How Does Aging Affect Whole-brain Functional Network Connectivity? Evidence from An ICA Method

Yuhui Du*, Yating Guo, Vince D Calhoun

***Abstract*—Many studies have shown that changes in the functional connectivity are diverse along with aging. However, few studies have addressed how aging affects connectivity among large-scale brain networks, and it is challenging to examine gradual aging trajectories from middle adulthood to old age. In this work, based on large-sample fMRI data from 6300 subjects aged between 49 to 73 years, we apply an independent component analysis-based method called NeuroMark to extract brain functional networks and their connectivity (i.e., functional network connectivity (FNC)), and then propose a two-level statistical analysis method to explore robust aging-related changes in functional network connectivity. We found that the enhanced FNCs mainly occur between different functional domains, involving the default mode and cognitive control networks, while the reduced FNCs come from not only between different domains but also within the same domain, primarily relating to the visual network, cognitive control network and cerebellum. Our results emphasize the diversity of brain aging and provide new evidence for non-pathological aging of the whole brain.**

***Clinical Relevance*—This provides new evidence for non-pathological aging of functional network connectivity in the whole brain.**

I. Introduction

The problem of population aging is becoming increasingly serious. As people age, the brain naturally changes, affecting memory, learning, and other cognitive functions. It is urgently expected to disclose the mechanism of brain aging so as to help mitigate the progression. In fact, neuroimaging-based studies using functional magnetic resonance imaging (fMRI) data can provide objective measures of how the brain function changes in the aging process [1].

Generally, the functional connectivity between networks tends to be enhanced while that within networks is weakened along with aging [2]. Many studies explore specific brain functional networks by selecting networks relating to cognitive functions [3]. For example, regarding the default mode network, the enhancement of connectivity between networks is found. Also, as the brain ages, the communication between the default mode network and other networks is enhanced [4]. In fact, the aging effect on the brain is also associated with other brain function involving such as somatosensory, motor, and subcortical networks with more complex variations. A previous review summaries that different networks show diverse changes during aging in different studies, such as enhanced functional connectivity, no change, and nonlinear changes [2]. Those studies are often aimed at specific brain functional networks to explore aging, ignoring the overall changes in FNC among whole-brain functional networks. They also do not separate the positive and negative connectivity in the analysis methods, thus missing more detailed changes of FNC. In addition, the analysis method and sample size affect the effectiveness of brain aging exploration. Many studies only used the young and elder two-group populations to detect their differences in the brain, which hinders revealing progressive brain change [5]. Some studies worked on a relatively small size of data [6] or unbalanced male and female samples [7], consequently, their findings probably are not convincing to some extent. Therefore, a comprehensive study at the whole-brain level using a large-data sample would provide new insights into aging.

Based on the data from the UK Biobank project [8], in this paper, we analyze a large sample size of fMRI data including 6300 healthy subjects aged between 49 to 73 years to investigate the robust and progressive aging effect on brain function. Importantly, we strictly control the data quality to make the subjects balanced between the genders (3150 females) as well as among different age groups (126 females for each age group), with an expectation to disclose the progressive brain change for both females and males. After employing our previously proposed independent component analysis (ICA) method called NeuroMark [9] to obtain whole-brain functional networks and their connectivity, we propose a two-level statistical analysis method to detect how aging progressively affects the brain function, and identify the most robust aging-related brain alterations. In our work, we carefully design the changing patterns for the positive and negative connectivity separately to detect the complex aging paths.

II. Materials and Methods

A. Data acquisition and preprocessing

The used fMRI data were from the UK Biobank project. FMRI data of all healthy subjects were preprocessed using RESTplus [10]. For the fMRI data of each subject, we discarded the first ten image volumes, and then performed slice-time correction, motion correction, spatial normalization by the echo-planar imaging (EPI) template, and spatial

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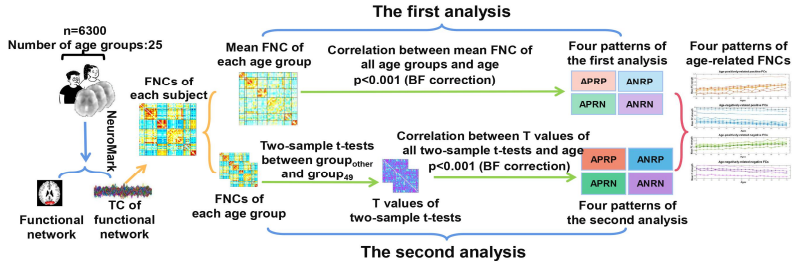

Figure 1. A framework of our study.

smoothing using a Gaussian function with FWHM = 6mm. Next, we carried out the quality controls on the preprocessed fMRI data to only select the subjects' data with slight head motions. After that, we maintained 6300 healthy subjects (mean age: 61 years, the number of females: 3150) that cover most healthy subjects with fMRI data aged from 49 to 73 years in the UK Biobank project. It is known that the age range is an important aging period including the main middle adulthood and old age. Particularly, the sample number was identical for each age group (i.e., the group of subjects at 49 years) in order to explore the progressive aging path. In our study, all 6300 subjects were grouped by age to 25 groups, with each age group consisting of 252 subjects (126 females). Specifically, we strictly balanced the proportion of males and females and women in each age group to avoid a bias of finding due to the gender effect.

B. Computation of Brain Functional Networks and Connectivity Via a NeuroMark

To extract accurate whole-brain functional connectivity, we applied our previously proposed ICA-based NeuroMark method [9] to obtain brain functional networks (FNs) and their time courses (TCs) that were then used to calculate the whole-brain functional network connectivity (FNC). NeuroMark is superior to region-of-interest methods since it automatically extracts large-scale brain functional networks based on reliable functional network templates in a data driven manner. Due to that the 53 network templates were arranged into seven functional domains according to their functional and anatomical roles, including the subcortical (SC: 5 FNs), auditory (AU: 2 FNs), sensorimotor (SM: 9 FNs), visual (VI: 9 FNs), cognitive control (CC: 17 FNs), default mode (DM: 7 FNs) and cerebellar (CB: 4 FNs) domains, the obtained individual-level networks also belonged to these domains.

In order to compute FNC, we performed the following process on each TC in advance: 1) transforming TC to Fisher's Z-score; 2) using the head motion parameters to regress TC; 3) removing linear trends and spikes; 4) filtering via a band-pass filter with [0.01–0.15] Hz. Next, an FNC matrix was obtained for each subject via computing Pearson correlation between all pairs of the 53 TCs. To further remove the effect of head motion, we also regressed motion parameters from each FNC. Thus, for each subject, we obtained an FNC matrix consisting of 1378 FNCs for the following analyses.

C. Functional network connectivity analyses

As shown in Fig. 1, in this paper we propose a two-level statistical analysis framework to maximize the reliability in identifying the aging-related FNCs. Basically, we performed two types of statistical analysis for each FNC, and then identified the FNCs that are significantly associated with aging in both analyses as the robust aging-related FNCs. More importantly, we carefully designed multiple changing patterns to detect the various brain aging paths.

In the first analysis, for each FNC, we first calculated its mean strength in each age group (e.g., the group of age 70: group$_{70}$), and then computed Pearson correlation between the mean strength at different age groups and the age to evaluate if it is significantly associated with aging ($p<0.001$, Bonferroni (BF) correction). Each significant age-related FNC was then assessed by evaluating four patterns defined according to the mean strength of FNC of group$_{49}$ and FNC-age correlation: 1) the age-positively-related positive FNC (APRP); 2) the age-negatively-related positive FNC (ANRP); 3) the age-positively-related negative FNC (APRN); 4) the age-negatively-related negative FNC (ANRN). Taking the APRP pattern of FNC as an example for explanation, the mean FNC strength of group$_{49}$ was positive, at the same time the mean FNC strength across different ages had a positivity correlation with the age.

In the second analysis, for each FNC, we first performed a two-tailed two-sample t-test between group$_{other\text{-}age}$ (e.g., group$_{50}$) and group$_{49}$, and then utilized 24 T values of all two-sample t-tests to calculate Pearson correlation with age (from 50 to 73) to assess if it is significantly associated with aging ($p<0.001$, BF correction). Each significant age-related FNC was then assessed by evaluating four patterns defined according to the mean FNC strength at group$_{49}$, T value, and correlation between T values and ages. For example, we regarded an FNC to belong to the APRP pattern if the mean FNC strength of group$_{49}$ was positive, more than 80% T values were positive, and T values had a positivity correlation with ages. In addition, we calculated the number of FNCs with statistical significance ($p<0.01$) in each comparison between group$_{other\text{-}age}$ and group$_{49}$ to investigate whether FNCs gradually change along with the aging.

In order to obtain reliable age-related FNCs, we determined each FNC's pattern only if it simultaneously conforms to the same pattern in both analyses, and averaged the correlations in two analyses to reflect its relation with age. Furthermore, since each FNC links two FNs, we assessed their domains to explore the within-domain and between-domain connectivity property for each pattern. Also, we selected significantly age-related FNCs with mean correlation absolute values greater than 0.93 in both analyses to demonstrate their properties.

III. Result

Fig. 2(A) shows that the number of statistically significant FNCs that were obtained from comparing $group_{other\text{-}age}$ and $group_{49}$ increases greatly with age. Since our two-level statistical analysis resulted in four patterns of FNCs that correlated with age, we summarized the FNCs of each pattern in Fig. 2(B). Regarding the APRP FNCs, they were distributed in different brain networks, and included 48 FNCs accounting for 3.96% of all positive FNCs, with a mean correlation as 0.89. Regarding the ANRP FNC, they included 48 FNCs accounting for 3.96% of all positive FNCs, with a mean correlation as -0.89. Regarding the APRN FNC, they included 49 FNCs accounting for 3.07% of all negative FNCs, with a mean correlation as 0.88. Regarding the ANRN FNC, they included 51 FNCs accounting for 3.20% of all negative FNCs, with a mean correlation as -0.89.

For each pattern, we summarized age-related FNCs each of which linked different brain domains in Fig. 3(A) and age-related FNCs each of which linked the same brain domain in Fig. 3(B), respectively. For the APRP FNCs, there were 43 FNCs linking different domains, wherein 29 FNCs of them linked with the DM, and 21 FNCs linked with the CC, and each of the rest of 5 FNCs linked the same domain, wherein 3 FNCs of them linked within the DM. For the ANRP FNCs, there were 26 FNCs linking different domains, wherein 19 FNCs of them linked with CB, while other 22 FNCs linked within-domains, wherein 8 FNCs of them linked within CC, and 6 FNCs linked within VI. For the APRN FNCs, there were 48 FNCs linking different domains, wherein 31 FNCs of them linked with VI, and 27 FNCs linked with the CC, and only one FNC linked within the CC domain. For the ANRN FNCs, there were 45 FNCs linking different domains, wherein 23 FNCs of them linked with SC, 23 FNCs of them linked with CC, and 23 FNCs of them linked with DM, while other 6 FNCs linked within-domains, wherein 4 FNCs of them linked within CC, and 2 FNCs linked within DM. Overall, there were far more aging related FNCs that occurred in different domains than in the same domain.

From those significantly age-related FNCs, we selected the most important FNCs with absolute mean correlation > 0.93 to display the mean strength at $group_{49}$ and the changing trend of mean strength across different ages for each FNC in each pattern (Fig.4). In summary, APRP pattern comprised 8 FNCs, six of which linked between the DM and the other domain (CC, VI, or SC); ANRP pattern comprised 9 FNCs, four of which were related to the CB; APRN pattern comprised 7 FNCs, four of which linked the VI and the other domain (CC, DM, or CB); ANRN pattern comprised 5 FNCs, four of which linked the DM and the other domain (CC, SM, or SC).

IV. Discussion and Conclusion

In the work, we took advantage of the large number of fMRI data combined with an advanced ICA to explore significant aging-related changes in FNC on a whole-brain scale. We proposed a two-level statistical analysis method and carefully defined four patterns for a comprehensive

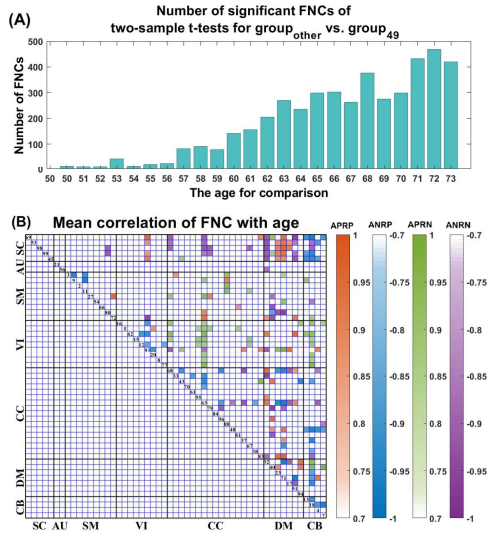

Figure 2. (A) Number of significant FNCs of each comparison for $group_{other\text{-}age}$ vs $group_{49}$; (B) Mean correlation of age-related FNCs for two analyses; orange, blue, green, and purple represent patterns of APRP FNC, ANRP FNC, APRN FNC, ANRN FNC, respectively.

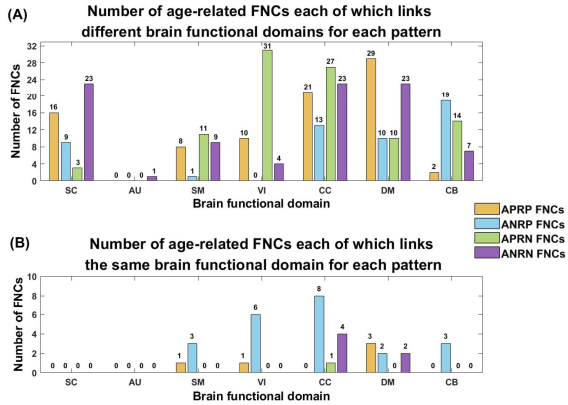

Figure 3. Number of age-related FNCs corresponding within and among different brain functional domains for four patterns. Orange, blue, green, and purple represent patterns of APRP FNC, ANRP FNC, APRN FNC, ANRN FNC, respectively.

investigation, consequently revealing robust aging effect on brain function

Our study shows a progressive change in brain aging. By distinguishing the positive and negative connectivity, we found that different FNCs show different changing patterns along with the aging. Specifically, our study suggests that the enhanced positive FNCs were diverse but mainly affected the between-domain FNCs involving the DM and CC. Regarding the enhancement of negative FNCs, our study suggests that most of them linked different domains relating to the CC, DM, and SC. Combining the two patterns, our results supported that the enhanced positive and negative strengths mainly involved the DM and CC domains. Many previous studies have shown enhanced connectivity between DM and other domains as well as CC and other domains, which is consistent with our findings [5, 11]. There have been studies suggesting a generally compensatory effect when connectivity appears enhanced in older adults [12].

Our study suggested that the diminished connectivity

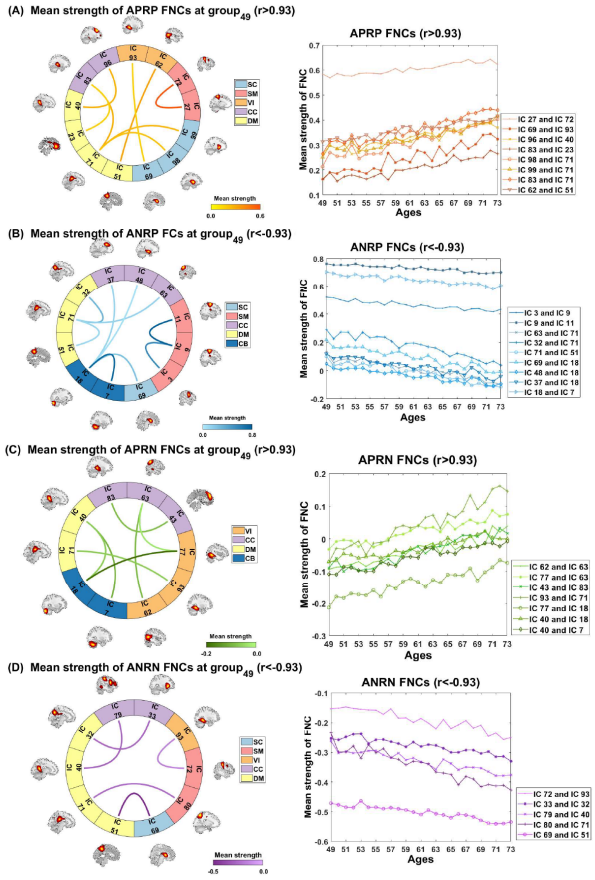

Figure 4. Significantly aging-related FNCs with the mean correlation (r) absolute values greater than 0.93 of both analyses for each of the four patterns ((A), (B), (C) and (D)). In each subfigure, the left shows the mean strength of each FNC at group$_{49}$, and the right shows the changing trend of mean strength along with the increasing age. Each independent component (IC) corresponds to one functional network, and r is the FNC-age mean correlation.

strengths were mostly related to CC and VI. Specifically, we found that the weakened positive FNCs not only involved between-domain, but also came from within-domain. Specifically, between-domain connectivity mainly linked the CB and other domains, and within-domain connectivity mainly occurred interior of the CC and VI. Regarding the weakened negative connectivity, we found that most of them linked CC and other domains as well as VI and other domains. Some previous studies have reported weakening FNCs between CB and other domains [13, 14], which can provide supports for our work. In addition, some previous studies have also reported decreased within-network connectivity in the dorsal attention network and VI [14, 15], which can support our findings, but our work suggests the above changes only occur in attenuated strength of positive connectivity. And previous studies found the connections between the VI and SM, CC and other domains are negatively correlated with age [15, 16], which is consistent with our work. Combining the two patterns, a more interesting thing is that the negative connectivity linked CC and others (i.e., SM), VI and others (i.e., CB and DM), as well as CC and VI, while the positive connectivity within CC and VI were evident.

Our study discloses that healthy aging is associated with whole-brain functional network connectivity changes even in the absence of neurodegenerative diseases, especially involving important brain functions in terms of DM, CC, VI and CB. These findings provide comprehensive evidence for age-related changes in whole-brain functional network connectivity.

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ETHICS STATEMENT

We used data from the UK Biobank datasets with the agreement of project 34175. The studies involving human participants were reviewed and approved by Research Tissue Bank (RTB) approval.

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