RESEARCH ARTICLE

Trait- and State-Dependent Changes in Cortical–Subcortical Functional Networks Across the Adult Lifespan

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Background: How the functional interactions of the basal ganglia/thalamus with the cerebral cortex and the cerebellum change over the adult lifespan in movie-watching and resting-state is less clear.
Purpose: To investigate the functional changes in the organization of the human cortical–subcortical functional networks over the adult lifespan using movie-watching and resting-state fMRI data.
Study Type: Cohort.
Subjects: Healthy 467 adults (cross-sectional individuals aged 18–88 years) from the Cambridge Centre for Ageing and Neuroscience (www.cam-can.com).
Field Strength/Sequence: fMRI using a gradient-echo echo-planar imaging (EPI) sequence at 3 T.
Assessment: Functional connectivities (FCs) of the subcortical subregions (i.e. the basal ganglia and thalamus) with both the cerebral cortex and cerebellum were examined in fMRI data acquired during resting state and movie-watching. And, fluid intelligence scores were also assessed.
Statistical Tests: Student's *t*-tests, false discovery rate (FDR) corrected.
Results: As age increased, FCs that mainly within the basal ganglia and thalamus, and between the basal ganglia/thalamus and cortical networks (including the dorsal attention, ventral attention, and limbic networks) were both increased/decreased during movie-watching and resting states. However, FCs showed a state-dependent component with advancing age. During the movie-watching state, the FCs between the basal ganglia/thalamus and cerebellum/frontoparietal control networks were mainly increased with age, and the FCs in the somatomotor network were decreased with age. During the resting state, the FCs between the basal ganglia/thalamus and default mode/visual networks were mainly increased with age, and the FCs in the cerebellum were mainly decreased with age. Moreover, inverse relationships between FCs and fluid intelligence were mainly found in these network regions.
Data Conclusion: Our study may suggest that changes in cortical–subcortical functional networks across the adult lifespan were both state-dependent and stable traits, and that aging fMRI studies should consider the effects of both physiological characteristics and individual situations.
Evidence Level: 2.
Technical Efficacy: Stage 3.

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The basal ganglia, which includes the caudate nucleus, putamen and globus pallidum, is positioned deep below the cortical manifold and is an important network hub and relay.[1] The basal ganglia receives inputs from the neocortex and sends a considerable number of projections to thalamic nuclei by way of their output nuclei.[2] Anatomical evidence from monkeys shows that both cortical and cerebellar projections are integrated within the basal ganglia.[3] The basal ganglia and thalamus interconnect distant parts of the cerebral cortex via cortico-basal ganglia-thalamo-cortical loops[4] and the cerebellum via the cerebello-thalamo-striatal pathway.[5] Similar organization is implicated in humans using probabilistic diffusion tractography.[6,7] Therefore, it is suggested that even small lesions in the basal ganglia and the thalamus can be neurologically devastating.[8,9] Given their centrality, cerebello-basal ganglia-thalamo-cortical loops also appear to underlie many neurological and psychiatric disorders, including Parkinson's disease,[10] dystonia,[10] and Tourette syndrome.[10] In the aging process, the basal ganglia might play a regulatory role to compensate for the dysfunction of other functional systems.[11] Thus, the integrity of these loops is likely important for healthy aging, and a better understanding of the functional organization of the subcortical subregions (e.g., basal ganglia and thalamus) and their connectivities to the cerebral cortex and cerebellum may improve understanding typical and atypical brain function.

Recently, several studies[12,13] have shown that brain functional networks via functional connectivities (FCs) are related to the behavioral state of the individual being evaluated (e.g. resting- and movie-watching states), that is, they are state dependent. It has also been shown that FCs combining different behavioral states can predict individual differences in cognitive performance.[13] As a naturalistic stimulus condition, free movie-watching offers rich and complex stimulation including visual and auditory stimulus, which may closely approximate daily life, and experiments under a movie-watching state can reliably reflect human brain activity relative to processes of emotion, attention and memory.[14–16] For instance, an fMRI study has shown that movie-watching can evoke widespread intersubject synchronization of cerebral cortical activity, including primary and secondary visual and auditory areas as well as the inferior frontal gyrus and the cingulate gyrus in the associated cortices.[16] Resting-state FC is directly linked to human cognition and has potential as a biomarker of disease and as an early objective marker of treatment response. Numerous research groups have investigated the use of resting-state fMRI in the adult lifespan.[17,18] These studies imply that combining movie-watching and resting-state fMRI may reveal more information on brain functional organization.

Brain functional networks may be trait dependent. The focus of previous studies[19–21] has been on the examination of age in relation to functional networks, especially on how the patterns of functional architecture within and between brain networks change with age. For example, using resting-state fMRI, Geerligs et al. found that the aging brain exhibited modularity and local efficiency reduction, and that the distinction between the default mode network (DMN) and frontoparietal control network (FPN) diminished.[19] Tomasi and Volkow found that the dorsal attention network (DAN) is also sensitive to aging effects.[20] The intersubject synchronization in the cortical cortex has also been shown to decline with age, and this decreased synchrony relates to cognitive performance.[15,22] Therefore, considering the natural stimulation and brain adaptation constantly occurring in daily life, characterizing the lifespan differences in the functional interactions of cortico–subcortical regions by studying both movie-watching and resting-state FCs may help improve the current understanding of the patterns by which the brain maintains daily behavioral functions during the healthy aging process.

However, little is known about subregional commonality and specificity of state and trait effects on subcortical FCs, such as the FCs of the basal ganglia/thalamus with both the cerebral cortex and cerebellum. In this study, we hypothesized that cortical–subcortical functional networks relative to the basal ganglia/thalamus during movie-watching and resting states may show both trait- and state-dependent connectivity patterns across the adult lifespan. Thus, the aim of this study was to investigate the functional changes in the organization of the human cortical–subcortical functional networks across the adult lifespan in healthy individuals from the ages of 18–88 years using movie-watching and resting-state fMRI data.

Materials and Methods

Current study followed the principles of the Cambridge Centre for Aging Neuroscience (CamCAN, http://www.cam-can.org/) study, which was followed the Helsinki Declaration and approved by the Cambridgeshire 2 Research Ethics Committee, United Kingdom. Informed consents were also obtained from all participants.

Participants

Participants (18–88 years old, Fig. S1) were selected from the CamCAN dataset, which includes structural and functional images, as well as cognition assessments.[23,24] For all participants, detailed demographic information, relevant life experience and responses to a self-administered questionnaire of physical health were recorded. In addition, the general cognitive function of the participants was investigated by the Mini-Mental State Examination (MMSE). Participants included in the current study met the following criteria: 1) had normal performance on the MMSE (25 or higher); 2) had normal or corrected-to-normal vision and hearing; 3) were native English speakers; 4) had no brain abnormalities or neurological disorders; and 5) had no contraindications to MRI. The data were selected from 647 structural MRI (sMRI) samples, movie-watching fMRI samples and resting-state fMRI samples. After excluding samples with poor imaging quality (head motion criteria [patients with

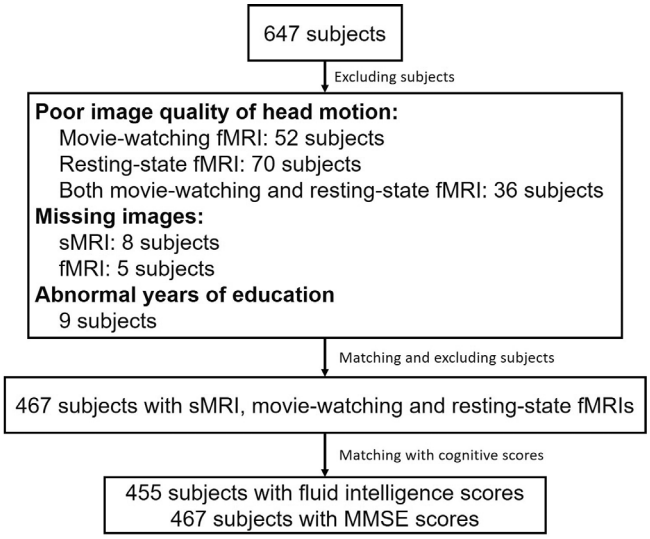

FIGURE 1: Flow chart of subject selection.

translation >2.5 mm, rotation >2.5° or mean framewise displacement >0.5 mm], both movie-watching and resting-state images were poor [36 subjects], only movie-watching images were poor [52 subjects], only resting-state images were poor [70 subjects]), missing structural (8 subjects) or functional (5 subjects) images, or abnormal age of completing full time education (with missing or recording abnormal age value, 9 subjects), 467 subjects who had full sMRI, movie-watching fMRI and resting-state fMRI data remained in the final study (see Fig. 1). Finally, fluid intelligence scores (Cattell Culture Fair Test) were used to match the movie-watching and resting-state fMRI data, and a subset of 455 participants with fluid intelligence scores was analyzed (Table 1).

Fluid Intelligence Assessment

In this study, the Cattell Culture Fair Test, Scale 2 Form A, was used to assess fluid intelligence scores (from the CamCAN).[24] The Cattell test is a pen-and-paper test, including four subtests, that contains a series of nonverbal "puzzles." Each subtest has a time limit: the time limit for the first subtest is 3 minutes, that for the second subtest is 4 minutes, that for the third subtest is 3 minutes, and that for the last subtest is 2.5 minutes. In each test, subjects choose one answer from multiple choices and record it on paper. If the answer is correct, one point is awarded (46 points in total).

Image Acquisition

Imaging data were collected using a 3 T Siemens TIM Trio System (Erlangen, Germany, 32-channel head coil).[24] A 3D T1-weighted structural image volume was obtained using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following parameters: repetition time/echo time (TR/TE) = 2250 msec/2.99 msec, inversion time (TI) = 900 msec, flip angle (FA) = 9°, field of view (FOV) = 256 mm × 240 mm × 192 mm, voxel size = 1 mm isotropic, and acquisition duration = 272 seconds.

Resting-state fMRI images were acquired using a gradient-echo echo-planar imaging (EPI) sequence with the following parameters: TR/TE = 1970 msec/30 msec, FA = 78°, FOV = 192 mm × 192 mm, voxel size = 3 mm × 3 mm × 4.44 mm, number of slices = 32 (descending order), slice thickness = 3.7 mm, gap = 0.74 mm (20%), and acquisition duration = 520 seconds. All participants kept their eyes closed during the imaging process.

Participants were also scanned while they watched a movie called "Bang! You're Dead".[24] This was a black and white television drama. The duration of the movie was reduced from 30 minutes to 8 minutes while ensuring that key plots elements were covered. All participants did not know the content of the movie and had not seen it before. Images were acquired using a multiecho, T2*-weighted EPI sequence with the following parameters: TR = 2470 msec, 5 echoes (TE = 9.4 msec, 21.2 msec, 33 msec, 45 msec, and 57 msec), FA = 78°, FOV = 192 mm × 192 mm, voxel size = 3 mm × 3 mm × 4.44 mm, number of slices = 32 (descending order), slice thickness = 3.7 mm, gap = 0.74 mm (20%) and acquisition duration = 493 seconds.

Image Analyses

DATA PREPROCESSING. For sMRI data, the brain volume was extracted from T1-weighted imaging data. Before data preprocessing, images with artifacts or other structural anomalies were visually assessed (J.Y. and Z.Z.) and rejected (eight subjects were excluded). Then, the sMRI data were preprocessed using Statistical Parametric Mapping (http://www.fil.ion.ucl.ac.uk/spm/software/spm12, SPM12) and the Computational Anatomy Toolbox for SPM (http://dbm.neuro.uni-jena.

TABLE 1. Basic Demography Information of Participants

	Number	Male/Female	Range	Mean	Standard Deviation
Age (years)	467	239/228	18–88	50.88	17.54
Age of completing full time education (years)	467	239/228	14–52	21.04	3.93
MMSE scores	467	239/228	25–30	28.98	1.29
Fluid intelligence scores	455	235/220	12–44	33.05	6.32

MMSE = Mini-Mental State Examination.

de/cat/, CAT12). The images were preprocessed as follows: 1) the origin of all structural MRI scans was manually adjusted to the anterior junction; 2) images were divided into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF); 3) GM and WM were registered to the Montreal Neurological Institute (MNI) standard space using a tissue probability map template; 4) the volumes were modulated by the Jacobian determinant to correct changes caused by spatial registration; 5) abnormal points were checked (J.Y. and Z.Z.), and no participants with poor segmentation were excluded (0 subjects); and 6) GM images were then smoothed with an 8-mm full width at half maximum (FWHM) kernel.

Movie-watching and resting-state fMRI data were preprocessed using SPM12 as implemented in the Neuroscience Information Toolbox vision 1.3 (http://www.neuro.uestc.edu.cn/NIT.html, NIT v1.3).[25] The first five scans were removed from the fMRI data. Images were then preprocessed by the following steps: realignment, slice time correction, spatial normalization (using parameters from individual T1 segmentations and normalizing to MNI space with $3 \times 3 \times 3$ mm^3) and smoothing (FWHM = 8 mm). To control for the influence of excessive head movement on functional connection analysis, we used multiple motion criteria. Samples with excessive head movement (translation >2.5 mm or rotation >2.5°; resting-state: 34 subjects; movie-watching state: 65 subjects) and subjects with mean framewise displacement (mFD) greater than 0.5 mm (resting-state: 72 subjects; movie-watching state: 23 subjects) were excluded. Finally, 12 head motion parameters (6 parameters of translation and rotation and their derivatives) and linear drift signal and mean signals of voxels in WM, CSF, and the global brain signal were regressed from fMRI signals. The regressed signals were filtered with a bandpass filter of 0.01–0.08 Hz.

FC ANALYSIS. In this study, temporal correlation analysis was used to calculate the time synchronization of spontaneous activity between remote brain regions, using the Resting-State fMRI Data Analysis Toolkit V1.8 (http://restfmri.net/forum/REST_V1.8, REST_V1.8). Based on the automated anatomical labeling (AAL) template, the bilateral caudate, putamen, pallidum and thalamus were used as regions of interest (ROIs). Then, the FCs between the mean signals of each ROI and brain voxel signals were calculated as follows: 1) the Pearson's correlations between mean signal of each ROI and time course of each voxel in the whole brain were calculated; and 2) correlation coefficients of FCs were transformed using Fisher's z transform to make them more consistent with the normal distribution.

STATISTICAL ANALYSIS. Relationships between FCs and age/age^2 were investigated to explore the changes in cortical–subcortical functional networks across the adult lifespan. To determine linear or quadratic age effects, a GLM was used to fit whole brain FCs (Y_{FC}) over age and age^2 (X_{age} and $X_{age}{}^2$) along with four covariates (education [$X_{education}$], sex [X_{sex}], total intracranial volume [X_{volume}] and a head motion index [mean framewise displacement, X_{mFD}]) (GLM1, Eq. 1). An additional GLM analysis (GLM2) was conducted to fit FCs over fluid intelligence scores ($X_{behavior}$ in Eq. 2) with the same covariates. Of note, because the ages and fluid intelligence (behavioral scores) were strongly correlated (Fig. S2), two independent GLMs were used to avoid collinearity problems. The significance level of the Student's t-test was set as $P < 0.05$ and was false discovery rate (FDR) corrected. All clusters had 30 or more voxels. In addition, the 7-network[26] of the cerebral cortex was used as a metric of segmentation and differentiation of distributed cerebral cortical networks, and significant FC connections (one sample t-test across all subjects, $P < 0.05$, FDR corrected, cluster size ≥30 voxels, Figs. S5 and S6) were used as Y_{FC} in the following equations:

$$YFC = \beta_0 + \beta_1 \cdot X_{age} + \beta_2 \cdot X_{age^2} + \beta_3 \cdot X_{education} + \beta_4 \cdot X_{sex} + \beta_5 \cdot X_{volume} + \beta_6 \cdot X_{mFD}, \quad (1)$$

$$YFC = \beta'_0 + \beta'_1 \cdot X_{behavior} + \beta'_2 \cdot X_{education} + \beta'_3 \cdot X_{sex} + \beta'_4 \cdot X_{volume} + \beta'_5 \cdot X_{mFD}. \quad (2)$$

Results

Changes in FCs With Age Within the Basal Ganglia and the Thalamus

As shown in Fig. 2, similarities of the FCs in the basal ganglia and the thalamus during movie-watching and resting states were noted for caudate, putamen, pallidum, and thalamus ROIs. Age-related decreases were pronounced in FCs within a large part of the basal ganglia (i.e. parts of the head of the caudate, putamen, and pallidum) and the thalamus (i.e. anterior thalamus) (see Fig. 2). Age-related increases were pronounced in FCs within the head of the caudate and the pulvinar thalamus as well as FCs between the caudate and thalamus pulvinar (see Fig. 2). For more detailed information about the basal ganglia and the thalamus, see Supplementary materials (Table S1 and S2). We further calculated the GM volumes in the basal ganglia and thalamus, which decreased with age (Fig. S4).

Changes in FCs With Age Between the Basal Ganglia/Thalamus and the Cerebellum

As age increased, the FCs between the basal ganglia and cerebellum and between the thalamus and cerebellum showed differences during movie-watching and resting states. As shown in Fig. 3, FCs of the basal ganglia and the thalamus in the movie-watching state were mainly positively related to the cerebellum (i.e. Cerebellum_Crus1 and Cerebellum_Crus2) with age and negatively related to several small areas in the cerebellum (eg Vermis, Cerebellum_8, and Cerebellum_9). The resting-state FCs between the basal ganglia/thalamus and the cerebellum were mainly negatively related to age. For more detailed information about the cerebellum, see Supplementary materials (Tables S1 and S2).

Changes in FCs With Age Between the Basal Ganglia/Thalamus and The Cortical Networks

The connectivities of the caudate, putamen, pallidum, and thalamus to the association networks in the cortex, including the DMN, FPN, DAN, ventral attention network (VAN)

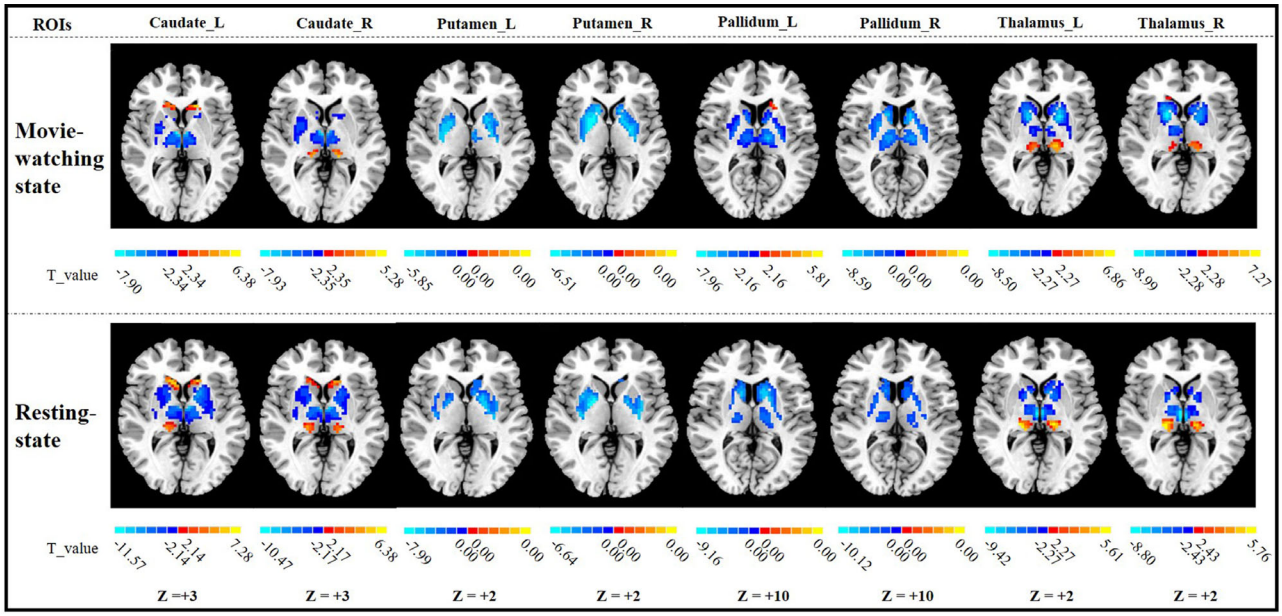

FIGURE 2: Age-related changes in functional connectivities within the basal ganglia and thalamus in movie-watching and resting states. The results were corrected for multiple comparisons by FDR ($P < 0.05$, cluster size ≥30 voxels). The first row is seed regions of ROIs. Warm colors: FCs were positively related to age; Cool colors: FCs were negatively related to age. Color bar represents the T values. Z: slices positioned in the z-axis. L: left; R: right.

and limbic network, exhibited positive or negative relationships with age, both in the movie-watching and rest states (Fig. 4). However, FCs between the basal ganglia/thalamus and cortical association networks also showed state-dependent components with advancing age. As shown in Fig. 4, the FCs of the basal ganglia/thalamus in the movie-watching state mainly increased with the FPN (eg the dorsolateral prefrontal cortex and superior and inferior parietal gyrus), while the resting-state FCs of the basal ganglia/thalamus mainly increased with the DMN (eg lateral temporal cortex).

FCs of the basal ganglia/thalamus with sensory-motor areas in the cerebral cortex showed a more state-dependent component with advancing age. As shown in Fig. 4, the FCs of the basal ganglia/thalamus in the movie-watching state were decreased with the somatomotor network (SMN) (eg Supp_Motor_Area, Precentral and Postcentral). In the resting state, only the FCs of the caudate showed a significant positive relationship with the SMN with age. For the visual network (VN), the movie-watching cortical–subcortical connectivity showed variability with age (Fig. 4). Age-related

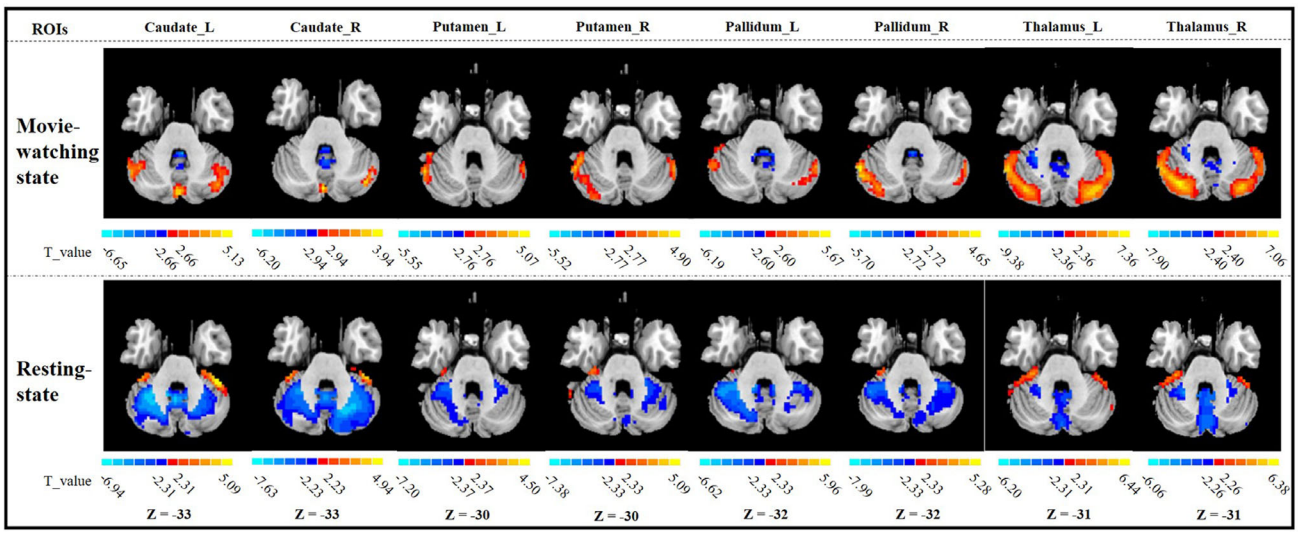

FIGURE 3: Age-related changes in functional connectivities between the basal ganglia/thalamus and cerebellum during movie-watching and resting states. The results were corrected for multiple comparisons by FDR ($P < 0.05$, cluster size ≥30 voxels). The first row is seed regions of ROIs. Warm colors: FCs were positively related to age; Cool colors: FCs were negatively related to age. Color bar represents the *T* values. Z: slices positioned in the *z*-axis. L: left; R: right; ROI: regions of interest.

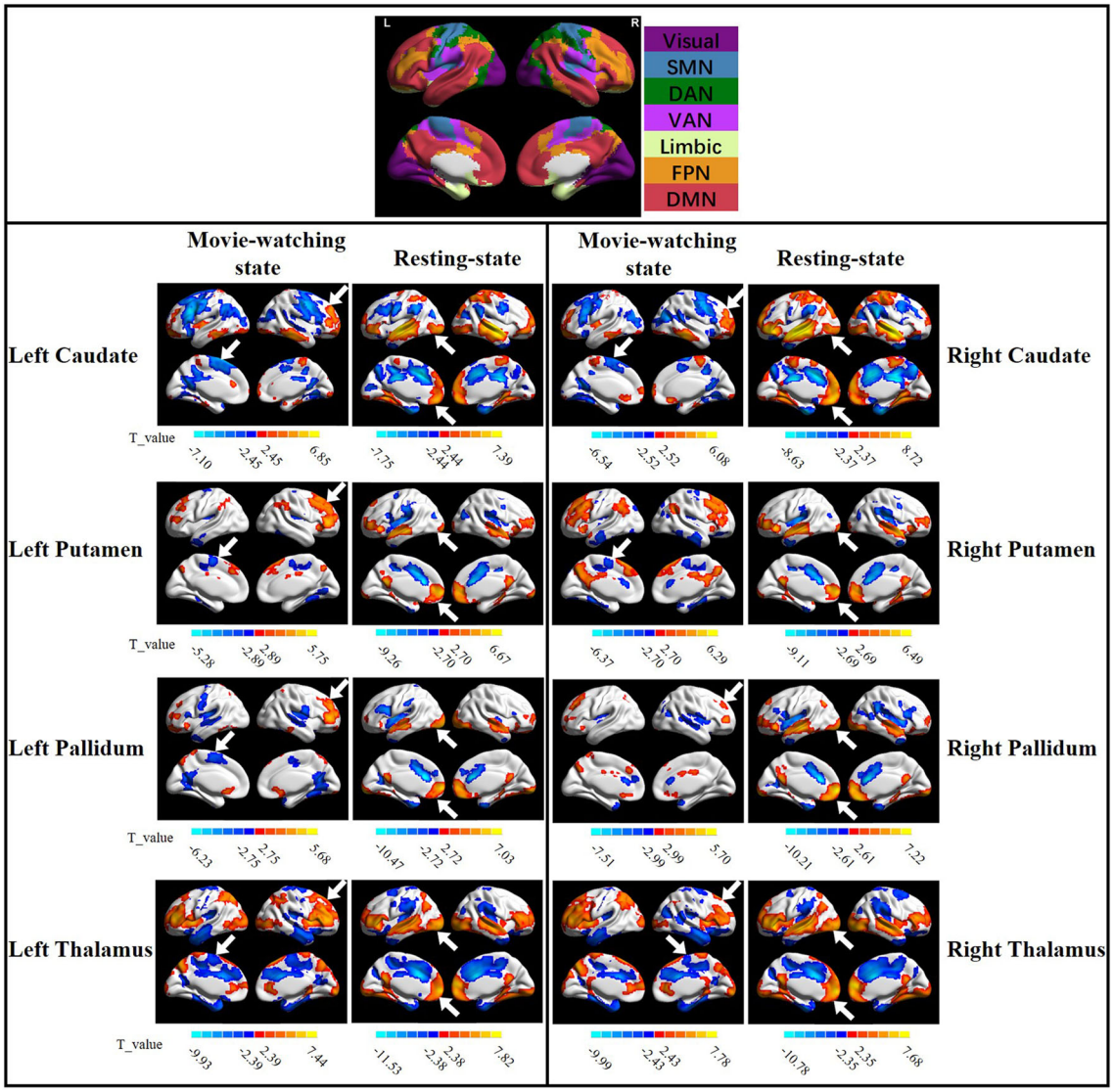

FIGURE 4: Age-related changes in functional connectivities between the basal ganglia/thalamus and cortical networks in movie-watching and resting states. The results were corrected for multiple comparisons by FDR ($P < 0.05$, cluster size ≥30 voxels). The first and last columns are the seed regions of ROIs. Warm colors: FCs were positively related to age; Cool colors: FCs were negatively related to age. ROI: region of interest; SMN: somatomotor network; DAN: dorsal attention network; VAN: ventral attention network; DMN: default mode network; FPN: frontoparietal control network. Color bar represents the *T* values. L: left; R: right; ROI: regions of interest.

increases were pronounced in FCs between the caudate/pallidum/thalamus and the central VN (i.e. the bilateral inferior occipital gyrus) as well as FCs between the thalamus and the peripheral VN (i.e. bilateral lingual, calcarine and middle occipital gyri). Age-related decreases were found in the FCs between the caudate/pallidum and lingual gyrus and FCs between the thalamus/putamen and bilateral fusiform. However, in the resting state, FCs of the basal ganglia/thalamus mainly showed a positive relationship with the VN. More details are provided in the Supplementary materials (Tables S1 and S2).

Changes in FCs With Age^2

As illustrated in Fig. S3, age^2-related changes in FCs during the movie-watching state were identified. For example, positive quadratic age effects on FCs were mainly observed from the left caudate to the left thalamus, limbic network, and VN regions (eg lingual gyrus). Negative quadratic age effects on FCs in the thalamus to the SMN (eg Rolandic_Oper) and the right putamen/pallidum to the left VAN (i.e. left insula) were noted.

For resting-state FCs, age^2-related changes in FCs were also observed (Fig. S3). Significant positive quadratic age effects on FCs were mainly shown in the putamen/pallidum to the thalamus, SMN and VN. Significant negative quadratic age effects on FCs were observed in the basal ganglia/thalamus to the putamen, cerebellum (i.e. Cerebellum_Crus1 and Cerebellum_Crus2) and association networks.

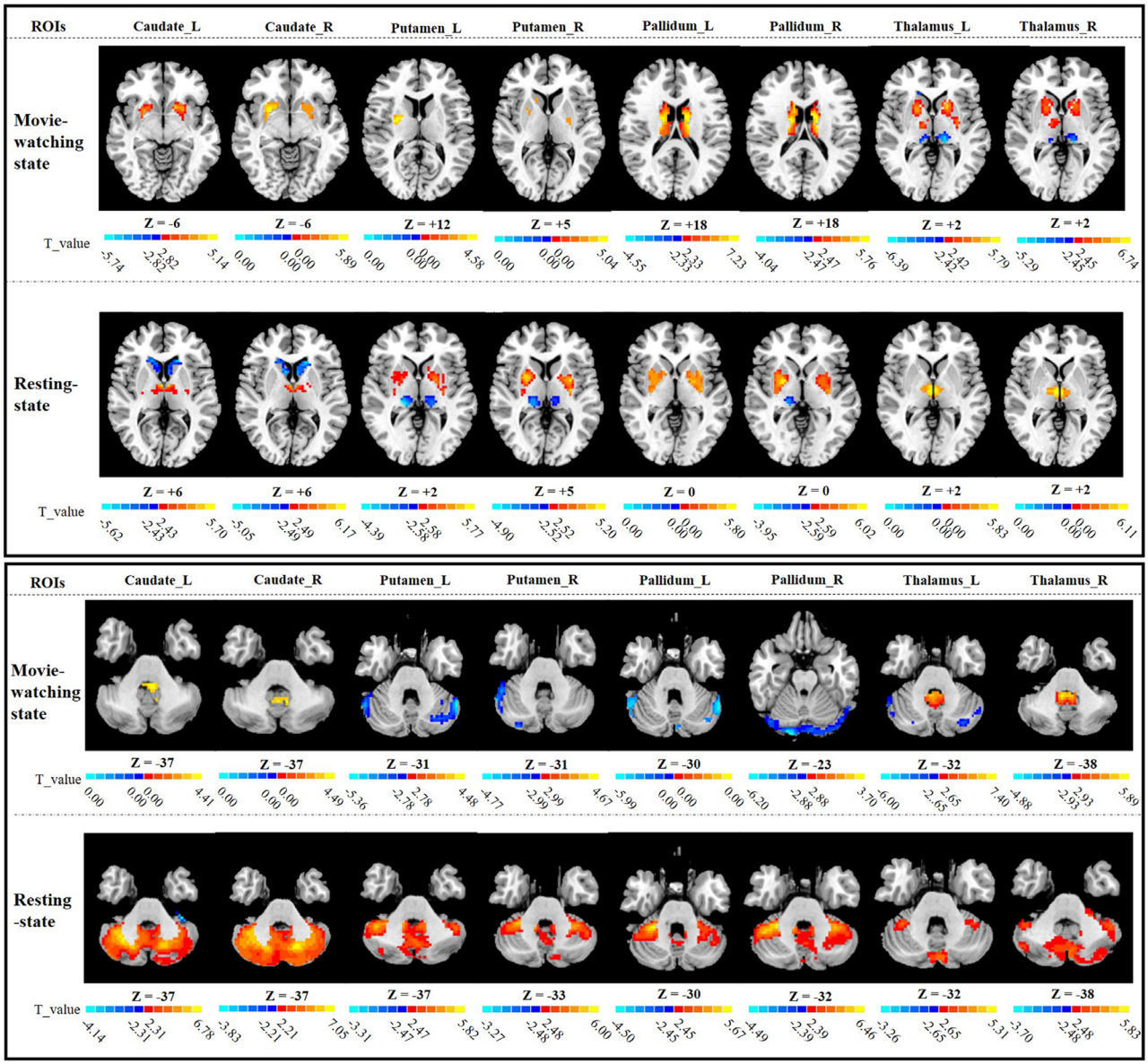

FIGURE 5: Relationships between fluid intelligence and the functional connectivities of the internal basal ganglia/thalamus and the basal ganglia/thalamus with the cerebellum in movie-watching and resting states. The results were corrected for multiple comparisons by FDR ($P < 0.05$, cluster size ≥30 voxels). The first and sixth rows are seed regions of ROIs. Warm colors: FCs were positively related to fluid intelligence scores; Cool colors: FCs were negatively related to fluid intelligence scores. Color bar represents the *T* values. *Z*: slices positioned in the *z*-axis. L: left; R: right; ROI: regions of interest.

Relationships Between FCs and Fluid Intelligence

As shown in Figs. 5 and 6, fluid intelligence scores were positively associated with both movie-watching and resting-state FCs mainly between the caudate and the FPN (i.e. dorsolateral prefrontal cortex) but negatively associated with both movie-watching and resting-state FCs mainly within the pulvinar thalamus and between the caudate and DMN (eg lateral temporal cortex). Moreover, fluid intelligence scores were positively related to resting-state FCs within the posterior putamen and anterior thalamus and between the basal ganglia/thalamus and cerebellum (e.g., Vermis), and negatively related to resting-state FCs between the basal ganglia/thalamus and SMN/VN. However, fluid intelligence scores did not show a significant relationship with movie-watching FCs in these regions.

In addition, we summarized main findings in Fig. 7. And, a split-half cross-validation was further used to validate the age-related changes of FCs during movie-watching and resting states. Half of the subjects were sampled uniformly at random, and then; the same analysis approach was conducted on the split-half datasets. Results of split-half datasets also showed similar changes in FCs across the adult lifespan (see Figs. S8–S13). We also calculated spatial correlations among age/age^2 beta maps of all, split-half 1 and split-half 2 datasets. For age beta maps during movie-watching and resting states,

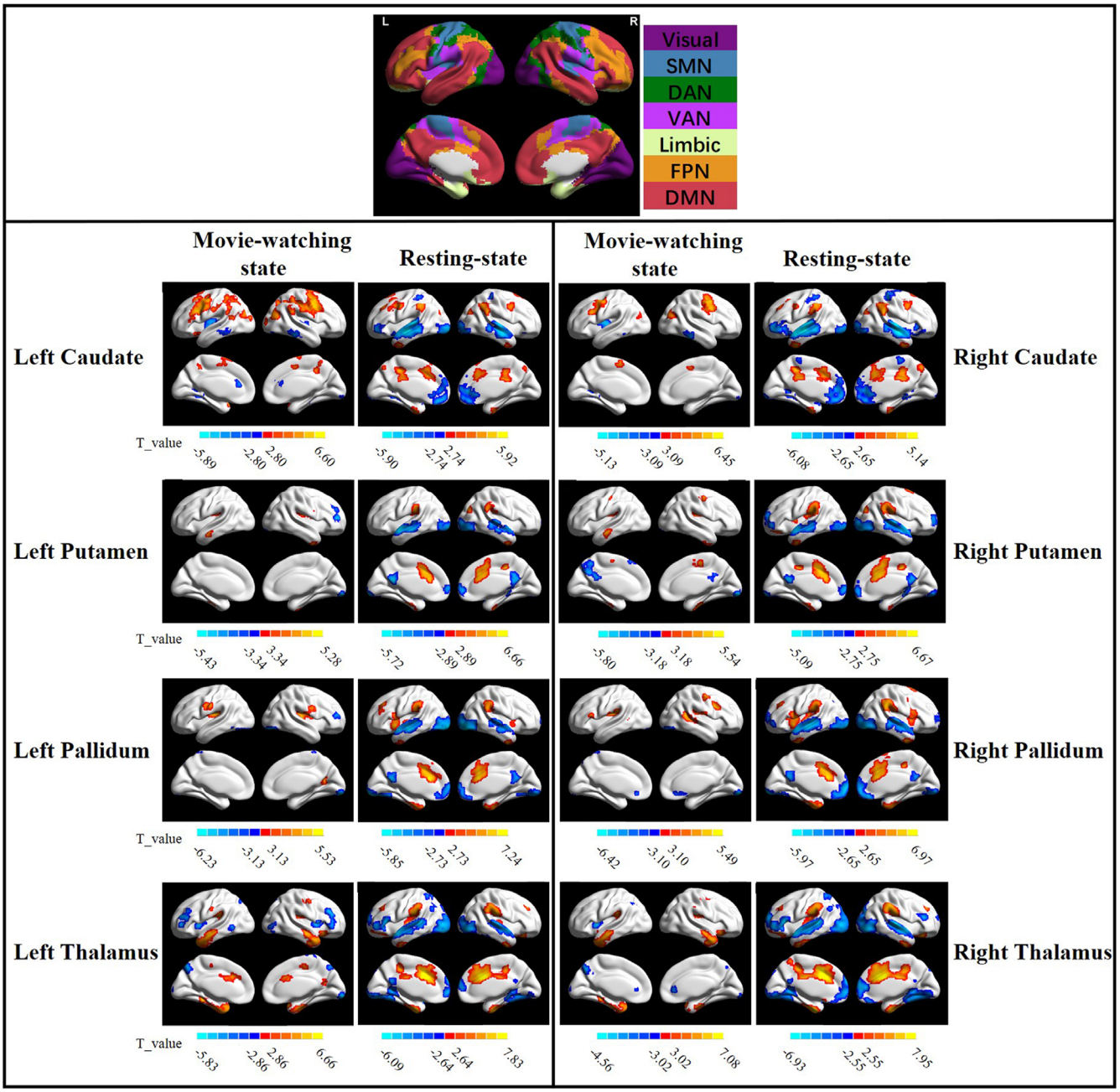

FIGURE 6: Relationships between fluid intelligence and the functional connectivities of the basal ganglia networks with cortical networks in movie-watching and resting states. The results were corrected for multiple comparisons by FDR ($P < 0.05$, cluster size ≥30 voxels). The first and sixth rows are seed regions of ROIs. Warm colors: FCs were positively related to fluid intelligence scores; Cool colors: FCs were negatively related to fluid intelligence scores. SMN: somatomotor network; DAN: dorsal attention network; VAN: ventral attention network; DMN: default mode network; FPN: frontoparietal control network. Color bar represents the T values; ROI: regions of interest.

spatial correlations among them were 0.64–0.95 ($P < 0.005$, Fig. S14). For age^2 beta maps, correlations were 0.46–0.92 ($P < 0.005$, Fig. S15).

Discussion

The aim of this study was to better understand the functional interactions within the subcortical network (including the basal ganglia and the thalamus) and the patterns of the basal ganglia/thalamus linked to the cerebral cortex and cerebellum during movie-watching and resting states across the adult lifespan. The results demonstrated that during the two scanned states, the connectivities of the basal ganglia/thalamus uniformly decreased within a large part of the basal ganglia/thalamus and were increased/decreased with the cerebral cortex and the cerebellum from the ages of 18–88 years.

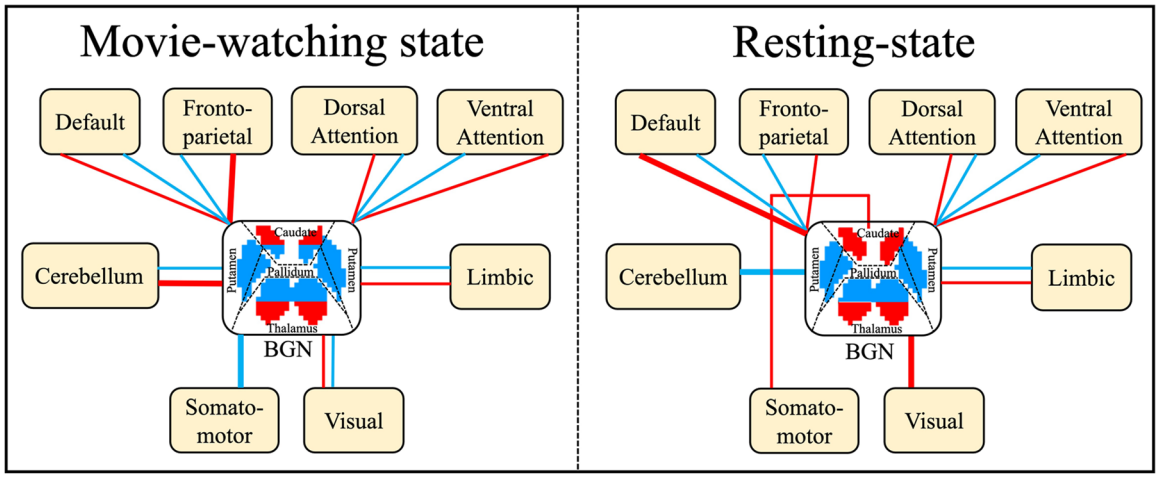

FIGURE 7: Relationships between the basal ganglia/thalamus and other networks in movie-watching and resting states across the lifespan, by summarizing the results from Fig. 2 to Fig. 6. Red lines: FCs were positively related to age; blue lines: FCs were negatively related to age. Bold lines: The voxels of positive (red lines) or negative (blue lines) age-related FCs were ≥ 50% of the total voxels; thin lines: The voxels of positive (red lines) or negative (blue lines) age-related FCs were < 50% of the total voxels.

Moreover, the FCs of the basal ganglia/thalamus in the movie-watching state mainly increased with the FPN with age and decreased with the SMN with age, while the resting-state FC of the basal ganglia and thalamus mainly increased with the DMN and VN and decreased with the cerebellum across the adult lifespan. We also found positive and negative quadratic age trajectories within the basal ganglia/thalamus and from the basal ganglia/thalamus to the cerebral cortical networks and cerebellum. In addition, fluid intelligence was linked to age-related FCs in both cortical and subcortical regions.

Subcortical Networks Change With Age

The caudate and the putamen (which compose the striatum) mainly constitute the input areas of the basal ganglia and receive inputs from a range of cortical and subcortical areas; also, the globus pallidus is the main output station from the basal ganglia[27] and sends outputs to the thalamus.[28] The thalamus receives inputs from the globus pallidus, substantia nigra, cerebral cortex, and cerebellum and sends outputs back to the cortex. The caudate nucleus and the anterior putamen are involved in associative (cognitive) and limbic (motivation and emotion) functions, whereas the posterior putamen is engaged in sensorimotor function.[27] By using precision functional mapping to characterize the functional architecture of the basal ganglia and thalamus in individuals, previous studies showed that the caudate nucleus converges to the DMN and multiple control networks, the ventral intermediate thalamus (motor) converges to the cingulo-opercular control network and SMN, and the pulvinar converges to the DAN and VN.[8,29,30] By combining 18C-fluorodeoxyglucose (FDG) PET and resting-state fMRI, a previous study suggested that there are connections between the caudate and the ipsilateral dorsolateral prefrontal cortex and between the caudate and the contralateral cerebellum (the ipsilateral dorsolateral prefrontal cortex and contralateral cerebellum are part of networks involved in executive and cognitive processes).[31] The globus pallidus supports association (cognition), motor, and motivational functions by composing functional circuits in the basal ganglia and frontal cortical areas. The above studies demonstrated that the basal ganglia and thalamus are integrative hubs involved in cerebello-basal ganglia-thalamo-cortical loops for functional brain networks and are components of networks controlling behavior.

Our study showed that the connectivities within the basal ganglia and thalamus were changed across the adult lifespan in both movie-watching and resting states. We found that as age increased, FC mainly increased within the caudate head and the pulvinar thalamus but mainly decreased within the posterior putamen, globus pallidum, and anterior thalamus. These results indicate that aging may cause structural atrophy and may alter the subcortical functional connectivities such that cognitive and emotional connections strengthened while motor connections weakened with age. Moreover, altered connectivities of the basal ganglia and thalamus were negatively associated with fluid intelligence scores (reflecting frontal and parietal cortical function[32]), which suggested that subcortical networks changed by aging are involved in cognitive performance modulation. These results may support the theory that, as important hubs involved in cortical–subcortical functional networks, the basal ganglia and thalamus are change with age.

Trait Dependence in the Basal Ganglia and Thalamus

By using both ROI- and voxel-based approaches, a previous study[33] explored the relationship between FCs in the basal ganglia/thalamus and the variables related to demographics,

impulsive behavior, self-paced tasks, mood, and motor correlates. The results showed that age was the only correlate of FC in the basal ganglia/thalamus that was consistently significant with both analyses. Moreover, age-dependent differences may be attributed to lower consistency in network organization between states among older adults.[21] The current study showed that with age, the FCs within the basal ganglia and thalamus were similar in movie-watching and resting states. Notably, the main difference between the two states was the FC density in local regions, which suggested that the FCs within the basal ganglia and the thalamus were mainly trait dependent (age) but not state dependent.

State Dependence in Cortical–Subcortical Functional Networks

Previous studies have confirmed that behavioral states could modulate functional connectivities, with results demonstrating striking intersubject synchronization within cerebral cortical networks when individuals were watching a movie.[15,34] Hasson et al observed that not only the visual and auditory areas but also the association and limbic networks were synchronized across individuals watching the same movie.[16] Compared with resting-state FCs, Koskentalo et al reported that FCs in the movie-watching state had higher within- and between-subject correlations, and that interindividual variability in the frontoparietal network FC was highest.[35] They found that resting-state FCs exhibited high intrinsic stability in high-order association networks and low intrinsic stability in primary sensory-motor cortices (eg auditory, somatosensory, visual, and motor regions), while FCs in the movie-watching state showed increased stability in higher-order regions in the ventral and dorsal visual stream and decreased stability in the primary visual cortex. The current study aimed to explore the functional connectivities between cortical and subcortical networks by calculating FCs among eight ROIs (the bilateral caudate, putamen, pallidum, and thalamus) and whole brain voxels. We found that compared with the resting state, movie stimuli modulated connectivity across the adult lifespan, not only between the basal ganglia/thalamus and cortical networks (eg the SMN, VN, FPN and DMN) but also between the basal ganglia/thalamus and the cerebellum. The resting-state FCs of the basal ganglia/thalamus mainly increased with the DMN and VN and decreased in the cerebellum with age, while the FCs of the basal ganglia/thalamus in the movie-watching state mainly increased in the FPN and decreased in the SMN with age. However, the internal basal ganglia and thalamus were relatively stable under the two different states. In addition, age^2-related changes in FCs were identified. The effects of quadratic age on brain function and structure over the adult lifespan have been found in many previous studies.[11,36,37] In our study, for the movie-watching state, we found that positive quadratic (inversed U shaped) age effects on FCs were mainly observed from the left caudate to the left thalamus, limbic network, and VN. For the resting state, positive quadratic (inversed U shaped) age effects on FCs were mainly shown in the putamen/pallidum to the thalamus, SMN, and VN. For the negative quadratic (U shape) age effects on FCs, during the movie-watching state, the thalamus to the SMN and the right putamen/pallidum to the left VAN were noted. For resting-state, negative quadratic (U shape) age effects on FCs were observed in the basal ganglia/thalamus to the putamen, cerebellum, and association networks. Such results showed that there was a difference in quadratic age effects on cortical–subcortical FCs during movie-watching and the resting states. Some of these results were consistent with previous works.[36,38] Moreover, fluid intelligence was positively related to resting-state FCs within the posterior putamen and anterior thalamus and between the basal ganglia/thalamus and cerebellum and negatively related to resting-state FCs between the basal ganglia/thalamus and SMN/VN. However, no significant relationship was found in FCs in the movie-watching state, which further indicated that fluid intelligence-related sensory-motor networks change with state. It perhaps implied that free movie-watching could modulate internetwork connectivity of cortical–subcortical regions, while internetworks of subcortical areas may be mainly affected by trait-dependent factors (e.g., age) in healthy aging. Hence, we argue that both traits and states should be considered when studying the functional organization of the cerebello-basal ganglia-thalamo-cortical loops. We support the idea that studying individual variability in functional connectivity during a wider range of mental states may provide a more complete picture of the mechanisms of aging.[39]

Age as an Important Trait for Functional Mapping

Previous studies have confirmed that aging impacts FCs both within and between the different networks in the brain.[19] In the resting state, cortical association networks exhibit greater age-accompanied decreases in segregation compared with sensory input and motor output. For instance, FCs in the DMN and FPN were significantly decreased with age, while FCs in the SMN and VN increased with age.[19] For cortical–subcortical studies, resting-state FCs within the basal ganglia,[33] between the pallidum/putamen and DMN,[40] and between the pallidum/posterior putamen and somatomotor cortex[40] were significantly decreased with age. The connectivities between the caudate head and a large area of the ventromedial prefrontal/medial orbitofrontal cortex increased with age.[40]

It has also been shown that age influences intersubject synchronization and, older adults exhibited decreased intersubject synchrony than younger adults.[15] In addition, reductions in synchrony are associated with regionally distinct temporal profiles and FC patterns; pertinently, higher synchrony with age was associated with stronger connectivities

within the FPN and the DAN, as well as between the FPN and the DAN, between the VN and DAN, and between the FPN and the VN.[22] Compared with resting-state FCs, the current study found that connectivities between the basal ganglia/thalamus and primary networks (i.e. SMN and VN) and between the basal ganglia/thalamus and the DMN in the movie-watching state decreased with age. Conversely, the connectivities between the basal ganglia/thalamus and the FPN and between the basal ganglia/thalamus and prefrontal projection of cerebellum (i.e. Cerebellum_Crus1 and Cerebellum_Crus2) in the movie-watching state increased with age. Also, our results added to evidence that age-related synchronization strengthened frontal connections. Furthermore, we found that the connectivities within the basal ganglia/thalamus, between the basal ganglia/thalamus and the DAN, between the basal ganglia/thalamus and the VAN and between the basal ganglia/thalamus and the limbic network exhibited variability across the lifespan in both the movie-watching and resting states, which was consistent with the idea of age-related functional dedifferentiation.

Fluid intelligence, which has been defined as the ability to think logically and solve problems, lies at the core of psychometric analyses of intelligence, predicts real-world outcomes (eg life expectancy, expected income and work performance), and correlates highly with tests that assess successful day-to-day functioning in society (eg the Basic Skills Test). Functional neuroimaging studies have demonstrated that participants with higher fluid intelligence scores had greater event-related neural activity in the lateral prefrontal and parietal regions of the cerebral cortex, as well as fluid intelligence loss linked to damage in the posterolateral frontal, dorsomedial frontal, and mid-parietal cortex.[32] In our study, the fluid intelligence scores were negatively correlated with age in the lifespan, while they were positively associated with both movie- and resting-state FCs mainly between the caudate and the FPN and were negatively associated with both movie- and resting-state FCs mainly within the pulvinar thalamus and between the caudate and DMN. Because the caudate nucleus converges to the DMN and multiple control network, and the pulvinar converges to the DAN and VN,[8] these results provide further evidence for age being an important trait for functional mapping.

Limitations

First, given that our study involved a cross-sectional sample, we observed age differences that may be due to cohort differences within our sample. These effects were reduced by including education, sex, volume, and head motion as covariates in all analyses. However, determining the true effect of age on network responsivity requires further longitudinal studies. Second, behavioral data were relatively insufficient. Further research should involve more behavioral data to reveal more detailed relationships between FCs and cognitive functions, including working memory, motor ability, and emotion recognition. Third, we used head motion exclusion criterion (mFD >0.5 mm), which might reduce specificity of FC biomarkers. In this study, to decrease the effect of motion, mFD was added as a covariate in the statistical models. Fourth, the GLM was used to model lifespan trajectories of age as either linear or quadratic relationships. The first- and second-order polynomial models may not capture more complex nonlinear trajectories across the lifespan, and it would be useful to explore other modeling options, such as nonparametric or deep learning methods. In addition, because a GLM only generated a whole brain *T*-value map for each state, the difference between two states in FC changes with age was explored by contrasting two *T*-value maps. Fifth, given the superiority of electroencephalography (EEG) with high temporal resolution for noninvasive and direct detection of brain activity on the scalp, EEG data are needed to further study the changes in brain network synchrony in the movie-watching state across the adult lifespan.

Conclusion

This study involved a cross-sectional sample and showed that brain cortical–subcortical functional networks showed both trait and state dependent changes across the adult lifespan. In general, the connectivities of the basal ganglia/thalamus within the basal ganglia/thalamus showed more trait dependent changes in aging, connectivities of the basal ganglia/thalamus to the cerebellum showed more state dependent changes in aging, and connectivities of the basal ganglia/thalamus to the cortical networks showed both trait- and state-dependent changes across the adult lifespan. These results build on an emerging body of evidence suggesting that functional imaging studies may consider the effects of both physiological characteristics and individual situations.

Author Contributions

Li Dong conceived the project. Ziqi Wang wrote the original draft. Jie Yang, Zihao Zheng, Ziqi Wang, Hechun Li, Xin Wen, and Li Dong performed the experiments and the statistical analysis. Ziqi Wang, Jie Yang, Weifang Cao, Li Dong, and Dezhong Yao wrote and revised the paper. Cheng Luo, Qingyan Cai, and Wei Jian provided critical suggestions for the manuscript.

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Conflict of Interest

All authors have no conflicts of interest to disclose.

Data Availability Statement

The datasets [CamCAN] for this study can be found in the Cambridge Centre for Aging Neuroscience (http://www.cam-can.org/).

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