Hidden state dynamics reveals metastability across the adult lifespan

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Abstract

Adult lifespan is accompanied by functional reorganization of brain networks, but the dynamic patterns behind this reorganization remain largely unclear. This study focuses on modelling the time-varying process of spontaneous activity of large-scale networks using hidden Markov model (HMM), and investigates how it changes with age. The HMM with 12 hidden states was applied to temporally concatenated resting state fMRI data of 422 subjects (aged 19-80 years), and each hidden state was characterized by distinct activation patterns of 17 brain networks. Results showed that (a) the elder were probable to spend more time on an 'inactive' state with only mean-level activation of all networks. (b) The elder tended to spend less time on states showing antagonistic activity between various pairs of networks including default mode network, control and salience/ventral attention networks. (c) The transition probabilities between certain pairs of states that default mode or control networks showed opposite activation level exhibited significant increases/decreases with age. (d) Lifespan trajectories of subjects' fractional occupancy and transition probability exhibited U-shaped or linear trends. These results demonstrated that the particular network state with lower transition probability and higher fractional occupancy in old cohort could be detected using HMM, and proved that HMM is a huge potential tool to reveal the metastability, the ability of the system to transition

between different cognitive states, across the adult lifespan.

Key words: Lifespan; Hidden Markov model; Resting state fMRI

1. Introduction

Accumulating evidence has demonstrated that human brain undergoes structural and functional changes across the whole lifespan (Grady et al., 2006; Riddle et al., 2010; Vannest et al., 2015; Kennedy et al., 2017; Narvacan et al., 2017). These functional changes between large-scale networks could be investigated using resting-state fMRI (rs-fMRI) (Biswal et al., 1995; Grecius et al., 2003; Fox and Raichle, 2007; Onoda et al., 2012; Ferreira and Busatto, 2013; Keller et al., 2015). Although a multitude of studies have unveiled the lifespan changes in functional networks (Chan et al., 2014; Betzel et al., 2014; Yang et al., 2014; Finotelli et al., 2018) via static functional connectivity, the underlying dynamic processes of the human brain across the adult lifespan are poorly understood. In recent years, dynamic functional connectivity (dFC) studies based on sliding window (SW) approach (Allen et al., 2014) and co-activation patterns (CAPs, Liu et al., 2013) suggested that the resting brain activity are highly dynamic and could be clustered into discrete and recurring 'states'. Statistics like dwell time (proportion of time spent visiting each state) and transition probability (the frequency of transition between a pair of states) were also introduced to measure specific network dynamics of some brain disorders like schizophrenia (Rashid et al., 2014; Damaraju et al., 2014; Rabany et al., 2019), Parkinson's (Kim et al., 2017; Zhuang et al., 2018; Diez-Cirarda et al., 2018) and Alzheimer's (De Vos et al., 2018; Fu et al., 2019; Schumacher et al., 2019).

Actually, Naik et al. (2017) suggested the complexity of brain dynamic processes in aging is better understood using the notion of metastability (the ability of the system to transit between different cognitive states) , which could be approximately measured using functional connectivity dynamics (FCD). And expected that lower transition probability and/or higher dwell time would be found in the old cohort. Although a few recent studies began to explore the relationship between dynamic states and age,. their findings did not fit very well with such prediction. For example, while it has been

discovered that the dwell time of some FC states with weak interactions (Tian et al., 2018) or negative connectivity (Xia et al., 2019) throughout the brain was correlated with age, they did not report the age related correlation on transition probability.(Tian et al., 2018) or found positive correlation between transition probability and age. Chen et al. (2018) only reported that the transition probabilities of specific FC states differed between different age groups, but did not find differences on dwell.time. One of the important reasons for the mismatch may be that the aforementioned dFC studies employed sliding window approaches which suffers from a number of severe limitations such as window length (Hindriks et al., 2016; Leonardi & Van De Ville, 2015) and extent of overlap (Betzel et al., 2016). Another reason is that methods like sliding window and CAPs are based on k-means clustering which needs the number of clusters to be predefined (Chen et al., 2017) and is unable to embed the the sequential transitions between brain states into the model (Chen et al., 2016). Judging from these concerns, the metastability underlying the adult lifespan may be captured by a more appropriate approach.

Hidden markov model (HMM) (Rabiner et al., 1989) is one of the promising techniques (Solo et al., 2018) to address such issues. HMM assumes that brain activity could be decomposed into a number of hidden states, which could be inferred from the observed data (i.e fMRI time-series). The transition probability between the hidden states and the fractional occupancy (FO, similar with the concept of dwell time, but is characterized in terms of probability) (Baker et al., 2014), are often used to quantify the temporal dynamics of the inferred hidden states. HMM has been applied to neuroimaging studies of multiple modalities such as EEG (Hunyadi et al., 2019; Stevner et al., 2019), MEG (Baker et al., 2014; Vidaurre et al., 2016; Quinn et al., 2018) and fMRI (Ryali et al., 2016; Vidaurre et al., 2017a; Vidaurre et al., 2017b; Taghia et al., 2018; Kottaram et al., 2019). HMM is the most effective when sample size is large due to the expanded feature space inherent in the probabilistic model (Chen et al., 2017), and is sufficient to capture quasi-stationary states of activity that are consistently recurring over a population (Baker et al., 2014). The capacity of HMM in discovering the switching dynamics in developmental maturation (Ryali et

al., 2016), schizophrenia (Kottaram et al., 2019), multiple sclerosis (Van Schependom et al., 2019) and non-REM sleep (Stevner et al., 2019) provethat HMM is sufficient for characterizing the dynamic pattern of spontaneous brain activity across the adult lifespan.

In this study, we utilized HMM to estimate subject-specific FO and transition probabilities of discrete hidden states from rs-fMRI data, and investigated the relationship between these properties and age within a large sample cohort (n > 400, aged 19-80 years). Previous studies have revealed the age-difference in the functional interactions between default mode and control networks (Turner et al., 2015; Keller et al., 2015; Spreng et al., 2017). Therefore, we aimed to find significant age-related correlation of FO and transition probability in states associated with these networks. Moreover, according to the expectation of Naik et al., (2017), we expected to find the state with lower transition probability and/or higher dwell time in the old cohort.

2. Materials and Methods

2.1. Participants and image acquisition

Data used in this study was selected from Southwest University adult lifespan dataset (http://fcon_1000.projects.nitrc.org/indi/retro/sald.html) (Wei et al., 2018). This dataset included 494 healthy subjects, none of which had a history of psychiatric or neurological disorders. Additionally, subjects who didn't satisfy the following criteria were excluded: 1) data loss, 2) excessive head motions (max head motion > 2.0 mm or 2.0 degree or mean framewise displacement (FD) > 0.2 mm), 3) extremely poor data quality (which cannot be successfully normalized). As a result, 422 subjects were included in this study (aged 19-80; mean age = 44.10; SD = 17.25; 166 males). The dataset collection was approved by the Research Ethics Committee of the Brain Imaging Center of Southwest University.

All of the data were collected at the Southwest University Center for Brain Imaging using a 3.0 T Siemens Trio MRI scanner. Each participant took part in 3D structural MRI and a rs-fMRI scan. For functional data, a 8-min scan of 242 contiguous

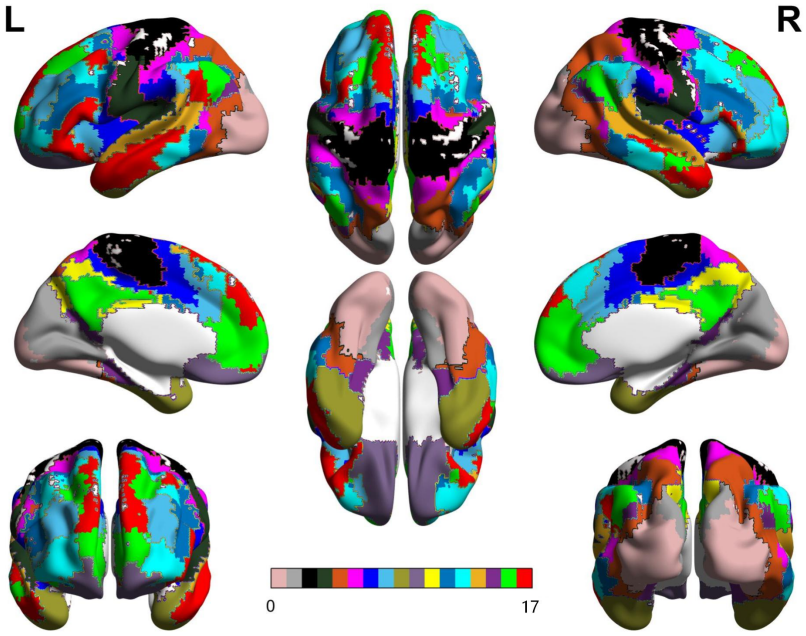
whole-brain resting-state functional images was obtained using a gradient echo echo-planar-imaging (GRE-EPI) sequence with the following parameters: 32 axial slices, repetition time (TR)/echo time (TE) = 2000/30 ms, flip angle = 90 degrees, field of view (FOV) = 220 x 220 mm2, thickness/slice gap = 3/1 mm, resolution matrix = 64 × 64. During the rs-fMRI scan, the subjects were instructed to lie quietly, close their eyes, and rest without thinking about any specific things but to refrain from falling asleep. For the structural data, a magnetization-prepared rapid gradient echo (MPRAGE) sequence was used to acquire high-resolution T1-weighted anatomical images (repetition time = 1,900 ms, echo time = 2.52 ms, inversion time = 900 ms, flip angle = 9 degrees, resolution matrix = 256 × 256, 176 sagittal slices, thickness = 1 mm, FOV = 256 × 256 mm2).

2.2. Image preprocessing

The data were preprocessed using data processing assistant for resting-state fMRI (DPARSF, http://rfmri.org/DPARSF) (Yan et al., 2016) with the following steps: removing the first 10 time points of each subject, slice timing correction, realignment to the mean functional volume to correct for head motion, nuisance regression including 24 motion parameters (Friston et al., 1996), linear trend and signals from white matter and cerebrospinal fluid, normalized to Montreal Neurological Institute space using the EPI template (Calhoun et al., 2017), smoothing (FWHM = 4 mm) and bandpass filtering (0.01 - 0.10 Hz).

2.3. Definition of functional networks

Our definition of resting-state networks (RSNs) was based on reference maps of 17 networks supported by Yeo and his colleagues (Yeo et al., 2011). The network names were consistent with Betzel et al. (2014) and were shown in Fig.1. For each subject, the averaged time course within each of the 17 RSNs were extracted from Yeo's template and then normalized separately (zero mean and unit standard deviation). The normalized time courses were temporally concatenated across all subjects, resulting in a two-dimensional matrix (networks × (time points × subjects)) to be input into HMM.



Network number and color	1	2		4	5	6	7	8	9	10	11	12	13	14	15	16	17
Network name	Visual peripheral	Visual central	Somatomotor A	Somatomotor B	Dorsal attention A	Dorsal attention B	Salience / Ventral attention A	Salience / Ventral attention B	Limbic A	Limbic B	Control C	Control A	Control B	Default D	Default C	Default A	Default B

Fig. 1. Yeo's 17-network parcellation of human cerebral cortex. The parcellation are mapped on the smoothed ICBM 152 surface using BrainNet Viewer. Network names are identical with Betzel et al., (2014).

2.4. Hidden markov model

A brief flowchart of our approach was shown in Fig.2. HMM assumes that brain activity (observation sequence), is generated by a number of hidden states (state sequence) that are considered to be random variables following a Markov chain. The Markov chain could be fully determined by a set of basic parameters including initial probability distributions and the transition probability matrix of the hidden state variables. In a homogeneous Markov chain, probabilities of the current states only

depend on those at the previous time point and the transition probability matrix (i.e. probabilities of states transiting from the previous to the current time point). The observation matrix stands for the conditional probabilities of the observed data on hidden states, and has the distribution of multivariate Gaussian with the mean μ and covariance matrix Σ.

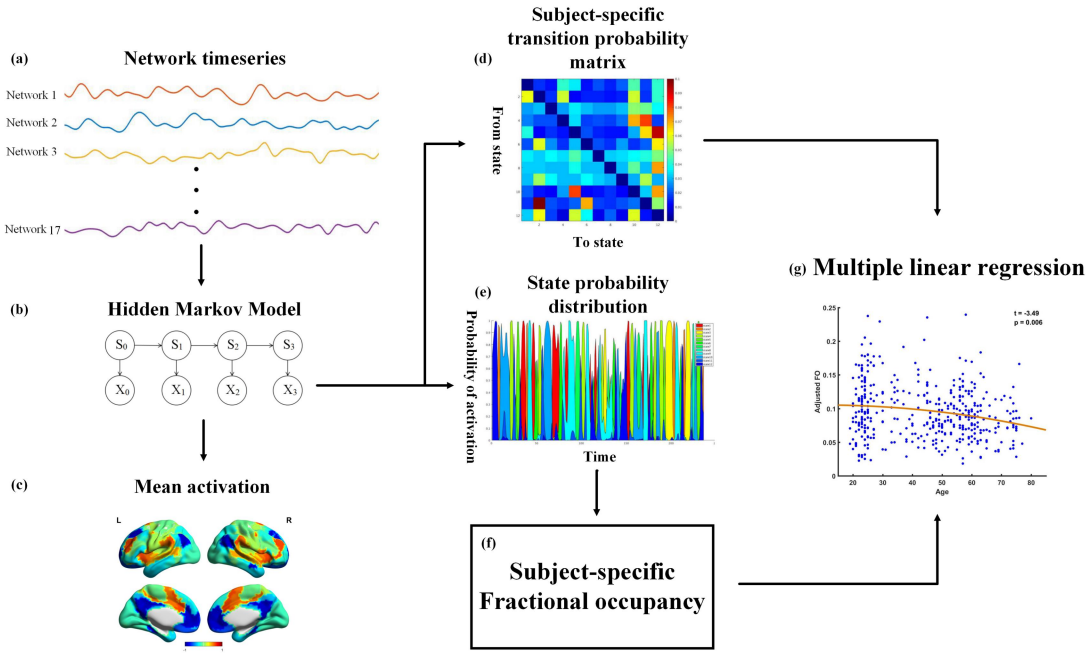


Fig. 2. The brief flowchart of our approach. (a) Network-averaged fMRI timeseries were temporally concatenated and fed into HMM. (b) Hidden Markov model. S_t are random variables following a Markov chain, which denotes the hidden states in time point t. Similarly, Xt denotes the observed values from networks-averaged timeseries in time point t. The conditional probabilities of the observed data on hidden states have the distribution of multi-Gaussian with mean vectors μ and covariance matrices Σ . (c) Mean activation of states. Mean vectors μ are projected to the ICBM 152 surface using BrainNet toolbox. (d) Subject-specific transition probability matrix. Elements Aij denotes the transition probability $P(S_t \mid S_{t-1})$ from one state i to another state j. (e) State distribution of K = 12 states. The posterior probability of K states is estimated via variational Bayes inference, with each color representing a particular state. (f) Subject-specific fractional occupancy, which is defined as the temporally

averaged posterior probability of state k in one scan. (g) Multiple linear regression analysis. Subject-specific FO and transition probability are modeled as explained variables, while age is modeled as a explanatory variable (mean framewise displacement and sex are modeled as covariables).

In this study, the HMM parameters were estimated by the HMM-MAR toolbox (https://github.com/OHBA-analysis/HMM-MAR) (Vidaurre et al., 2016; Vidaurre et al., 2017) using improved variational Bayes inference (Rezek and Robert, 2005), a popular inference paradigm that assumes certain simplifications in the HMM model (Jordan et al., 1998; Jaakkola et al., 2000). In this approach, traditional maximum-likelihood estimators are improved and replaced by free energy, which includes Kullback-Leibler divergence between the real and the factorised distribution and the entropy of the factorised distribution (Vidaurre et al., 2018). Therefore, parameters of HMM could be derived by minimization of the free energy. In this study, we ran HMM for 400 cycles with different initialization and chose the cycle with lowest free energy. Previous studies using HMM suggested that 8-12 states were suitable to get physiologically reasonable as well as replicable findings (Baker et al., 2014; Vidaurre et al., 2017; Vidaurre et al., 2018; Kottaram et al., 2019). Here, we choose K = 12 as number of states in accordance with Vidaurre et al., 2017 and Kottaram et al., 2019.

By applying variational Bayes inference on the entire data, we firstly estimated the group-level transition probability, the posterior probability of each state at each time points (or state time courses), the mean activation (μ, a 17 x 1 vector) and the covariance matrix (Σ, 17 x 17). The mean activation of sub-networks were firstly averaged for each network, and then were deemed as three levels according to the following criteria, (1) if the result was larger than 0.25, then the mean activation of this network was defined as 'high', (2) if the result was smaller than -0.25, then the mean activation of this network was defined as 'low' and (3) if the result was between -0.25 and 0.25, then the mean activation level of this network was defined as

‘moderate’.

In addition, due to our interest in subject-specific patterns of brain dynamics, subject-specific state variables were then calculated by making use of state time courses for each subject (Van schependom et al., 2019). These variables included subject-specific fractional occupancy (FO) and transition probability. Subject-specific FO was defined as the temporally averaged posterior probability of state k in one scan, which denoted the proportion of time spent visiting each state (Vidaurre et al., 2017).

2.5. Multiple linear regression

We employed a general linear model (GLM) to investigate the relationships between HMM parameters (subject-specific FO or transition probability) and age while taking the confounding effect of mean framewise displacement (FD) and sex into consideration. The effect of age was estimated by the t values of the corresponding regressors. Bon-ferroni correction was applied to correct for multiple comparisons. Subsequently, the adjusted FO (or transition probability) were obtained by removing contributions of mean FD and sex and were further plotted against age. The quadratic fit was applied to the scatter plots of adjusted FO (or transition probability) and age to illustrate the lifespan trajectories of FO (or transition probability).

3. Results

3.1. Mean activation patterns of the hidden brain states

Mean activation of the 12 hidden states were illustrated in Fig.3. Generally, there were no one-to-one mapping between these states and the typical RSNs, but these states could be roughly grouped into three categories according to their mean activation levels. 1) Antagonistic states. For state 1, salience network (SN) and ventral attention network (VAN) showed high-level activation while DMN and limbic regions showed low-level activation. For state 2, DMN, limbic regions and somatomotor network (SMN) showed high-level activation while cognitive control (CCN), SN and VAN showed low-level activation. For state 7, both DMN and CCN showed high-level activation while SN and VAN showed low-level activation. For state 11, dorsal

attention network (DAN) shows high-level activation while DMN and visual network showed low-level activation. For state 12, CCN showed high-level activation while SN, VAN and SMN showed low-level activation. 2) Co-activation/deactivation states. States 3, 4, 5, 6 and 10 exhibited the similar patterns that almost all networks showed high/low-level activation. 3) Inactive states. State 8 and 9 were two inactive states in that all RSNs showed moderate-level activation.

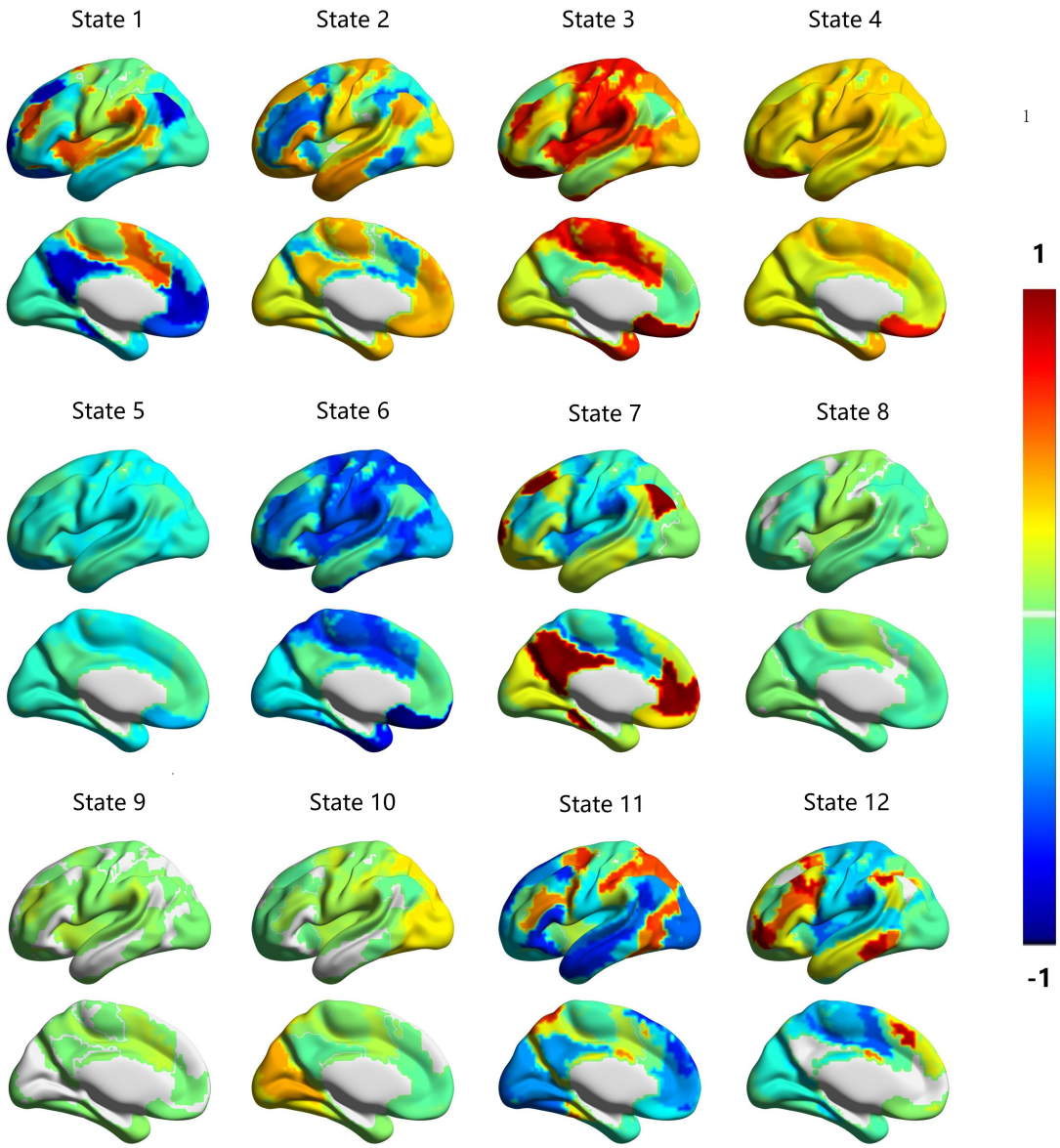


Fig. 3. Mean activation of the 12 hidden states. Positive values were shown in

warm color and negative values were shown in cool color. Positive values which is less than 0.01 and negative values which is more than -0.01 were filtered out.

3.2. Relationships between FO and age

For states 1, 2 and 12, their FO exhibited significant decreases with age (Fig.4, $p < 0.05$, corrected). The FO of state 8 exhibited significant increase with age (Fig.4, $p < 0.05$, corrected), and showed a U-shaped lifespan trajectory with the valley around 32 years of age (Fig.5c), while the FO of states 1, 2 and 12 showed slow declines with age (Fig.5a, b, and d).

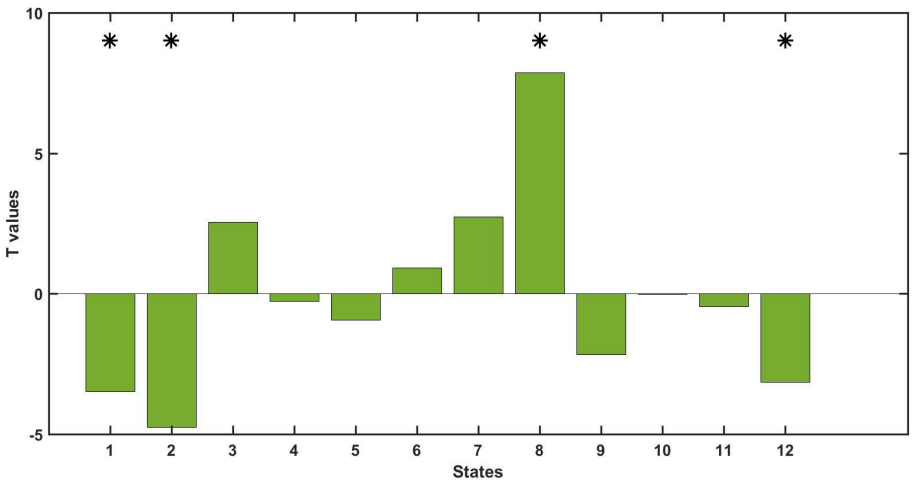


Fig. 4. Significant age-related changes of subjects' fractional occupancy. The value of each bar denotes the t value of age coefficient (β_1) of MLR model for FO and age (including mean FD and sex as covariables). Asterisks (*) denote $p < 0.05$ (Corrected).

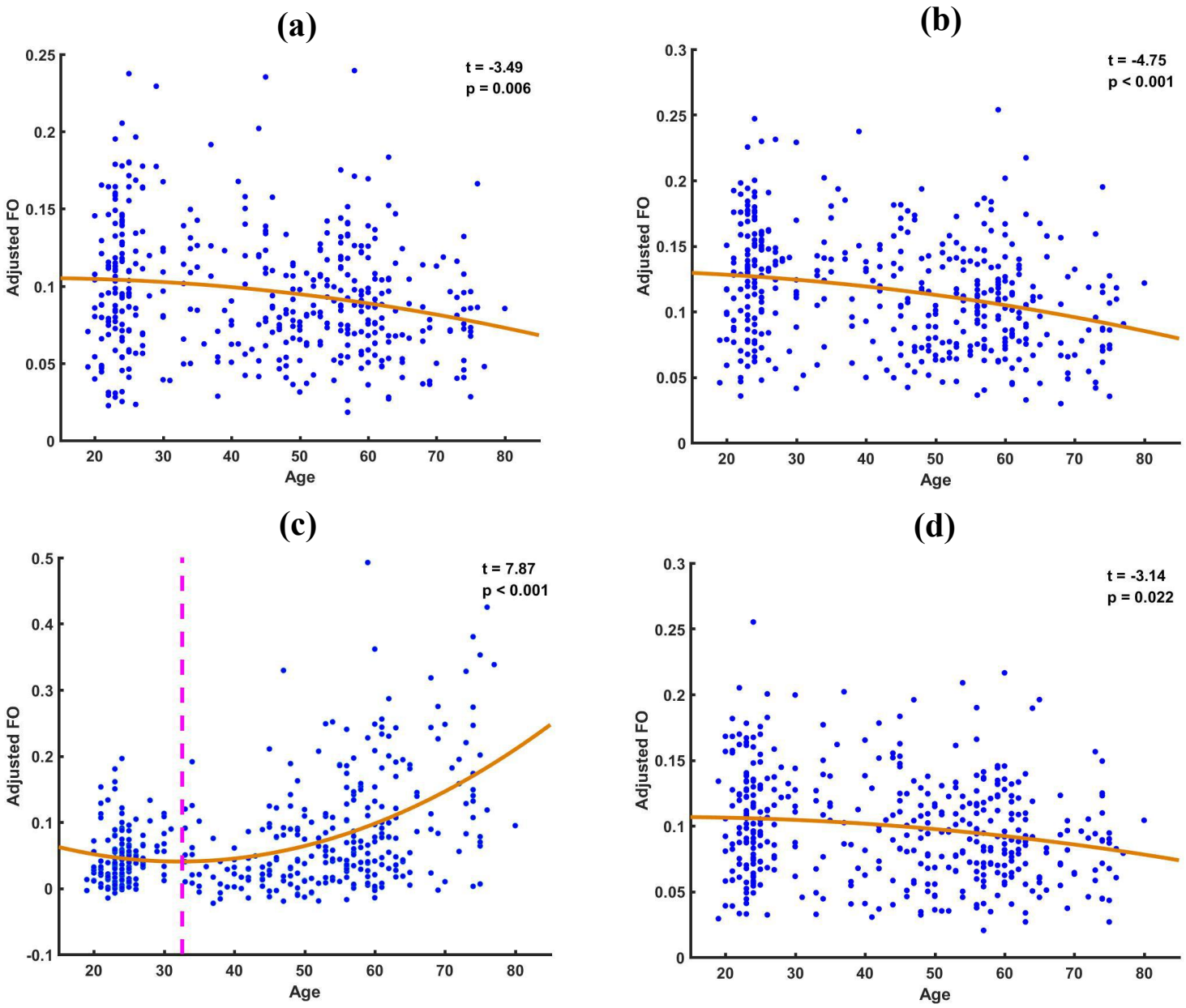


Fig. 5. Lifespan trajectories of subjects' fractional occupancy. Each dot denotes the adjusted FO value of each subject. The dashed line denotes the valley of the quadratic fitting curve. (a) Lifespan trajectories of the fractional occupancy of state 1. (b) Lifespan trajectories of the fractional occupancy of state 2. (c) Lifespan trajectories of the fractional occupancy of state 8. (d) Lifespan trajectories of the fractional occupancy of state 12.

3.3. Relationships between transition probability and age

First, the transition probabilities from all states except 8 and 9 to state 8 showed

significant increases with age while those from state 8 to states 1, 2, 5, 9 and 12 showed significant decreases with age (Fig.6, $p < 0.05$, corrected). Second, we found significant decreases for the transition probabilities from states 3 and 11 to state 2, and from state 7 to state 1 with age (Fig.6, $p < 0.05$, corrected). More interestingly, for the states 2 and 8, similar age-related patterns were found between their FOs and subject-specific transition probabilities. For example, the FO of state 8 increased with age, and the transition probabilities from the other states to state 8 increased with age as well.

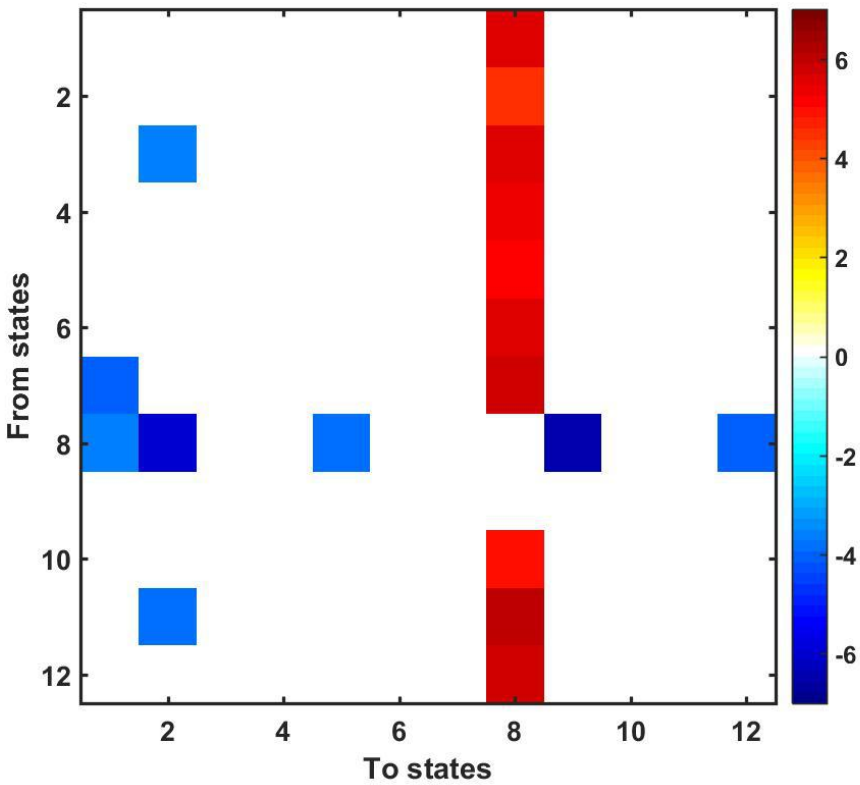


Fig. 6. Significant age-related changes of subjects' transition probabilities. Diagonal and non-significant ($p > 0.05$, corrected) elements were removed. Colorbar denotes the t value of age coefficient (β_1) of MLR model for transition probability and age (including mean FD and sex as covariables).

Lifespan trajectories of some examples of adjusted transition probability are shown in Fig.7. Among them, the transition probabilities from state 7 to state 1 and from state 3 to state 2 decreased linearly with age (Fig.7a and b, $p < 0.05$, corrected). And the transition probabilities from state 11 to state 8 increased linearly with age (Fig.7e, $p < 0.05$, corrected). Besides, the transition probabilities from state 11 to state 2 and from state 8 to state 9 showed inverted U-shaped trajectories with age with peak ages at about 30 years (Fig.7c and f, $p < 0.05$, corrected), while the transition probabilities from state 7 to state 8 showed an U-shaped trajectory with age with peak ages at about 30 years (Fig.7d, $p < 0.05$, corrected).

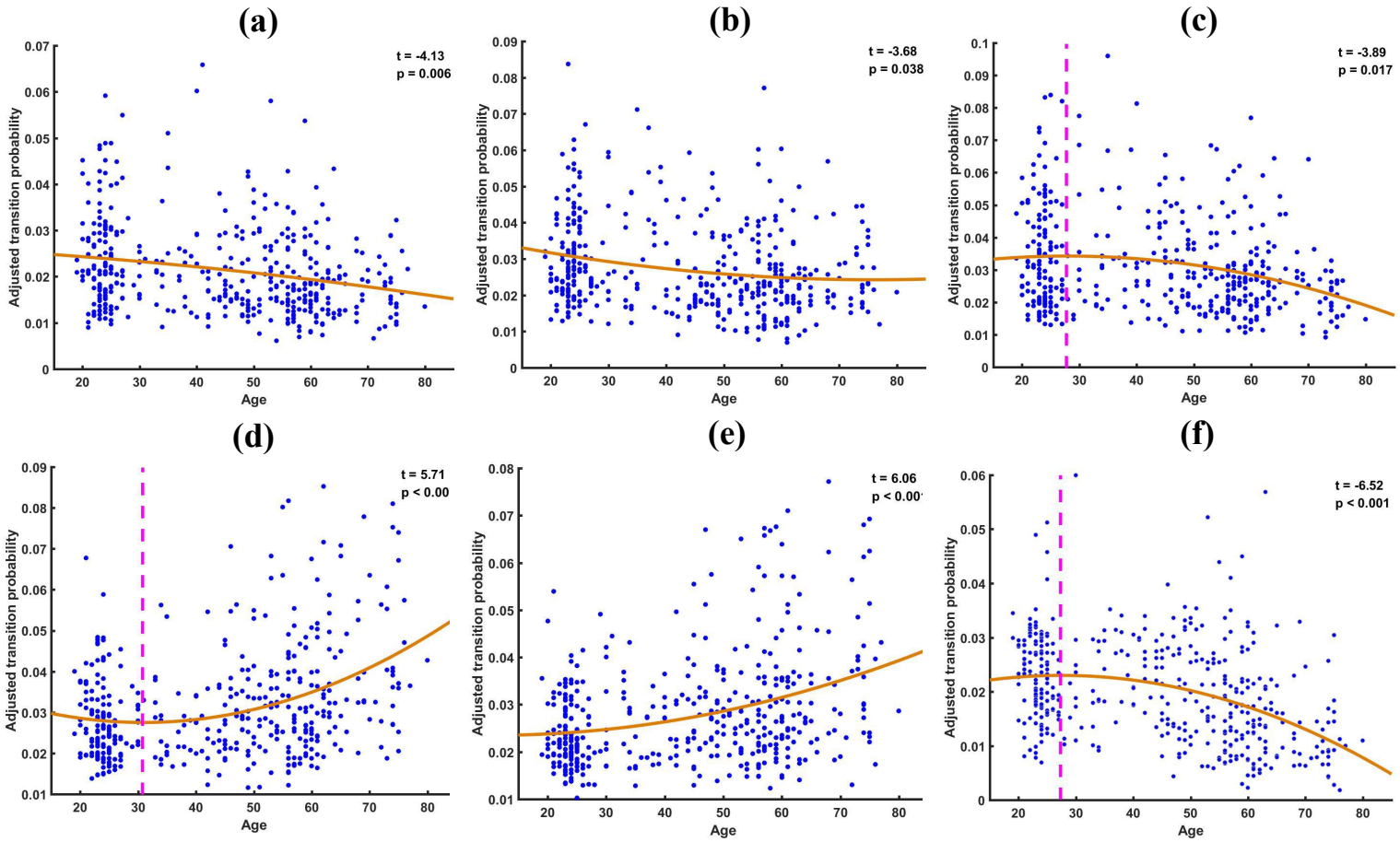


Fig. 7. Lifespan trajectories of subjects' transition probability. Each dot denotes the adjusted transition probability of each subject. The dashed line denotes the peak/valley of the quadratic fitting curve.(a) Lifespan trajectories of the transition probability from state 7 to state 1. (b) Lifespan trajectories of the transition probability

from state 3 to state 2. (c) Lifespan trajectories of the transition probability from state 11 to state 2. (d) Lifespan trajectories of the transition probability from state 7 to state 8. (e) Lifespan trajectories of the transition probability from state 11 to state 8. (f) Lifespan trajectories of the transition probability from state 8 to state 9.

4. Discussion

In the present study, we probed into the relationships between the metastability revealed by HMM and age using an relatively large sample adult-lifespan rs-fMRI dataset. Significant age-related changes of FO and transition probability were found in three hidden states involved in higher cognitive and default functions as well as one 'inactive' state. The age related changes of FO and transition probability for the inactive state correspond perfectly with the prediction by Naik et al. (2017). Our findings thus suggest that on one side, HMM methodology is effective in uncovering some intrinsic characteristics related to adult lifespan; On the other side, the human brain across the lifespan undergoes changes in the switching dynamics of spontaneous brain activity that may be critical for our better understanding about the normal development of the human brain functions.

4.1. Association between FO and age

Our results showed that the FO of states 1, 2 and 12 decreased linearly with age. States 1 and 2 demonstrated almost orthometric patterns. Specificlly, state 1 is characterized by low-level activation of DMN and limbic regions and high-level activation in SN-VAN,, whereas state 2 is characterized by high-level activation of DMN, limbic regions and SMN and low-level activation in CCN, SN and VAN. The observation that states 1 and 2 were visited less frequently in the elder might suggest weaken antagonistic relationships between DMN and task-positive networks. Our results are in agreement with the default-executive coupling hypothesis of aging (DECHA) model (Turner et al., 2015). Coupling between DMN and CCN were reported to be significantly higher in the elder (Turner et al., 2015; Keller et al., 2015; Ng et al., 2016; Spreng et al., 2017), and the enhanced coupling between these two

networks indicated poorer autobiographical memory (Spreng et al., 2017) in old cohort.. Additionally, the weaken antagonistic relationships between DMN and SN-VAN with the increase of age was in line with Tsvetanov et al. (2016) and Monteiro et al. (2019) that the functional connectivity between DMN and SN-VAN increased with age. Of note, there is conflict between our findings and two recent studies using sliding window approaches to explored the dynamic activity (Tian et al., 2018; Xia et al., 2019) where the dwell time of states characterized by positive coupling between DMN and CCN (Tian et al., 2018; Xia et al., 2019) and between DMN and SN (Xia et al., 2019) were found to be inversely correlated with age. The discrepancy may be due to that the number of the brain states, obtained by k-means clustering, was so small (lower than 7) that one FC state may include more complicated spacial patterns than one HMM state.

State 12 denotes high-level activation in CCN and low-level activation in the other networks. The negative correlation between FO of this state with age may indicated that the decreased segregation or modularity of CCN in the elder. Numerous studies have found decreased segregation or modularity of functional networks in older adults (Cao et al., 2014; Chan et al., 2014; Betzel et al., 2014; Geerligs et al., 2014; Archer et al., 2016; King et al., 2018), and lower values of these measures were also associated with lower cognitive performance (Chan et al., 2014; King et al., 2018). More specifically, Betzel et al. (2014) and Monteiro et al., (2019) found that the decreased modularity/segregation of the control networks was significantly ($p < 0.05$, corrected) correlated with age, which were consistent with our results. This finding may cater to the dedifferentiation hypothesis that aging was associated with decreased specialization of functional networks (King et al., 2018).

Interestingly, the FO of state 8 was positively correlated with age, suggesting that the elder generally spent more time on this inactive state since all networks only showed moderate-level activity. Such inactive state was also found in Chen et al (2016) using HMM to explore the dynamical activity within healthy young adults (age: 22 - 36) and Kottaram et al., (2019) who applied HMM to explore the dynamical activity

within the schizophrenia patient. Similarly, Tian et al. (2018) and Xia et al. (2019) employed the sliding window approach and also found that a state characterized by weak regional interaction throughout the brain was positively correlated the age. Chen et al., (2016) also found that most states often switch to this state and then transit back to other states from it. This state might reflect a transient 'ground state' (Chen et al., 2016) of the spontaneous brain activity.

Of note, the U-shaped lifespan trajectory of FO for the state 8 against age suggests the nonlinear relationship between the occurence of this state and age. The U-shaped lifespan trajectories were also observed for the mean between-network functional connectivity strength (Betzel et al., 2014), and the local and global efficiency in structural connectivity (Zhao et al., 2015) with similar valley around 30 years. Thus, our findings add further support to the view that non-linear trend might reveal the functional and structural turning point of adult lifespan. The quadratic decrease before 30 years might be highly related to maturation, and the quadratic increase after 30 years might be closely correlated with aging.

Similar with state 8, state 9 could be also considered as an 'inactive' state. However, it should be noted that there were a few subtle differences between them. First, the differences among the activity level of most networks were relatively modest in state 8, while the activity level of SN and VAN were relatively higher than other networks in state 9. Second, DMN and CCN showed negative activity in state 8, whereas almost all networks showed positive activity in state 9. Such differences imply that they may represent different functional states of the resting brain and may explain the reasons why the FO of state 9 did not show significant decrease with age, nor age-related transitions as found in state 8.

4.2. Association between state transition probability and age

Another intriguing finding is that there was a tight correspondence between FO and transition probability of several hidden states. This was more obvious for the state 8. The elder had greater FO in state 8 than the younger people, generally accompanied

by higher transition probabilities from other states to state 8 and lower transition probabilities from state 8 to other states. Although the causal relationship was unknown, the observed larger FO in the elder may be probably caused by the greater tendency of the spontaneous activity to enter the state 8 from the other states, and less tendency to leave state 8 for the other states. In that case, strong agreement was found between these two findings and the expectations of ‘lower transition probability and/or higher dwell-time in a particular network state’ by Naik et al., (2017).

Age-related transitions from state 11 to state 2 could account for the dynamic changes associated with aging. Our result indicated that the transition from the state with lower DMN.activity (i.e. state 11) to a state with higher DMN activity (i.e. state 2) become more difficult with the increase of age, which may explain why the elder spent less time in state 2, as reflected by their lower FO in state 2. This was in concordance with some stationary RSFC studies where they found the intra-connectivity of DMN decreased with age (Andrews-Hanna et al., 2007; Mevel et al., 2013; Betzel et al., 2014; King et al., 2018). Likewise, age related asssociation of transition probability from state 3 to state 2 suggested that the transition from a state with higher activity of control network (i.e. state 3) to the state with lower activity of control network (i.e. state 2) become more difficult with the increase of age, which may explain why the elder spent less time in state 2, as reflected by their lower FO in state 2. And this finding is consistent with some stationary RSFC studies where they found the intra-connectivity of control network decreased with age (Betzel et al., 2014; Geerligs et al., 2014). Nevertheless, the decreased transition probability from state 7 to state 1 with age seems conflict with our interpretations about the results of state 2 since they exhibited an antagonistic relationship. The difficulty might be owing to our quite limited understanding about the brain dynamics per se as well as how it changes across the life span, which may be rather complex than expected. The development of dynamic analysis approaches including HMM is just at the starting point. Much future work is needed to investigate the neural mechanism underlying the activation patterns of, and the transitions among HMM state.

4.3. Limitations

Several limitations should be taken into consideration. Firstly, it is worth mentioning that head motion can affect measures of functional connectivity (Power et al., 2012; Van Dijk et al., 2012), especially dynamic FC (Laumann et al., 2016). And functional imaging studies across development can suffer from age-related head motion and physiological noise (Power et al., 2012; Lehmann, White, Henson, & Geerligs, 2017). For this study, head motion may introduce false-positive age-related changes of FO and transition probability, though our strategies have included removing subjects with excessive mean FD, using 24 regression model in preprocessing step and selecting mean FD and age as covariables in multiple linear regression analysis. Secondly, imbalance of sex ratio in SALD dataset may induce gender effect. Although we only found significant sex-related change of state 7 ($p < 0.05$, corrected) in multiple linear regression analysis, the replicability of our study may be difficult due to the lack of sufficient male participants. The ongoing HCP-A (Human Connectome project in aging) project could be capable of tackling this issue in the future (Bookheimer et al., 2019). Thirdly, we estimated HMM parameters using concatenating data from all individuals, and thus every subject shared a common set of states, which was not suitable to capture subject-specific traits and make personalized diagnosis on disease. Future studies are expected to improve the specificity of this approach. Lastly, 400 training cycles of different initialization could not guarantee the global optimum solution, methods like simulated annealing (Lee et al., 2010) or genetic algorithm (Won et al., 2004) may applied to this model and solve this problem.

5. Conclusions

This study sharpened our understanding of the link between resting brain dynamics and adult lifespan. We found the elder were probable to spend more time on a state with moderate-level activation of all networks, and less time on states showing antagonistic activity between pairs of networks including DMN, control and SalVentAttn. In addition, the transition probabilities between certain pair of states also showed age-related changes, indicating the age-related regulation of default mode and control network. Moreover, these age-related FO changes may be due to the

transitions among the corresponding hidden states. Therefore, HMM is a huge potential tool for discovering the dynamic alteration across adult lifespan.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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