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Original Article

Vascular feature as a modulator of the aging brain

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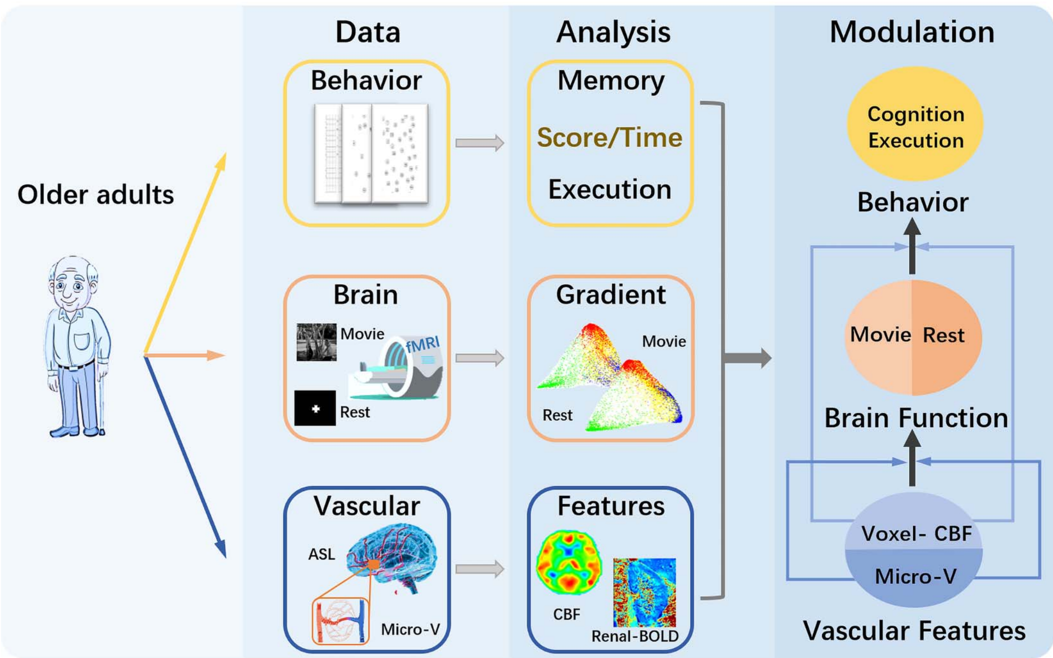
Abstract

The cerebral functional reorganization and declined cognitive function of aging might associate with altered vascular features. Here, we explored the altered cerebral hierarchical functional network of 2 conditions (task-free and naturalistic stimuli) in older adults and its relationship with vascular features (systemic microvascular and perfusion features, measured by magnetic resonance imaging) and behavior. Using cerebral gradient analysis, we found that compressive gradient of resting-state mainly located on the primary sensory-motor system and transmodal regions in aging, and further compress in these regions under the continuous naturalistic stimuli. Combining cerebral functional gradient, vascular features, and cognitive performance, the more compressive gradient in the resting-state, the worse vascular state, the lower cognitive function in older adults. Further modulation analysis demonstrated that both vascular features can regulate the relationship between gradient scores in the insula and behavior. Interestingly, systemic microvascular oxygenation also can modulate the relationship between cerebral gradient and cerebral perfusion. Furthermore, the less alteration of the compressive gradient with naturalistic stimuli came with lower cognitive function. Our findings demonstrated that the altered cerebral hierarchical functional structure in aging was linked with changed vascular features and behavior, offering a new framework for studying the physiological mechanism of functional connectivity in aging.

Graphical Abstract



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Significance statements

1) This is the first time to investigate the relationship among the cerebral functional gradient (movie-watching and resting-state), vascular features (noninvasive systemic microvascular and cerebral perfusion), and cognitive performance in aging.
2) Older adults showed the compressive gradient in the primary sensory-motor system and transmodal regions in aging and enhanced compression during movie-watching.
3) Systemic microvascular regulated not only the relationship between cerebral function and performance but also the relationship between perfusion and cerebral function in aging.

Key words: hierarchical functional connectivity networks; gradient analysis; aging; naturalistic stimuli; systemic micro-vascular feature.

Introduction

Aging is considered as an inexorable process of lifespan and brain aging is one of the major risk factors in dementia and neurodegenerative diseases (Niccoli and Partridge 2012; Bubbico et al. 2019). Healthy brain aging is a natural phenomenon characterized by degradation of the regional structure (such as slightly reduced gray matter volume and thinned cortical thickness) and function (altered functional connectivity and graph property) together with cognitive decline (declined memory and attention, reduced execution function) (Hedden and Gabrieli 2004; Whalley et al. 2004; Song et al. 2014; Chen et al. 2019). Up to now, a collection of functional magnetic resonance imaging (fMRI) studies based on blood oxygenation level-dependent (BOLD) focused on the alteration of cerebral functional connectivity in aging and its relationship with behavior (Tomasi and Volkow 2012; Chan et al. 2014; Petrican et al. 2017). However, aging is also accompanied by the decreased function of multisystems, such as vascular aging and declined kidney function. The kidney function (without kidney diseases) is a good indicator of vascular aging (Darsie et al. 2014). The study of healthy older adults found that poor kidney function accompanied by worsening cognitive function, speculating the altered cerebral function caused by systemic microvascular aging may influence the association between kidney function and cognitive function (Darsie et al. 2014). A few studies explored the effect of vascular factors on cerebral function and behavior (Li et al. 2019; Tsvetanov, Henson, Jones, et al. 2021). For example, a previous study showed that age-related resting-state fluctuation amplitudes were mediated by cardiovascular health and associated with the measures of neurovascular coupling (Tsvetanov, Henson, Jones, et al. 2021). Our previous study proved that systemic microvascular oxygenation (renal BOLD imaging) of healthy older adults was linked with cerebral functional connectivity (Li et al. 2019). Moreover, it has been demonstrated that cerebral perfusion was associated with functional connectivity and behavior (Liang et al. 2013). Thus, integrating the microvascular factor and perfusion to the models of successful aging can better understand the physiological mechanism of aging (Tsvetanov, Henson, et al. 2021). However, the relationship among cerebral functional connectivity, vascular (especial systemic microvascular) features and cognitive performance in aging is still vague.

Based on the above, we hypothesized that (1) the vascular feature is associated with the cognitive performance apart from cerebral function; (2) the vascular feature played the modulator on the relationship between the cerebral functional measures and cognitive performance; (3) microvascular feature could regulate the association between cerebral perfusion and cerebral functional measures/behavior. But actually, both the cognitive function and vascular function have the rich functional reserve in healthy adults (Stern 2009; Davenport et al. 2012). According to the view of the functional reserve, the behavior and vascular function should be independent in younger adults. Thus, to verify these hypotheses, aging is the appropriate condition due to the aging is a critical state accompanied by vascular aging rather than the pathological state.

In the current study, we used correlation and modulation analysis to explore the relationship among vascular features, cerebral functional connectivity, and cognitive performance and to evaluate the influence of vascular features on the association between the latter two. For vascular features, 2 indexes included systemic microvascular oxygenation and cerebral perfusion were brought. Microvascular oxygenation was presented by peripheral small vessel feature (renal medullary spin–spin relaxation rates R2* (MR2*)) as our previous study (Li et al. 2019). And the cerebral perfusion (cerebral blood flow, CBF) was described by the arterial spin labeling (ASL). For cognitive evaluation, memory (auditory verbal learning test, AVLT) and execution function (Trail Making Test, TMT) were collected. For the brain, the functional measures included 2 levels: task-free (resting-state) and naturalistic stimuli (movie-watching). And the cerebral functional patterns were analyzed using the gradient analysis, which can describe the macro cerebral hierarchical architecture and obtain the key characteristics of how sensorimotor and high-level networks assemble together and interact in aging (Margulies et al. 2016; Bethlehem et al. 2020).

Materials and methods

Participants

The current study recruited 95 older healthy adults (66.94 ± 7.23 years old) and 44 younger controls (21.8 ± 2.53 years old). All participants were right-handed. The Montreal Cognitive Assessment (MoCA) and Activity of Daily Living Scale (ADL) were used to screen older adults. The subjects with MoCA score > 25 and ADL score < 23 were viewed as the normal cognition and were included in the current study (Supplementary Table S1). Other exclusion criteria included: any psychiatric or neurological disorders, brain injury, diabetes, or hypertension; and years of education < 6. The same criteria were applied to the younger subjects. None of them had MRI contraindications. This study was approved by the local Ethics Committee of University of Electronic Science and Technology of China and all participants signed the informed consent forms.

Experiment design and behavior evaluation

All subjects participated in the MRI scan for the brain and kidney to acquire the cerebral and renal BOLD features. Before MRI scanning, each subject was asked to fast (solids and liquids) for approximately 12 h. The body indices (weight, height, and blood pressure) were measured on the morning of the scan, and then BOLD-fMRI scanning of the brain and kidney was performed. For the kidney, the multiecho BOLD-fMRI images were acquired. For the brain, when the subjects were conducted to close the eyes but remain awake and not move the head, the scan was performed and considered as resting-state fMRI. And the high-resolution T1-weighted image was also collected for each participant. Moreover, 52 of 95 older adults were performed an additional naturalistic stimuli fMRI scan, when the participants were asked to watch a black-and-white television drama ("*Bang! You're Dead*," which has been used to elicit neural synchronization, detailed information about this drama was shown in the Supplementary materials) (Hasson et al. 2010; Geerligs et al. 2018). In addition, these participants also underwent the ASL sequence to obtain the CBF. For behavior, memory and executive function tests were included in the study. However, only half of the older adults (41 subjects) accepted the evolution of AVLT for memory and TMT (include parts A and B) for execution. The TMT is a well-established test that sensitive to impairment in multiple cognitive domains (Kortte et al. 2002). The AVLT (evaluate learning and memory) and trail making test part B (TMT-B; detect the executive function, specifically flexibility performance (Oosterman et al. 2010)) are useful in detecting the changed cognitive function in aging. The brain fMRI (resting-state and movie-watching state), brain structure, ASL data, and renal fMRI were collected. The detailed parameters were displayed in the Supplementary materials. The pipeline of the whole analysis was shown in Figure 1.

Vascular features evaluation

The renal medullary oxygenation was measured to evaluate the systemic microvascular feature. The MR2* value was obtained from the average R2* value of regions of interest (ROIs) in the renal medulla, which can reflect the oxygenation of the microvessel. And the higher MR2* value represents poorer renal oxygenation and serious microvascular aging. The cerebral perfusion was evaluated by the CBF. For detailed calculation of MR2*/CBF, see Supplementary materials.

Cerebral fMRI data preprocessing

Before the preprocessing, we first checked the anatomical images of each participant to exclude the subjects with obvious brain structural lesion. The preprocessing of cerebral fMRI data included discarded first 5 volumes, slice-time corrected, realignment, and normalization with DARTEL. Then, the irrelevant signals which included the 24 head motion parameters, linear trend, white matter signal, CSF (CompCor, 5 principal components) (Behzadi et al. 2007), and global mean signals were regressed. Finally, a band-pass filter (0.01–0.1 Hz) was applied. All preprocessing steps were performed using the Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI v5.1) (Yan et al. 2016) and NIT toolboxes (Dong et al. 2018).

Cerebral connectivity gradient analysis

Connectivity gradient analysis was used to describe the topographic organization of the cerebral cortex and to capture a functional spectrum from the primary sensory regions to the transmodal areas. The connectivity gradient resulting from diffusion map embedding can account for the respective positions across the cerebral functional networks based on connection similarity (Margulies et al. 2016; Dong, Luo, et al. 2020; Dong, Yao, et al. 2020). In this study, we calculated the cortical functional gradient to detect the gradient distribution in different groups and different conditions.

For computational efficiency, the fMRI data (resting-state and movie-watching) was down-sampled to 5 mm isotropic voxels. All subjects were put together to perform the gradient analysis. First, the FC matrix based on the voxels of each subject was obtained and Fisher's-Z-transformation was performed. The matrix was threshold by retaining the top 10% of connections per row while the remainder was set as 0 (Margulies et al. 2016; Guell et al. 2018). Then, the cosine distance between each pair of voxels was calculated to estimate the similarity of the connectivity pattern. Next, we performed a nonlinear dimensionality reduction technique—diffusion map embedding, which can discern low-dimensional embedding from high-dimensional connectivity data. This approach used descending order to identify the principal gradient component accounting for the connectivity variance in an embedding space. In this space, the cortical points are closer together if they are strongly interconnected by either many connections

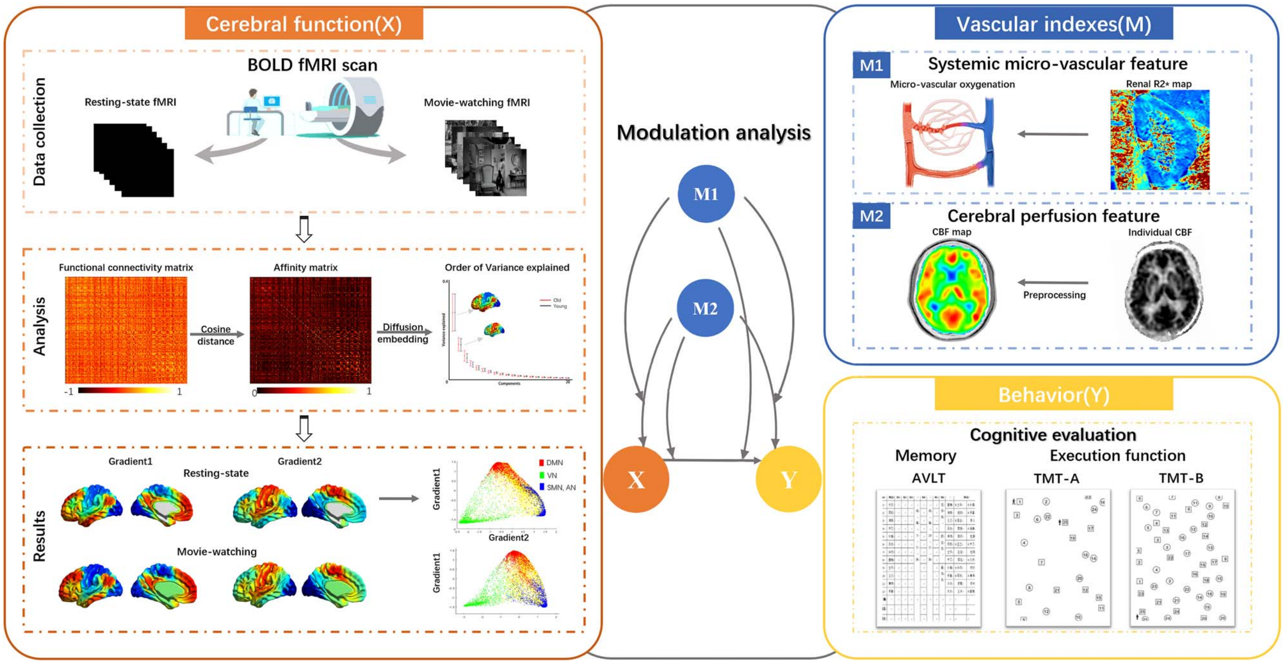

Fig. 1. The pipeline of the whole calculation. The left block diagram showed the flow of cerebral gradient analysis; the upper right block diagram displayed 2 vascular features (systemic microvascular feature (MR2*) and CBF); the low right block diagram represented the types of cognitive evaluation. In the modulation analysis, the vascular index was used as a modulator (M1(MR2*)/M2(CBF)), the cerebral function pattern (gradient) as the independent variable (*X*), and the behavior as the dependent variable (*Y*).

or few notably strong connections, and otherwise, points are farther apart if they have less or no connectivity with each other (Margulies et al. 2016). The resultant components of diffusion embedding are the "gradients," which are unitless and represent the similarity of each point's functional connections along the embedding space (Dong, Luo, et al. 2020; Dong, Yao, et al. 2020). Thus, the altered gradient scores in aging reflect the departure extent relative to the younger group. To compare 2 groups, the average connectivity matrix was calculated across all participants to generate a group-level gradient component template by using resting-state data. The Procrustes rotation was performed to align the gradients of the individual to this average template (Margulies et al. 2016; Guell et al. 2018). The movie-watching data were also aligned to this template (Fig. 1). And the Z-normalized (subtract mean value and then divide standard deviation) was performed on all individual gradient map. Then, spatial smoothing with 8 mm was performed for each gradient map. In the current study, we focused on the first component. To compare the difference in the 2 groups, the two-sample *t*-test was applied among the principal gradient with gender as the covariate. To obtain the altered connectivity gradient under the movie-watching condition, the paired *t*-test was applied between movie-watching and resting-state. All of the comparison results were corrected for the false discovery rate (FDR, $P < 0.05$) of multiple comparisons.

Cerebral function–vascular–behavior correlation analysis

According to the comparison results of 2 groups (older and younger group), the gradient scores of several ROIs were extracted. To detect the relationship between the connectivity and vascular features, the gradient scores of ROIs were correlated to the renal MR2* values/CBF of ROIs with gender as the covariate. In addition, the Pearson's correlations between the gradient scores of ROIs and the AVLT/TMT-A/TMT-B scores in the elderly group were also performed to explore the association of functional connectivity and cognitive performance. The same correlation steps were applied on the difference values of 2 states (gradient scores of movie-watching subtract of resting-state). Next, to investigate the relationship between vascular features and cognitive performance, the Pearson's correlation between the renal MR2* values/CBF of ROIs and AVLT/TMT-A/TMT-B scores were calculated. The larger AVLT scores and the lower TMT scores represent the better cognitive function. The education years and gender as the covariates.

Cerebral function–vascular–behavior moderation analysis

If there were any significant correlations between functional connectivity and cognitive performances were found, the moderation analysis would be employed to explore the influence of vascular features on the relationship between connectivity patterns and cognitive performance. The moderation analysis was completed by SPSS (Process 3.0) according to the multilinear regression model (Hayes and Rockwood 2017). Where the cognitive scores as the dependent variables (Y), gradient scores as the independent variables (X), the education years, and gender as the covariates. And MR2*/CBF was viewed as a moderator (M) in the model.

Control analysis

Control analyses were performed to ensure the robustness of the main findings. (1) The influence of data processing: the gradient analysis was repeated based on the brain fMRI data with resampling to 6 mm or without regress global signal. (2) To exclude the influence of gender difference in the aging brain: compare cerebral functional gradient between female and male in older adults. (3) To avoid the random chance for correlation analysis and moderation analysis: permutation test with 10,000 iterations (detailed information, see Supplementary material).

Results

Systemic microvascular features

According to the renal BOLD-fMRI, the mean MR2* value was 39.63 ± 3.63 in the older adults, and 36.37 ± 2.39 in the younger group (Supplementary Fig. 1). Comparative results suggested that the higher MR2* value of the older adults than of the younger group ($P < 0.001$). The higher MR2* value represents more hypoxia in the renal medulla, which reflects the microvascular oxygenation. Thus, the older adults with higher MR2* implied worse systemic microvascular oxygenation.

Cerebral functional gradients under resting-state

To maximize interpretability, only the first gradient was used in the follow-up analyses. The first gradient (also called principal gradient), which explained as much of variance in the data as possible, showed a similar spatial distribution and similar variance explained across gradients in the elderly and younger groups (Supplementary Fig. 2). The principal gradient displayed a bipolar distribution with primary sensory-motor systems (PSS) on one pole, and default mode network (DMN) areas on another pole, and the intermediary networks distributed between 2 poles, which represents the unimodal-to-transmodal organizational pattern in the cerebral cortex (Supplementary Fig. 2). Moreover, the older adults showed decreased gradient scores mainly located on the DMN and frontal cortex compared with the younger adults. And the increased gradient scores were found in the sensorimotor network, auditory network, and visual network. (Fig. 2A). Interestingly, the older adults appeared to tend to 0 (represent tend to average) regardless of increased or decreased gradient scores, which suggested the old adults exist the global compressive gradient.

Cerebral functional gradients under the movie-watching condition

Compared to the resting-state, the paired t-test showed the significant changed cerebral connectivity pattern under the movie-watching condition in the older adults (Fig. 2B), which is similar to the comparative results of the 2 groups. Specifically, the old adults showed the increased gradient score in PSS included visual network, auditory network, and sensorimotor network in the movie-watching state compared to the resting-state. And decreased gradient scores mainly located on the dorsal attention network (DAN) and part of the frontoparietal network and DMN.

Cerebral function–vascular–behavior correlation

A significant negative correlation was found between AVLT scores and MR2* values ($r = -0.44$, $P = 0.004$), and a significant positive correlation was found between TMT-B scores and MR2* values ($r = 0.33$, $P = 0.038$) (Fig. 3). These findings suggested that the declined cognitive function aggravated with worse systemic microvascular oxygenation in older adults. No significant correlation was found between TMT-A and MR2*/gradient scores.

Fourteen ROIs were selected according to the differences between the 2 groups. On the one hand, the MR2* values positive were correlated with the gradient scores in the bilateral insula (left insula: $r = 0.24$, $P = 0.019$; right insula: $r = 0.22$, $P = 0.035$ (Supplementary Fig. 3A)) in older adults, and these relationships were not found in the younger group. On the other hand, the significant positive correlations between TMT-B score and gradient score in bilateral insula (left insula: $r = 0.36$, $P = 0.021$, right insula: $r = 0.34$, $P = 0.032$ (Supplementary Fig. 3B)) were also found. And the gradient scores in bilateral angular gyri (left angular: $r = -0.35$ $P = 0.027$, right angular: $r = -0.35$, $P = 0.027$ (Supplementary Fig. 3B)) were negative correlated with TMT-B scores. Noted, the older adults showed increased gradient scores in the bilateral insula (trends to average) and decreased gradient scores in bilateral angular gyri (trends to average). Thus, these correlations showed that the more compressive gradient of resting-state in older adults accompanied with worse cognition and systemic microvascular oxygenation. In addition, only the significant positive correlations between CBF and gradient scores of resting-state in the bilateral insula (left insula: $r = 0.37$, $P = 0.016$; right insula: $r = 0.35$, $P = 0.023$ (Supplementary Fig. 3C)) were observed. The correlation between the CBF and renal BOLD feature/cognitive performance was not found.

Based on comparison results between 2 states, 10 ROIs were obtained. And the difference gradient scores in bilateral insula (right insula: $r = -0.33$, $P = 0.038$; left insula: $r = -0.42$, $P = 0.006$ (Supplementary Fig. 3D)) and in left angular ($r = 0.42$, $P = 0.007$ (Supplementary Fig. 3D)) were significant correlated with TMT-B scores. No significant correlation between difference gradient scores and MR2* was found. Therefore, the less compressive gradient came with the worse cognitive function under the higher cognitive load. The altered gradient score caused by the naturalistic stimuli in the right insula was negatively related to the CBF ($r = -0.42$, $P = 0.006$, Supplementary Fig. 3E).

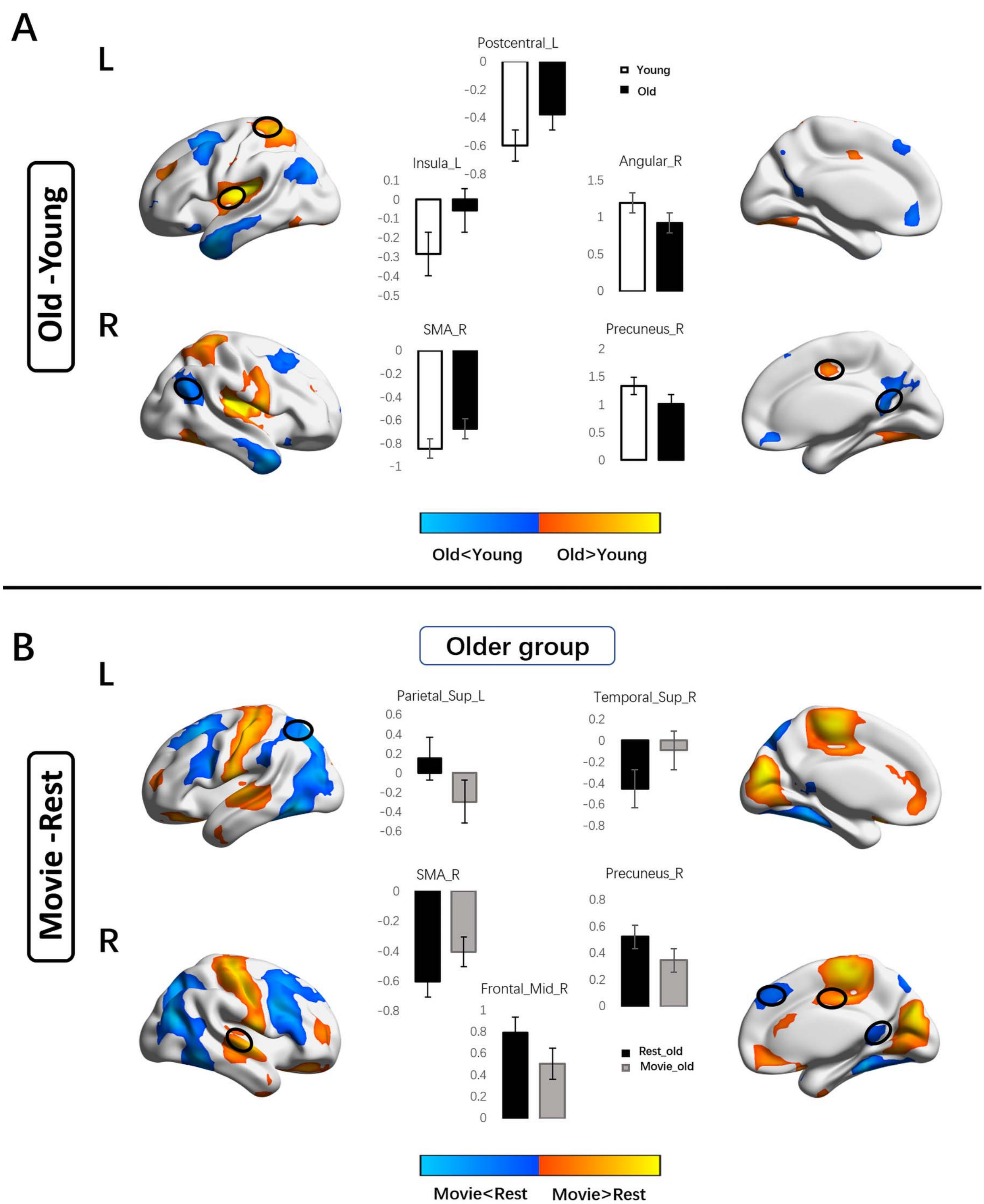

Fig. 2. The comparative results of cerebral connectivity gradient mapping between 2 groups (older and younger groups)/2 states (movie-watching and resting-state) in older adults. (A) The different connectivity gradient scores between older and younger adults. The increased/decreased gradient scores in older adults were displayed in red/blue color (FDR correction, $P < 0.05$). (B) The comparisons between movie-watching state and resting-state in older adults. The red/blue color represented the movie-watching state showed increased/decreased gradient compare to the resting-state (FDR correction, $P < 0.05$). The comparison in regions with black circle was also presented by bar chart. (white bar: younger group, black bar: older adults in resting-state, gray bar: older adults under the movie-watching condition).

Cerebral function–vascular–behavior moderation effect

According to the above results of correlation, the moderation analyses were performed. In the resting-state, the renal MR2* showed a significant moderation effect on the relationship between the TMT-B scores and gradient scores in the left mid-posterior insula ($P = 0.031$) (Fig. 4A, Supplementary Table S2). and this relationship was also regulated by the CBF in the left insula ($P = 0.018$, Supplementary Fig. 4A and Table S3). In detail, the positive correlation between gradient scores in the left mid-posterior insula and TMT-B becomes weaker

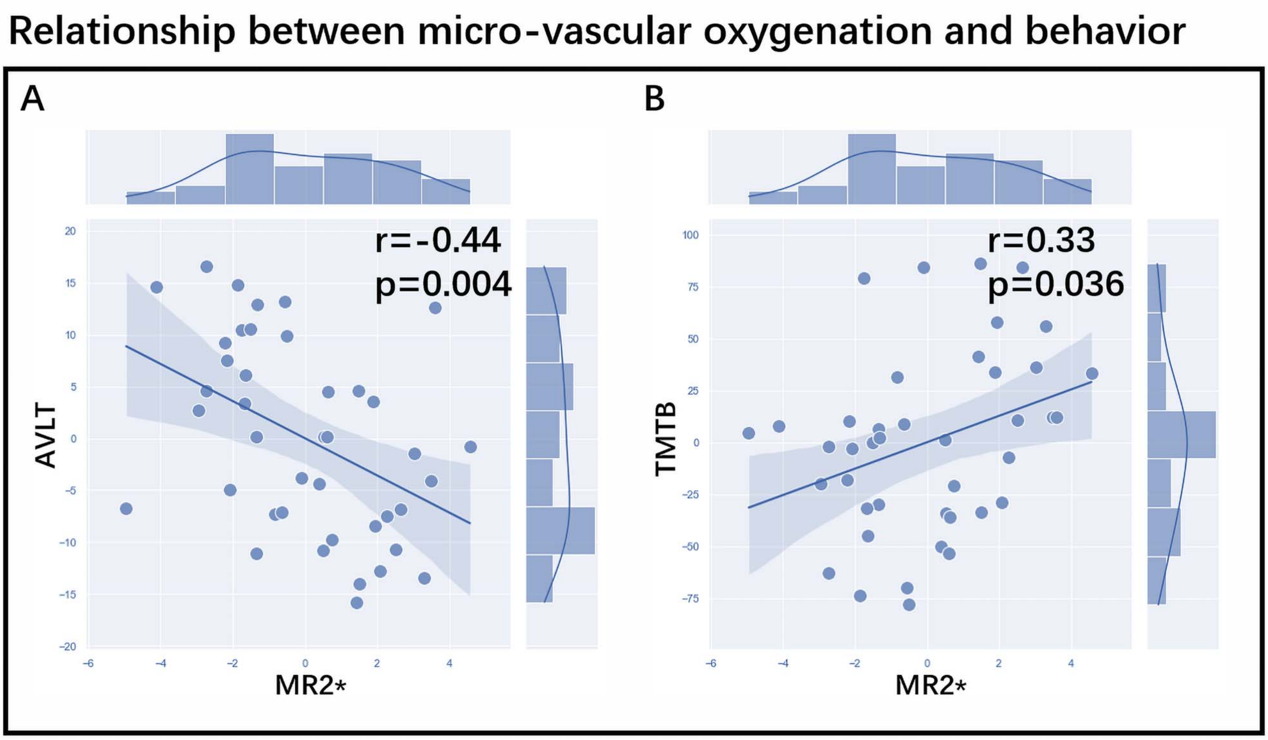

Fig. 3. The correlations between the microvascular oxygenation and cognitive performances. (A) The significant negative correlation between scores of AVLT and the MR2* value. (B) The significant positive correlation between scores of TMT-B and the MR2* value.

as MR2* increased/CBF decreased, which means the worse systemic microvascular oxygenation and cerebral perfusion disrupted the relationship between the cerebral functional connectivity and cognitive performance. Interestingly, additional analysis showed the renal MR2* also regulated the relationship between CBF and gradient scores of resting-state in the left mid-posterior insula ($P = 0.039$, Supplementary Fig. 5 and Table S4), that is the relationship between CBF and cerebral functional connectivity become stronger as systemic microvascular oxygenation decreased. Besides, the significant moderating effect of systemic microvascular features (MR2*: $P = 0.028$, Fig. 4B and Supplementary Table S5; CBF: $P = 0.016$, Supplementary Fig. 4B and Table S6) on the TMT-B scores and difference gradient scores (gradient scores of movie-watching subtract of resting-state) in the right mid-posterior insula was also found, that is the relationship between changed gradient scores in the right mid-posterior insula and TMT-B becomes weaker as vascular features decreased.

Control analyses

Control analyses found the voxels' size and without regress global signal regress did not significantly affect trends of overall results (gradient analyses) (Supplementary Figs 6 and 7). Additionally, no significant difference was found in cerebral functional gradient between female and male in older group of our dataset. The permutation test illustrated that the results of correlation and moderation were meaningful, which ensured robustness of main results, see Supplementary Table S7 supplementary results for details.

Discussion

The present study illustrated the relationship among the cerebral function, vascular and cognitive performance, which is the first study that utilized these 3 to explore the mechanism of functional connectivity in healthy aging. For the brain, consistent with previous studies (Margulies et al. 2016), gradient analysis showed that the primary sensory systems distributed on 2 poles of the axis on the bottom end, and the DMN distributed on the top end whereas other networks in-between in both groups. In the elderly group, we found the compression principal gradient between the PSS and DMN (a shorter functional distance). Interestingly, older adults showed the more compressed principal gradient under the movie-watching state than resting-state. These findings suggested the compression of the cerebral functional gradient in older adults, and this compressed phenomenon will aggrandize when the old adults are exposed to extra stimulation. The correlation results showed that the increased cerebral functional compression of resting-state in the PSS (bilateral insula) was aggravated by declined systemic microvascular feature, and the compressed gradient in the PSS and DMN was associated with declined cognition. In addition, in these regions, we also found that the altered compression gradient caused by continuous naturalistic stimuli was linked with lower cognitive function. Further moderation

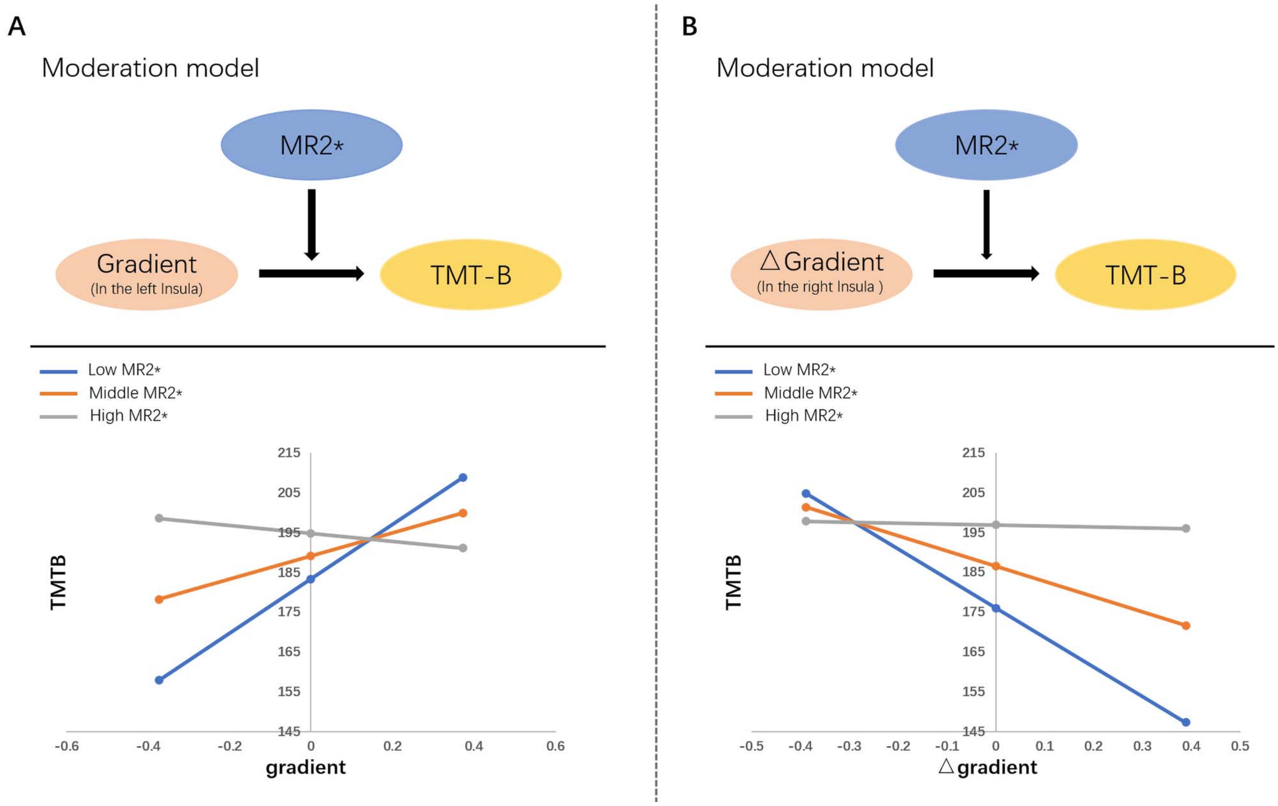

Fig. 4. The moderation model and results in the insula. The top: The moderator model to detect the effect of systemic microvascular feature (MR2*) on the relationship between functional measures (gradient scores/altered gradient scores (caused by the naturalistic stimuli)) and cognitive performance; the bottom: the significant moderation effect of MR2* on relationship between gradient scores (A)/altered gradient scores (B) in the insula and TMTB scores (interaction factor (gradient × MR2*): $P = 0.031/P = 0.028$). The blue/red/gray line represented under the low/middle/high level MR2* condition.

analyses suggested that the vascular features (both systemic microvascular and perfusion features) regulated the relationship between insular functional gradient scores and cognitive performance. Taken together, these findings implied the vascular state parameter played an important role on successful aging.

Age-related cerebral functional gradient and its relationship with behavior

Recently, gradient analysis provides a new global perspective to evaluate the hierarchical functional organization of the human brain. The gradient analysis, based on the differentiation of connectivity patterns, can explain the respective positions of cerebral networks (Margulies et al. 2016; Dong, Luo, et al. 2020; Dong, Yao, et al. 2020). In this study, this tool was adopted to uncover the cerebral functional integration between continuous naturalistic stimuli and task-free state in aging. The main change in the principal gradient compression in the resting-state was observed in the unimodal and transmodal regions in aging, suggesting dedifferentiation among the crucial cortical networks with aging (Hong et al. 2019). In addition, the more compressive gradient was also observed under the naturalistic stimuli whether in the older group or younger adults (Supplementary Fig. 8), which implied that the brain needs to reduce the functional distance between networks to mobilize more cognitive resources. Thus, these findings reflected compensation of cerebral functional integration in task-free and the flexibility of compensation linked to the cognitive loads with the extra stimulation in aging.

DMN regions are considered as the hubs (Sepulcre 2014; Pretus et al. 2019) and the top end of the hierarchical structure in the human brain (Margulies et al. 2016). Previous studies (Geerligs et al. 2015; Cao et al. 2016) focused on the DMN because it plays a crucial role in the neurobiological changes of dementia (Sala-Llonch et al. 2015). A great majority of aging-related researches have reported reduced FC within the DMN (Tomasi and Volkow 2012; Song et al. 2014) and these reductions were associated with cognitive performance (Andrewshanna et al. 2007; Damoiseaux et al. 2007; Onoda et al. 2012; Geerligs et al. 2015; Tsvetanov et al. 2016). In addition, researchers pointed out that the altered connectivity of DMN in normal aging was also associated with the amyloid-β and tau, which might relate to AD-pathology (Sepulcre et al. 2017; Franzmeier et al. 2019). And the changed connectivity within DMN precedes the manifestation of cognitive decline by years (Sepulcre et al. 2017). In the current study, the compressive gradient in the DMN regions was discovered in older adults and these compressions were associated with declined cognitive performance, suggesting a triggered role of the DMN in the changed cortical organization during aging. Furthermore, the DMN would reduce activation during the tasks that need high attentional load. The naturalistic stimuli involve the interaction of multiple cognitive functions (e.g. attention control, episodic memory, recall) (Geerligs et al. 2018). A previous study demonstrated that the DMN was suppressed during the movie-watching (Deng et al. 2019). Consistent with these findings, the compressive gradient in DMN was found in naturalistic stimuli. And the relationship between the altered gradient scores in DMN and cognitive performance suggested that humans can utilize more cognitive resources accompanied with better cognitive performance. In addition, altered connectivity within and between frontoparietal network and DAN have been found under the naturalistic stimuli condition (Shulman and Corbetta 2012; Geerligs et al. 2018). In line with the established role of DAN in attention (Rohr et al. 2018), present study also observed the decreased gradient in DAN under the naturalistic stimuli. These results further demonstrated that the compressive gradient in transmodal regions in older adults probably for response to high task load.

With aging, the PSS exhibited a more dedifferentiated attribute. For instance, researchers observed increased long-range functional connectivity with aging in the PSS (Tomasi and Volkow 2012). Sensorimotor systems also showed increased connections with attention networks and task-control networks with aging and our previous studies also reported increased FC in the sensorimotor network in older adults (Song et al. 2012, 2014; Tomasi and Volkow 2012; Li et al. 2019). The latest gradient study also found that the visual network became less differentiated from other networks with aging (Bethlehem et al. 2020). Consistent with these findings, this study also found that the older adults showed higher gradient scores in the PSS. Therefore, we presumed that the PSS might reflect a potential compensation for hubs in older adults. In addition, the more compression in the PSS accompanied with worse cognition, which further demonstrated the importance of PSS in aging. The increased gradient scores in PSS were also found under the naturalistic stimuli, which is consistent with previous results that increased inter- and intra-network connectivity were observed in the visual, auditory, and sensorimotor network (Lynch et al. 2018; Demirtas et al. 2019). However, combined the comparative resting-state results of 2 groups, we speculated the increased gradient scores of PSS in naturalistic stimuli state not just caused by the extra stimulation but also associated with compensation. This speculation was confirmed again because the less compressive gradient caused by the naturalistic stimuli in the PSS was also correlated with decreased cognition.

Cerebral functional feature, vascular features, and cognitive performance

In general, blood supply is important to the cerebral function, which was supported by the combing CBF and BOLD-fMRI in the brain (Liang et al. 2013). The decreased CBF was also associated with elevated amyloid-β and tau levels across the AD spectrum (Yan et al. 2018; Albrecht et al. 2020). Actually, the systemic microvascular state might be more sensitive to reflect the cerebral function than the regional blood flow. Whereas methods for assessing cerebral microvascular compromise in the general population are limited, validated measures of systemic microvascular function are available for the retina, kidneys, and heart (Harris et al. 2012). According to the anatomical of the kidney, the renal medullary BOLD features mainly reflected the tissue oxygenation (Textor et al. 2008). And higher MR2* means a lack of oxygen or the presence of pathologic anoxia in the tissues (Prasad et al. 2010; Yin et al. 2012), which might represent the declined kidney function. Older adults with lower kidney function would at higher risk of worse cognition (Darsie et al. 2014). In addition, the anoxia in the tissues in healthy older adults is caused by vascular aging to a great extent. The vascular factor is important for cognitive health. Previous studies (Seliger et al. 2004; Buchman et al. 2009) pointed out that the poor vascular health would contribute to age-related declines in cognition and brain. And vascular stiffening is common linked with cognitive impairment and dementia (Hanon et al. 2005; Barodka et al. 2011). Thus, it is appropriate to use renal BOLD-fMRI features presenting systemic microvascular state to investigate the relationship among cerebral functional organization, vascular features, and behavior in older adults. In line with previous findings, the current study found the increased MR2* value in older adults, reflecting the systemic microvascular aging. In addition, the systemic microvascular feature was significantly related to the cognition scores, which implied the aggravating cognitive decline with vascular aging. However, the association between CBF and the systemic microvascular feature was not found, one probable reason is that the cerebral perfusion exists compensation mechanism for cerebral microvascular oxygen saturation (Waltz et al. 2012), the slight microvascular aging will not affect the cerebral perfusion in healthy older adults.

The functional connectivity in the brain was associated with vascular factor (Sun et al. 2011; Li et al. 2019). Consistent with the previous study (Li et al. 2019), correlation analysis showed that compression gradient in the bilateral insula were aggravated by the worse systemic microvascular feature in the elderly group, while no significant correlation was found in younger controls. These findings provided more evidence to support the view that functional connectivity in the PSS was affected by vascular factors during aging. And the greater alteration of the brain functional organized feature is accompanied with more serious microvascular aging. Combining all correlation analysis findings, we speculated that the older adults with poor systemic microvascular state mobilized more cognitive resources in the resting-state, so as to they have fewer cognitive reserve resources to deal with the continuous cognitive task.

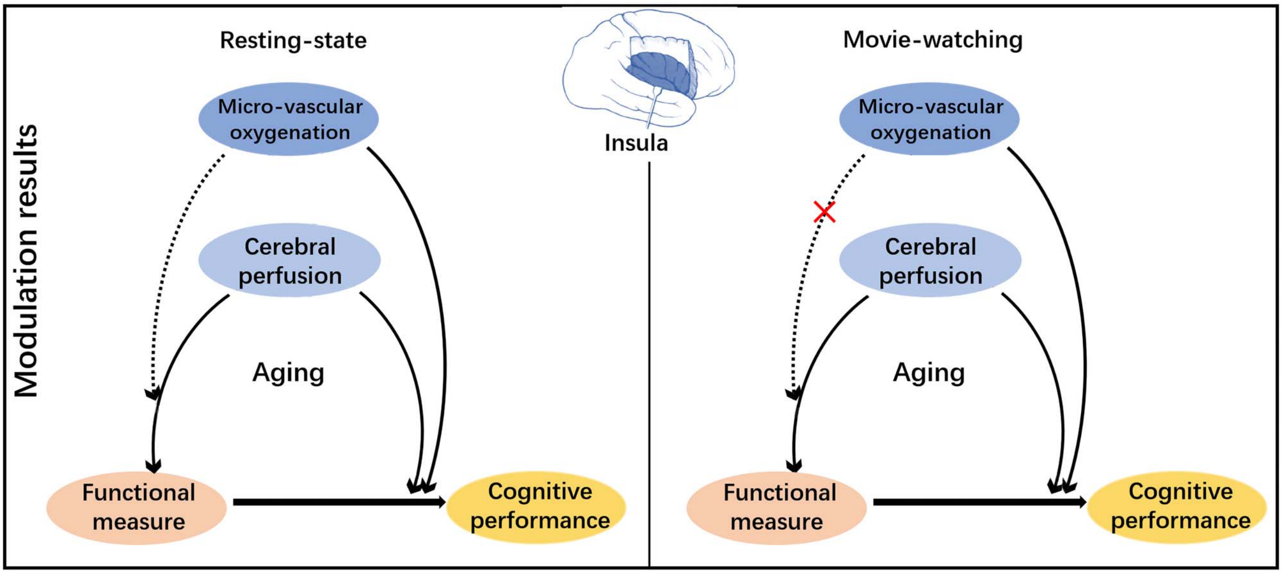

Fig. 5. The summary results in the current study. The dotted line represents the retro-regulation, and the full line represents the up-regulation.

Actually, there is the complex interaction among vascular features, cerebral function, and cognitive performance. Aging should interrupt the interaction. In the resting-state, the coupling between functional connectivity in the insula and cognitive performance was disrupted along with systemic microvascular feature/cerebral perfusion decrease, suggesting serious vascular aging would contribute to mismatch of cerebral function and behavior. Interestingly, the relationship between cerebral perfusion and cerebral functional connectivity in the insula became more closely with the worse microvascular feature, which implied that the slight altered cerebral perfusion would lead to the altered cerebral function under serious vascular aging. This phenomenon to some extent implied that the systemic microvascular feature might relate to cerebral perfusion only under the obvious vascular aging (reserves run out). Furthermore, the vascular features also regulated the relationship between altered functional gradient caused by the continuous naturalistic stimuli in the insula and cognitive performance, demonstrating the vascular features were also important for task activation. However, the regulation among systemic microvascular feature, perfusion and the difference of functional gradient caused by naturalistic stimuli was not observed (Fig. 5). Actually, the perfusion was not acquired during movie-watching but only measured in the resting-state in this study. Thus, it is reasonable that cerebral functional alteration caused by the naturalistic stimuli may be not related to cerebral perfusion in resting-state. These moderation effects should implicate microvascular aging influences the couple among the cerebral perfusion, insular organization, and cognitive performance.

It is interesting that both the correlation and moderation results were located in the insula. It would be considered as an alternative explanation that the primary function of the insular cortex includes interoception (the perception of bodily states). Insula would capture internal stimuli such as the afferent information reflecting the vascular state including microvascular oxygenation and perfusion (Gogolla 2017). In addition, the mid-posterior insula played an important role in sensorimotor processing and was able to integrate the information of different sensorimotor regions (Stephani et al. 2011). The consistent gradient findings in the mid-posterior insula suggested the age-related decline of sensorimotor information integrates and sensorimotor processing such as the movie-watching state. Furthermore, the insula would play a relay unit to distribute afferent information to emotional and cognitive cortices (Namkung et al. 2017). Thus, vascular disturbance should impact insular function to regulate performance.

There are some limitations to the current study. First, larger sample size is needed in the future. In this study, only a portion of older adults underwent the scan of cerebral perfusion and cognitive evaluation, which might increase the instability of the results. Besides, the cerebral perfusion of younger adults also should be collected to better verify our speculation. Furthermore, only 2 types of cognitive performance measures were collected, and multiple cognitive assessment need to be collected to better explain the relationship among functional features, vascular aging, and cognition. Actually, it would be more convincing by using the laboratorial indexes to conduct the study such as urine albumin-to-creatinine ratio and albuminuria, but the acquirement of renal BOLD feature is non-invasive and more convenient. And the renal BOLD feature has been demonstrated associated with laboratorial indexes. Besides, in the present study, the analyses were only restricted within the gray matter. But the BOLD signal of white matter may also reflect neurobiological significance (Ji et al. 2017), and its alteration has been demonstrated in neurodegenerative disorders (Ji et al. 2019). Thus, exploring the altered white matter BOLD signal in older adults might be helpful for further understanding the physiological mechanism of aging. Finally, for the alteration between the naturalistic stimuli and resting state, it has been demonstrated that the alteration in our older adults was similar as that of younger in open datasets. However, it would be better the relationship between the systemic microvascular features and cerebral function during the naturalistic stimuli could also be detected in the younger group if movie-watching state of the younger group was collected in our dataset.

Conclusion

This study combined the cerebral functional gradient, vascular features, and behavior to explore the mechanism of cerebral functional connectivity in aging. The altered cerebral connectivity is associated with vascular features and cognitive function in older adults. And the worse systemic microvascular feature is accompanied with lower cognitive function. In addition, the current study further confirmed the relationship between cerebral connectivity and behavior can be regulated by vascular features. Taken together, the vascular feature played a crucial role on successful aging and this study provides a new framework for understanding the physiological mechanism of functional connectivity in aging.

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Supplementary material

Supplementary material is available at *Cerebral Cortex Journal* online.

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Conflict of interest statement. None declared.

Data and code availability

The code for gradient analysis is openly available via the BrainSpace toolbox (http://brainspace. readthedocs.io) (De Wael et al. 2020). The imaging and behavior data are made available via a direct request to the corresponding author (Cheng Luo). Sharing and re-use of data need the expressed written permission of the authors and clearance from the relevant institutional review boards.

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