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Dynamic brain network evolution in normal aging based on computational experiments

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ABSTRACT

The mechanisms of normal aging of the human brain are insufficiently understood at present. This lack of systematic understanding impedes the exploration of new treatments for age-related diseases and approaches to extend our lifespan. The objective of this study was to develop a novel evolution model to simulate the dynamic alteration processes in functional brain networks that occur during normal aging, using computational experiments. Six global topological properties and a nodal metric were applied to characterize functional magnetic resonance imaging data on the brain networks of individuals from three different age groups. Comparing these real-world results to our simulation results showed that our evolution model captures well the dynamic processes of normal aging in functional brain networks. Our research shows that a tradeoff exists between the constraints on the degree distribution and the tendency toward clustered connections of functional brain networks during normal aging. These computational experiments provide a more comprehensive perspective that addresses dynamic alterations across a large time scale, which traditional research techniques cannot achieve. Our model is therefore of profound significance for exploring the mechanisms of normal aging.

1. Introduction

The human brain is known as one of the most complex systems, consisting of billions of neurons that form a hierarchical and highly self-adapting organizational structure [1]. The brain, as a plastic system, generally shows changes in morphology that are associated with a decline in cognitive function during normal aging, such as the loss of gray matter and thinning of the cerebral cortex on a macro scale [2,3]. The clinical manifestations of dementia and other age-related neurodegenerative diseases may be an amplification of this age-related neural dysfunction [4]. However, the dynamic processes and mechanisms of normal aging in the brain remain unclear. Addressing this issue is of profound significance not only for a better understanding of normal cognitive aging but also for the early diagnosis and treatment of age-related diseases.

Neuroimaging technology has been widely used to investigate the neural basis of age-related cognitive alterations in vivo [5]. Resting-state functional magnetic resonance imaging (fMRI) has been an important approach in the exploration of functional brain changes since 1995 because of its non-invasive nature and advanced methods of data acquisition. Numerous studies have assessed the abnormality of functional brain fluctuations during normal aging [6], and several brain regions with dysfunctional activity have also been reported [7].

Graph theoretic analysis provides a new perspective to characterize complex network properties. It has been recently widely applied to the study of the functional integration and segregation of the human brain. This analysis describes the brain as a graph consisting of numerous nodes and connections, which represent brain regions and functional inter-regional connectivity, respectively [8]. He et al. found that nodal degree is subject to an exponentially truncated power law in anatomical brain networks [9]. In a further study by Hayasaka and Paul, the same conclusion was drawn in macroscopic functional brain networks [10]. This conclusion is interpreted as beneficial resistance against massive epidemics in the human brain.

The graph theoretic method has also been used specifically in the study of alterations in functional brain networks during normal aging [11,12] and in age-related diseases, such as Alzheimer's [13] and Parkinson's [14]. Through graph theory, previous studies have demonstrated that the functional brain network exhibits a small-world architecture [11,15,16], which means that the functional brain network achieves a balance between functional segregation and integration. However, this organization becomes a segregated system during aging

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[15,17,18], i.e., information processing in the human brain becomes more localized among the old.

The clustering coefficient is a basic metric of network, which is considered an index of functional segregation [19]. Sala-Llonch et al. further indicated that the higher clustering coefficients of some brain regions are related to poorer performance in verbal and visual memory [15]. These researchers also attributed the increasing small worldness to the higher global clustering coefficient among older adults. The localized brain system may therefore result in age-associated dysfunction [15]. As a result, it can be inferred that the clustering coefficient would increase during normal aging.

Global efficiency and number of long edges in a functional brain network measure the parallel information transfer in the network [9,20], and they are the metrics of functional integration. Recent studies systematically investigated alterations in the topological organization of functional brain networks and suggested that global efficiency and long edges alter across the whole lifespan [21,22]. These changes may potentially underlie the degradation of functional brain network in normal aging.

On the other hand, the existence of a compensatory mechanism for the observed functional deficits has been demonstrated: the recruitment of more brain regions [23]. Gutchess et al. concluded that prefrontal regions serve a compensatory role for the age-related decline in medial temporal activation during scene encoding [24]. A more recent study by Cao et al. also indicated that the more proximal regions of the dorsal anterior cingulate cortex, which are connected with the insula, are recruited in older adults to maintain their capacity to respond to salient information [25]. This was suggested to be part of the reason why the old tend to show decreased cognitive performance but well-maintained emotional well-being [25]. These results indicate the potential for a general capacity for adaptation to the functional deficits that occur during normal aging [26], which reflects that increasing additional connections are established among newly recruited regions.

Most real networks, such as the internet, social networks, and power networks, generally change and develop at every moment, exhibiting dynamic behaviors and plastic structure rather than a static state [27]. Network evolution, as a simulation approach based on computational experiments, has been effectively applied by previous studies in exploring the dynamic characteristics of networks of real systems [28,29]. Vertes et al. established a hemisphere-brain network using several generative models to simulate the formation mechanism of the human brain [30]. They concluded that a preferential model accorded by clustering could better capture real brain networks. However, this is a generative model. It starts from an isolated node and continues adding nodes and edges in the network to ‘generate’ a final network, which is not an evolution process that changes from one existing state to another. A currently much-researched topic of dynamic brain connectivity in fMRI, which focuses on the alterations in functional connectivity during a whole fMRI scan, is evolution research on the time scale of minutes [31–33]. However, few studies have explored the evolution mechanism of either functional or anatomical brain networks during normal aging on a large time scale.

In the present study, we systematically investigated the topological properties of the functional brain networks of young and old adults. Our results suggested that the nodal degree of the networks of both groups exhibit an exponentially truncated power law. In addition, the old group had significantly more connections and higher clustering coefficients. In respect to these results, of particular interest to us was how the arrangement of connections in functional brain networks altered during normal aging to lead to such changes. More specifically, we tested the hypothesis that old adults recruit additional connections to generate a more segregated brain network and maintain nodal degree distribution simultaneously. To investigate this, a data-driven model was then proposed to simulate the continuous evolution process of functional brain networks from the young to the middle-aged to the old networks. Finally, we tested the model's capacity to emulate the alterations of topological properties observed in real data. This comparison demonstrates that our model captures the dynamic topological alterations of functional brain networks during normal aging. As far as we know, this is the first study to investigate the alterations of topological organization of functional brain network on a large time scale.

2. Materials and methods

2.1. Participants

A primary cohort and an independent cohort were included in our study. The raw scans of both cohorts were obtained from the International Consortium for Brain Mapping (ICBM) dataset, which is the largest sub-dataset of subjects of all age stages in the 1000 Functional Connectomes Project. To avoid the complications of different scan parameters, the raw scans from other sub-datasets in the 1000 Functional Connectomes Project were excluded in our study. We divided the participants in the ICBM dataset into three age groups and guaranteed a comparable number of participants in each group. Thus, those who were under 30, between 30 and 55, and beyond 55 years of age comprised the young, middle-aged, and old groups, respectively. The actual age distributions for both the primary and independent cohorts are included as Supplementary materials (Fig. S1).

According to the above criteria, the primary cohort consisted of 12 young adults (young group, 7 males, mean age: 22.8 years, range: 19–30 years), 12 middle-aged adults (middle-aged group, 7 males, mean age: 43.7 years, range: 32–51 years), and 12 old adults (old group, 6 males, mean age: 63.3 years, range: 56–79). The independent cohort consisted of 9 young adults (young group, 2 males, mean age: 22.6 years, range: 19–27), 9 middle-aged adults (middle-aged group, 7 males, mean age: 44.9 years, range: 35–54), and 9 old adults (old group, 4 males, mean age: 64.4 years, range: 56–73), which was applied to validate the involvement model. In each cohort, a significant difference in age was found among the different groups. No differences in age were found between corresponding age groups in the two cohorts. The demographic data are shown in Table 1.

2.2. Preprocessing

Functional MRI images were obtained on a 3T scanner. A total of 133 images were acquired for each subject using the following parameters: TR=2 s, image matrix 64*64*23. The first five images of each subject were discarded by ICBM to ensure magnetization equilibrium.

The raw scans were preprocessed with SPM8 [34]. First, slice timing was performed to correct all the datasets in the time domain. Second, realignment was applied to remove the movement artifact in the BOLD time courses. Subjects whose head translation was more than 2 mm or whose head rotation exceeded 2° were excluded

Table 1
Demographics of the two cohorts.

Cohort	Age phase	Sex	Mean age (years)	Range (years)	P
Primary	Young	7m/5f	22.8	19–30	
	Middle-aged	7m/5f	43.7	32–51	$< 10^{-13}$
	Old	6m/6f	63.3	56–79	
Independent	Young	2m/7f	22.6	19–27	
	Middle-aged	7m/2f	44.9	35–54	$< 10^{-9}$
	Old	4m/5f	64.4	56–73	

In each cohort, a significant difference in age was found between each of the two groups via *t*-tests (primary cohort with $P < 10^{-13}$; independent cohort with $P < 10^{-9}$).