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Research article

Decreased resting-state connections within the visuospatial attention-related network in advanced aging

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HIGHLIGHTS

- Elderly subjects responded to the target more slowly than young subjects did.
- Eleven ROIs were defined based on the activation map during the Posner task.
- Fifty-two of the 55 pairs of ROIs were positively correlated in the young group.
- Only 22 of the 55 pairs of ROIs were positively correlated in the elderly group.
- The SMA with the left AIC had reduced resting-state functional connectivity with age.

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ABSTRACT

Advanced aging is accompanied by a decline in visuospatial attention. Previous neuroimaging and electrophysiological studies have demonstrated dysfunction in specific brain areas related to visuospatial attention. However, it is still unclear how the functional connectivity between brain regions causes the decline of visuospatial attention. Here, we combined task and rest functional magnetic resonance imaging (fMRI) to investigate the age-dependent alterations of resting-state functional connectivity within the task-related network. Twenty-three young subjects and nineteen elderly subjects participated in this study, and a modified Posner paradigm was used to define the region of interest (ROI). Our results showed that a marked reduction in the number of connections occurred with age, but this effect was not uniform throughout the brain: while there was a significant loss of communication in the anterior portion of the brain and between the anterior and posterior cerebral cortices, communication in the posterior portion of the brain was preserved. Moreover, the older adults exhibited weakened resting-state functional connectivity between the supplementary motor area and left anterior insular cortex. These findings suggest that, the disrupted functional connectivity of the brain network for visuospatial attention that occurs during normal aging may underlie the decline in cognitive performance.

1. Introduction

Visuospatial attention is often studied within the context of the Posner paradigm [26]. In this paradigm, a spatially informative cue is presented to indicate the location of an upcoming peripheral target. Targets appearing in the predicted location (valid) are detected more rapidly and accurately than those that are not (invalid) [26]. Over the years, a considerable number of functional

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magnetic resonance imaging (fMRI) studies have revealed a frontoparietal network involved in controlling visuospatial attention using the Posner paradigm [4,9,14]. This network consists of the anterior insular cortex (AIC), supplementary motor area (SMA) and dorsolateral prefrontal cortex (DLPFC) as well as the intraparietal sulcus (IPS), frontal eye field (FEF) and middle temporal area (MT+) [4,9,14].

As a result of normal aging, a decline in various cognitive domains has been commonly observed. Using the Posner paradigm, previous studies have shown that elderly subjects responded to the target more slowly than young subjects [15,22,27]. One possible reason for this reduction in visuospatial attention is the dysfunction of specific gray matter areas. Electrophysiological studies have demonstrated that, aging has an impact on the neural activity in those attention-related brain regions [21]. In addition to changes in task-relevant regions, alterations in communication between the different nodes of brain networks have also been found to be correlated with normal aging [12,18,30]. For example, older adults' poorer performance on working memory tasks [18,30] and emotional memory tasks have been shown to be associated with increases and decreases in connectivity within and/or between task-related networks. Therefore, an investigation on the interactions between brain areas provides insight into the neural mechanisms underlying age-related changes.

Recently, resting-state fMRI (rs-fMRI) has become a powerful tool for understanding the functional organization of the human brain [2,11,32]. Based on the synchrony of spontaneous fluctuations in the blood oxygenation level dependent (BOLD) signal from functionally related brain regions, several large-scale coherent spatial patterns, namely resting-state networks (RSNs), have been identified [7]. An effect of aging on resting-state functional connectivity has been found within and/or between RSNs, such as the default mode network (DMN) and motor network [6,13,33]. In addition, age-related differences in functional connectivity have also been revealed between brain areas pertaining to the visuospatial attention-related network [1]. Specifically, the authors identified ROIs in the IPS, FEF and MT+, which comprised corresponding areas in both hemispheres, and observed age-related reductions in the resting-state functional connectivity between the IPS and MT+ [1]. Since the functional connectivity between the SMA and AIC play an important role in initiating and maintaining task-level control and in suppressing irrelevant distracting information [10], it has a great influence on behavioral performance during a visuospatial attention task. Therefore, including the SMA and AIC in a functional connectivity analysis is necessary to understand the effect of aging on the resting-state functional connectivity within the entire system that participates in visuospatial attention.

In the current study, we investigated age-related changes in resting-state functional connectivity between regions that are associated with visuospatial attention by combining task and rest fMRI. A modified version of Posner paradigm was used to determine visuospatial attention-evoked brain activation based on which eleven spherical ROIs (seeds) were defined. These ROIs were centered in the SMA, bilateral AIC, bilateral DLPFC, bilateral FEF, bilateral IPS and bilateral MT+. Then, for each subject, the mean time series within each ROI was extracted from the resting-state fMRI data, and Pearson correlation coefficients were calculated between every possible pair of ROIs. Finally, age-dependent differences in resting-state functional connectivity were examined using two-sample *t*-tests, corrected for multiple comparisons. The results showed a marked reduction in either the number of connections or the strength of interactions in older adults.

2. Methods

2.1. Subjects

Twenty-three healthy young volunteers (ages 21–32; mean 22.7; male/female 23/0) and 19 healthy older volunteers (ages 60–78; mean 66.5; male/female 16/3; MMSE score 29.5 ± 0.1) took part in the fMRI experiment. All subjects had normal or corrected-to-normal vision and reported that they were all right-handed. None of the subjects had a history of neurological or psychiatric dysfunction or a previous experience in a neuropsychological experiment. The study was approved by the ethics committee of Okayama University, and written informed consent was obtained before the study. Three young subjects with excessive head movements and one older subject for whom fMRI data acquisition failed were excluded. In addition, although we failed to record behavioral data for three other older subjects, their imaging data were available and analyzed in our study.

2.2. Experimental design

Resting-state fMRI data were first recorded with one scan when subjects were instructed to keep their eyes closed, not to fall asleep and not to think of anything in particular. This was followed by one scan during a simple visual spatial attention task consisting of 120 trials (Fig. 1A). Each trial began with the fixation display followed by an arrow appearing at the center of the visual field. This arrow was presented for 200 ms and served as a cue, instructing the subjects to pay attention to the left or right visual field. After an inter-stimulus interval (ISI) of 200, 400, or 800 ms, the target appeared for 100 ms on the side indicated by the arrow 90% of the time (valid trial) and on the opposite side 10% of the time (invalid trial). Subjects were instructed to indicate whether a target appeared in the left or right visual field by pressing the left or right key with the forefinger or middle finger of their right hand, respectively. The duration of each trial was 3000 ms, and there were equal numbers of left and right directional cues and targets on each side. Subjects were asked to hold their gaze on the central fixation cross throughout the trial and to press the key as quickly and accurately as possible. Stimuli were presented through a projector onto a paper screen located in front of the subjects' feet. Subjects viewed the screen via a 45° angled mirror attached to the head-coil of the MRI setup.

2.3. Data acquisition

All subjects were imaged using a 1.5 T Philips scanner vision whole-body MRI system (Okayama University Hospital, Okayama, Japan), which was equipped with a head coil. The imaging area consisted of 32 functional gradient-echo planar imaging (EPI) axial slices (TR = 3000 ms, TE = 50 ms, FA = 90°, acquisition matrix = 80×79, FOV = 240 mm^2, slice thickness = 4 mm, gap = 0.5 mm) that were used to obtain T2*-weighted fMRI images in the axial plane. We obtained 176 functional volumes for the resting-state session and 124 functional volumes for the task run. The first 4 images of each functional scan were discarded to allow for the equilibration of the magnetic field. After the EPI scans, a T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence was acquired (TR = 9.4 ms, TE = 4.6 ms, FA = 10°, acquisition matrix = 240×240, voxel size = $1 \times 1 \times 1$ mm^3, 200 contiguous axial slices).

2.4. fMRI data analysis

2.4.1. Preprocessing

The imaging data were analyzed using statistical parametric mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running

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