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Changes in dynamic functional connections with aging

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ABSTRACT

Despite numerous studies on age-related changes in static functional connections (FCs), the available literature on the changes in dynamic FCs with aging is lacking. This study investigated the changes in dynamic FCs with aging based on resting state fMRI data of 61 healthy adults aged 30–85 years. The time-resolved FCs among 160 pre-defined regions of interest (ROIs) were first estimated using sliding-window correlation. Based on the dynamic FC matrices, we then analyzed the dynamic switches between different FC states using k-means clustering, and correlated age with the dwell time of each FC state across subjects. The elderly were observed to spend more time in an FC state characterized by weak interactions throughout the brain and less time in an FC state characterized by strong interactions within the sensory-motor network and the cognitive control network. These results may reflect an overall weakening of connections in the elderly, which support less efficient information transfer in them. Based on the dynamic FC matrices, we also evaluated the variability and amplitude of FC time-series, which measure the relative (to mean) and absolute strength of FC fluctuations, respectively, and correlated age with the two measures across subjects. Relatively weak age-vs-variability correlations were observed, but we did observe significant negative age-vs-amplitude correlations at both the global and regional level. These results indicate that amplitude may be another effective metric for assessing FC fluctuations, in addition to the widely-used variability metric. Moreover, the observed declines in the amplitude of FC fluctuations in the elderly may support the assumption that it should be the weakening of absolute interactions between brain regions, rather than toggling between positive and negative correlations, that causes the repeatedly reported widespread (static) FC decreases with aging. Overall, the present results not only reflect an overall weakening of connections in the elderly, but indicate the potential of dynamic FC analyses in studies of age-related psychiatric and neurological disorders.

Introduction

Numerous resting state fMRI (RS-fMRI) studies have been performed on aging of the human brain (Ferreira and Busatto, 2013; Sala-Llonch et al., 2015). The majority of these studies analyzed age-related changes in functional connections (FCs), which are expected to reflect functional interactions between brain regions. According to these studies, the networks associated with primary functions (e.g., the somatosensory network and the motor network) are largely intact, while higher-level processing networks (e.g., the default mode network [DMN] and the fronto-parietal network [FPN]) often degenerate in the elderly (Naik et al., 2017). In these studies, FCs were evaluated in a time-averaged sense, based on the assumption that FCs are temporally stationary in the resting brain. The assumption of temporal stationarity provided a convenient framework with which to examine the average interactions among brain regions.

Recent investigations provided compelling evidence challenging the "stationary" assumption of resting state FCs (Deco et al., 2015; Ekman et al., 2012; Vanrullen et al., 2011). In light of this, an increasing number of recent studies analyzed the complex dynamic characteristics of FCs, rather than static FCs, based on resting state fMRI (Allen et al., 2014; Chang and Glover, 2010; Gonzalez-Castillo et al., 2015; Hutchison and Morton, 2015; Hutchison et al., 2013; Ma et al., 2014; Marusak et al., 2017; Shen et al., 2016; Shine et al., 2016; Suk et al., 2016; Yu et al., 2015; Zalesky and Breakspear, 2015; Zalesky et al., 2014). According to these studies, dynamic FCs are reproducible across time and subjects (Allen et al., 2014; Gonzalez-Castillo et al., 2015), and alter with maturation (Hutchison and Morton, 2015; Marusak et al., 2017), long-term training (Shen et al., 2016) and disease (Ma et al., 2014; Suk et al., 2016; Yu et al., 2015). In a recent review by Naik et al. (2017), it was pointed out that "the dynamic nature of FC is often not acknowledged by the current theories of aging." Naik et al. suggest that "age-related

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dynamic changes need to be quantified in terms of FC dynamics … to understand the dynamics of the aging brain better". Consistent with this suggestion, the purpose of this study was to investigate the changes in dynamic FCs with aging.

Dynamic FCs have traditionally been analyzed from two perspectives, namely, dynamic switches between FC states, and temporal fluctuations in FC time-series. Specifically, once the time-resolved FCs were mapped based on resting state fMRI (e.g., using a sliding-window approach), a time-series of FC matrices (time × regions × regions) could be obtained. FC states could then be obtained by clustering the FC matrices (regions × regions) into several network patterns that repeatedly occur across time and subjects. Considering the close link to EEG microstates, FC states have been suggested to reflect the coordination of large-scale neural assemblies supporting various cognitive processes (Allen et al., 2014). Individuals' dwell time in FC states has been reported to vary with maturation (Hutchison and Morton, 2015; Marusak et al., 2017), long-term training (Shen et al., 2016) and disease (Ma et al., 2014; Suk et al., 2016; Yu et al., 2015). Based on their "metastability" hypothesis, Naik et al. (2017) expected "slow switching between network states" and/or "higher dwell-time in a particular network state" in the elderly, while "the literature on aging lacks characterization of such 'switching dynamics'". To enrich our knowledge regarding changes in dynamic switches between FC states with healthy aging, we associated age with the dwell time of FC states in this study.

Despite the heavy dependence on factors such as size of window and extent of overlap (Betzel et al., 2016; Thompson and Fransson, 2015), there has been a surge of interest in analyzing the temporal fluctuations in FC time-series in recent years. Many studies have analyzed the *variability* of temporal fluctuations in FC time-series (Kucyi et al., 2013; Kucyi and Davis, 2014; Laufs et al., 2014), and the measure was reported to be sensitive to maturation (Hutchison and Morton, 2015; Marusak et al., 2017) and disease (Ma et al., 2014; Suk et al., 2016; Yu et al., 2015). The measure "variability" in these studies was used to evaluate the relative strength (relative to the mean) of FC fluctuations. Shen et al. (2016) recently introduced a measure named "amplitude of the low-frequency fluctuation of FC (ALFF-FC)" to assess the absolute strength (relative to zeros) of FC fluctuations. According to Shen et al. (2016), ALFF-FC was not only sensitive to long-term training, but also specific enough to decode individuals' experience in long-term training. We expect that "amplitude" may be an effective measure for connections that toggle between positive and negative correlations, which would reduce to zero in static FC analyses (Zalesky et al., 2014). To deepen our understanding of the changes in brain function with aging, age was also associated with the variability and amplitude of FC fluctuations in this study.

This study was performed on the RS-fMRI data of 61 healthy adults aged 30–85 years extracted from a publicly released dataset. The study was carried out by first evaluating the time-resolved FCs between each pair of 160 regions of interest (ROIs) for each subject using sliding-window correlation. To investigate the changes in dynamic switches between FC states with healthy aging, k-means clustering was then used to capture the FC states, and age was finally correlated with the dwell time of each FC state across subjects. To investigate the changes in temporal fluctuations in FC time-series with aging, age was also correlated with the variability and amplitude of FC fluctuations.

Materials and methods

Dataset

The data used in this study were selected from the publicly released dataset "the Nathan Kline Institute/Rockland Sample (NKI–RS)" (http://fcon_1000.projects.nitrc.org/indi/pro/nki.html) (Nooner et al., 2012), which has been used in several recent studies on age-related changes in brain function (Betzel et al., 2014; Cao et al., 2014; Tian et al., 2016; Yang et al., 2014). The data acquisition was approved by the institutional review board of the Nathan Kline Institute. The initial release of the NKI-RS dataset included 207 participants, each of whom underwent multimodal brain scans and a battery of psychiatric assessments. Subjects that satisfied the following criteria were included in the present study: 1) RS-fMRI data were available; 2) ≥30 years old; 3) with no mental disorder; 4) with no excessive head motions. That is, head motions were ≤2.0 mm displacement in any of the x, y, or z directions and ≤2.0° of any angular motion throughout the scan, and time points with framewise displacement >0.5 mm were less than 20% (Shine et al., 2016). According to the criteria, 61 subjects were included in the study (34 males, aged 30–85 years [mean ± standard deviation = 50.10 ± 14.59]). The ID list of subjects included in this study can be found in Table S1, and a bar plot of the distribution of subjects' ages can be found in Fig. S1.

The MRI data were acquired on a 3.0 T SIEMENS Trio scanner. RS-fMRI images were collected axially using an echo-planar imaging sequence sensitive to blood oxygen level dependent (BOLD) contrast with the following parameters: TR/TE = 2500/30 ms, FA = 80°, FOV = 216 mm, matrix = 64 × 64, slices = 38, thickness = 3.0 mm, 260 volumes. A total of 260 vol of RS-fMRI images were obtained. High-resolution T1-weighted images were acquired using the magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR/TE = 2500/3.5 ms, FA = 8°, thickness = 1.0 mm, slices = 192, matrix = 256 × 256, FOV = 256 mm. Other images not used in the present study will not be described here.

Data preprocessing

RS-fMRI data preprocessing was performed by use of FSL (Jenkinson et al., 2012; Smith et al., 2004) (http://www.fmrib.ox.ac.uk/fsl). The following processing steps were applied to the RS-fMRI data of each subject: 1) removing the first 5 vol; 2) correcting for head motion with MCFLIRT; 3) removing the non-brain tissues with BET; 4) spatial smoothing using a Gaussian kernel of full width at half maximum 5 mm; 5) high-pass temporal filtering to remove slow drift (cut-off frequency = 0.01 Hz); 6) registering the subject's RS-fMRI data to his/her high-resolution structural image, then to Montreal Neurological Institute 152 standard space using FLIRT and FNIRT tools, and resampling the subject's registered RS-fMRI data to 2 × 2 × 2 mm resolution; 7) regressing out nuisance including white matter, cerebrospinal fluid, and global signals and their derivatives, in addition to 24 movement regressors derived by Volterra expansion (Power et al., 2014; Shine et al., 2016); 8) band-pass filtering (0.01 < f < 0.1 Hz) of the time-series of each voxel.

Analysis of dynamic FCs

We defined the 160 ROIs by setting ten-mm-diameter spheres centered at the meta-analysis-based activity peaks reported in the study by Dosenbach et al. (2010). The mean time-series of each ROI was obtained by averaging the signals of all voxels within the ROI. For display convenience, the ROIs were divided into four networks following the same strategy as that in the study by Dosenbach et al. (2010). The four networks are the cognitive control network (CCN), the DMN, the sensori-motor network (SMN) and the occipital-cerebellum network (OCN).

The time-resolved FCs were mapped based on the mean time-series of 160 ROIs using a sliding window approach. Specifically, we calculated the Pearson's correlation between each pair of ROI time-series using a sliding temporal window of 45 s (18-point Tukey window, with the ratio of the length of taper section to the total length of the window set to 0.5, slid in steps of 1 TR [2.5 s]) (Rashid et al., 2016). According to Zalesky and Breakspear (2015), this window length ensures the detection of non-stationary fluctuations in FC while controlling false positives. The correlation coefficients were finally transformed into z-scores using Fisher's r-to-z transformation to improve normality. These analyses produced a time-series of FC matrices (238 windows × 160 × 160) for each subject, and later analyses were based on these matrices.