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Small-worldness and modularity of the resting-state functional brain network decrease with aging

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HIGHLIGHTS

- Graph theory can be used to estimate brain network efficiency.
- We investigated the effects of aging on small-worldness and modularity of the functional brain network.
- Small-worldness and modularity were negatively correlated with age.
- Node strengths for sensorimotor regions showed positive correlations with age.
- Efficiency of the human functional brain network gradually decreases with age.

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ABSTRACT

The human brain is a complex network that is known to be affected by normal aging. Graph-based analysis has been used to estimate functional brain network efficiency and effects of normal aging on small-worldness have been reported. This relationship is further investigated here along with network modularity, a statistic reflecting how well a network is organized into modules of densely interconnected nodes. Modularity has previously been observed to vary as a function of working memory capacity, therefore we hypothesized that both small-worldness and modularity would show age-related declines. We found that both small-worldness and modularity were negatively correlated with increasing age but that this decline was relatively slow.

1. Introduction

Human cognitive decline reflects various brain changes in a complex network [6]. Each brain region has its own function and different regions are continuously sharing information with each other. Functional connectivity is defined as a temporal dependency between spatially separate regions, and is calculated as the co-activation level of spontaneous BOLD time series recorded during rest. Functional connectivity changes as individuals age [4,12].

In graph theory, the functional brain network is defined as a graph with nodes and edges, reflecting brain regions and connections between the regions. Graph-based analyses of the functional brain network have shown that the brain forms an integrative complex network [7,13]. Functional segregation is the occurrence of specialized processing within densely interconnected groups of regions, and is quantified using a clustering coefficient or modularity value. Higher values for these indices are interpreted as the presence of clusters or modules within the functional brain network. Functional integration is the ability to rapidly combine specialized information from distributed brain regions and is quantified as characteristic path length or global efficiency. Shorter paths and higher global efficiency mean higher integration in the brain. The brain network simultaneously reconciles opposing demands of functional segregation and integration. A well-designed network could therefore combine functionally specialized modules with a robust number of intermodular connections. Such a network is called a small-world network, defined as a network that is more clustered than a random network yet has approximately the same characteristic path length as a random network.

Few studies have investigated potential changes in resting-state network properties with aging. Bullmore and his colleague examined the efficiency of functional networks in younger and older adults, and found that older adults show decreases in global and local efficiency [1]. This research team has also studied whether age affects functional network modularity [10], reporting that the modularity of the older brain network was not significantly different from that of the younger, implying that whole brain module

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organization is conserved over the adult age range. However, they also reported decreased intermodular connections to frontal modular regions. The absence of a significant aging effect on whole brain modularity might be due to the relatively small sample size ($n = 17$ for young and 13 for old) used in this study. In the present study we used a larger sample size to explore the effects of aging on the properties of the resting-state functional network. A recent study showed that resting-state network modularity is associated with working memory capacity [17]. We hypothesized that both small-worldness and functional network modularity would decrease with age, consistent with a general reduction in cognitive functioning typically observed in the elderly.

2. Materials and methods

Two hundred and eight adult and elderly individuals without a history of neurological or psychiatric disorders participated in the present study. We discarded from our analyses the participants whose images showed excessive head movement (over 2 mm or 2°) during acquisition. We also removed participants whose images indicated bran atrophy, silent bran infarction and/or pathological subcortical white matter lesions. After such removals our study included 193 participants (115 men, 78 women). The mean age was 60.1 ± 12.1 (sd) years old, and the age range was 34–87 years old. The Shimane University Medical Ethics Committee approved the study and all participants gave their written informed consent.

Imaging data were acquired using a Siemens AG 1.5 T scanner. Twenty axial slices parallel to the plane connecting the anterior and posterior commissures were measured using a T2*-weighted gradient-echo spiral pulse sequence (TR = 2000 ms, TE = 46 ms, flip angle = 90°, scan order = interleave, matrix size = 64 × 64, FOV = 256 mm × 256 mm, slice thickness = 5 mm, gap = 1 mm). All participants underwent this five-minute rs-fMRI scan only after being instructed to remain awake with their eyes closed. After the functional scan, T1-weighted images (MPRAGE) of the entire brain were measured (192 sagittal slices, TR = 2170 ms, TE = 3.93 ms, inversion time = 1100 ms, flip angle = 15°, matrix size = 256 × 256, FOV = 256 mm × 256 mm, slice thickness = 1 mm).

We used Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/) for spatial preprocessing. The first 10 functional images for each participant were discarded for magnetic field stabilization. The remaining 140 functional images were realigned to remove any artifacts from head movement and to correct for differences in image acquisition time between slices. Next, the functional images were normalized to the standard space defined by a template T1-weighted image (MNI) and then resliced with a voxel size of 3 mm × 3 mm × 3 mm to agree with the gray matter probability maps. Spatial smoothing was applied with the FWHM equal to 8 mm. After the spatial preprocessing, we did temporal preprocessing using the functional connectivity toolbox (conn, http://www.alfnie.com/software). Temporal smoothing was performed using a band-pass filter (0.01–0.08 Hz). Head movement time series, white matter signal, and cerebral spinal fluid signal were regressed out from each voxel, based on CompCor Strategy [2]. To define brain nodes, an automated anatomical labeling atlas (AAL) was employed to divide the whole brain into 90 volumes of interest. The mean time course of the voxels within each atlas region was extracted for network construction. A Pearson correlation coefficient matrix was calculated for all time course pairs. We then applied a power adjacency function called 'soft thresholding':

$$w_{ij} = \left(\frac{r_{ij}+1}{2}\right)^{\beta}$$

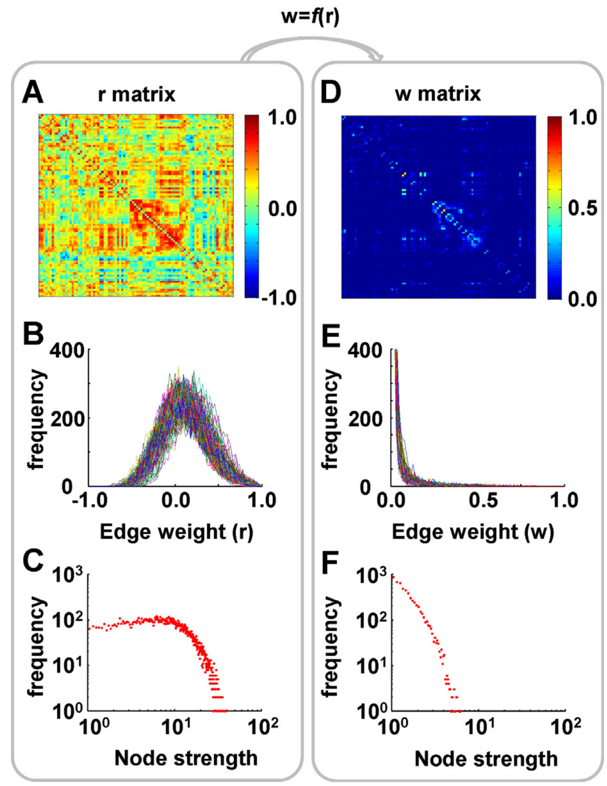

Fig. 1. The soft thresholding approach aims to retain all edges, replacing the thresholding operation with a continuous mapping of correlation (r) into edge weights (w) using the power adjacency function. Top: matrixes of correlation r [−1 1] and edge weight w [0 1] for a sample participant (A and D). Middle: edge r/w distributions of the original and soft-thresholded networks (B and E). Different colored lines indicate different participants. Bottom: distributions of node strength in the original (r) and soft-thresholded (w) networks (C and F).

where $w_{ij} = f(r_{ij})$ describes a continuous, non-linear mapping of correlation coefficients. Correlation coefficients in the range [−1 1] were translated to edge weights [0 1] with a power law [14]. Based on evidence provided by Schwarz and McGonigle [14], we set 12 as β because small-worldness of soft-thresholded networks is demonstrated at parameter values of $\beta \geq 12$. Edge histograms (r_{ij}/w_{ij}) before and after soft-thresholding transformations are illustrated in Fig. 1B and E. In the soft-thresholded networks, the edge weight distributions became skewed toward lower values of w_{ij}. The resulting histograms of node strength distribution are shown in Fig. 1C and F. The soft-thresholded distribution approached a profile similar to the power law observed with binary networks.

We estimated small-worldness and modular organization using the brain connectivity toolbox (BCT, https://sites.google.com/site/bctnet/). Small-worldness was quantified using characteristic path length and the clustering coefficient [20]. Characteristic path length is defined as the average of the shortest path length between all pairs of nodes, and the path length represents the number of steps along the route between the pairs. A shorter characteristic path length indicates a higher level of communication efficiency between global brain regions. The clustering coefficient is defined as the fraction of the node's neighbors that are also neighbors of each other, and reflects the prevalence of clustered connectivity around individual nodes. We normalized the characteristic path length and the clustering coefficient by dividing by the value for the same variable calculated for a randomly rewired null model. The characteristic path length and the clustering coefficient of the random network were the average of the values calculated from 100 randomly rewired null models. Small-worldness "sigma" was computed as the ratio of