function. In normal aging, distinct prefrontal cortex regions (PFC) exhibit different patterns of functional changes, suggesting that age-related changes in PFC functions are not homogeneous in nature. Specifically, it is hypothesized that normal aging is related to the differentiation of cortical function in a bilateral ventral PFC and deficits in function of the right dorsal and anterior PFC.[22]

To prove direct consequences of brain aging, this study took the advantage of calculating brain atrophy as one of the most important effects of age on the brain. We initially found the amount of brain volume decrease in the elderly and this confirms that some age related changes have taken place in the old group. Besides, we showed that there are some factors in the brain apart from atrophy that will affect the brain's activation pattern. Using un-normalized activation intensity and cluster size, we have evaluated both the effects of atrophy and those other changes related to aging. However, using normalized values, we tried to remove the atrophy effect as much as possible, and any remaining activation changes may mostly be due to those alternative aging processes.

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