Cognitive decline is associated with frequency-specific resting state functional changes in normal aging

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Abstract

Resting state low-frequency brain activity may aid in our understanding of the mechanisms of aging-related cognitive decline. Our purpose was to explore the characteristics of the amplitude of low-frequency fluctuations (ALFF) in different frequency bands of fMRI to better understand cognitive aging. Thirty-seven cognitively normal older individuals underwent a battery of neuropsychological tests and MRI scans at baseline and four years later. ALFF from five different frequency bands (0.01 - 0.25 Hz; slow-6 to slow-2 band) were calculated and analyzed. A two-way ANOVA was used to explore the interaction effects in voxel-wise whole brain ALFF of the time and frequency bands. Paired-sample *t*-test was used to explore within-group changes over four years. Partial correlation analysis was performed to assess associations between the altered ALFF and cognitive function. Significant interaction effects of time × frequency were distributed over inferior frontal lobe, superior frontal lobe, right rolandic operculum, left thalamus, and right putamen. Significant ALFF reductions in all five frequency bands were mainly found in the right hemisphere and the posterior cerebellum; whereas localization of the significantly increased ALFF were mainly found in the cerebellum at slow-6, slow-5 and slow-4 bands, and left hemisphere and the cerebellum at slow-3, slow-2 bands. In addition, ALFF changes showed frequency-specific correlations with changes in cognition. These results suggest that changes of local brain activity in cognitively normal aging should be investigated in multiple frequency bands. The association between ALFF changes and cognitive function can potentially aid better understanding of the mechanisms underlying normal cognitive aging.

Introduction

Functionally related brain regions exhibit correlation of low frequency (0.01–0.1 Hz) fluctuations in the resting state fMRI, and the amplitude of low frequency fluctuations (ALFF) is higher in grey matter than in white matter (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995). Researchers use ALFF to characterize resting state blood oxygenation level dependent (BLOD) signal power (Zang et al., 2007). A distinct ALFF difference was found between eyes-open and eyes-closed conditions in the visual cortex, which suggest that ALFF may represent physiological states of the brain (Yang et al., 2007). In fact, with the application of ALFF in neurodegenerative diseases, studies have demonstrated that the specific changes of ALFF in some brain regions can be used to characterize normal and abnormal aging.

For example, inter-subject ALFF variability was larger (L. Yan, Zhuo, Wang, & Wang, 2011) and the ALFF of the default mode network demonstrated a decrease (La, Nair, et al., 2016) in older compared to younger subjects. A general pattern of $ALFF_{AD} < ALFF_{MCI} < ALFF_{healthy\ older}$ was found in the posterior cingulate cortex (PCC), and the ALFF value of the PCC was positively correlated with mini-mental state examination (MMSE) score (Z. Wang et al., 2011). There was a significant positive relationship between amyloid-β, the peptide that is abnormally deposited in AD, and memory among individuals (healthy older participants and MCI) with low levels of fractional ALFF in the left insula and left inferior frontal gyrus, which suggested that the effects of AD pathology on cognitive performance is modified by fractional ALFF in frontal regions (F. Lin et al., 2017). Reduced fractional ALFF (0.009-0.08 Hz) in prefrontal/frontal

regions is associated with decreased inhibitory control occurring during healthy aging (Hu, Chao, Zhang, Ide, & Li, 2014). Compared with cognitively normal older adults, older adults with excellent cognition showed higher oscillations (0.01-0.08 Hz) in the right fusiform gyrus, left middle temporal gyrus, and lower oscillations in right anterior cingulate cortex, right middle frontal gyrus, and left precentral gyrus (X. Wang et al., 2017). In addition, the ALFF in the BOLD signal is highly correlated with regional metabolic rate of glucose (Nugent et al., 2015), as well as functional connectivity within brain networks, regional homogeneity, degree of centrality, and fractional ALFF (Jiao et al., 2019), which is physiologically meaningful (Z. Wang et al., 2011; Zang et al., 2007).

Other previous studies have pointed out that the most commonly used low frequency band between 0.01-0.1 Hz may not be adequate to fully investigate resting brain activity (Zuo et al., 2010). Zuo et al. (2010) differentiated four frequency bands from 0.01-0.25 Hz, including slow-5 (0.01–0.027 Hz), slow-4 (0.027–0.073 Hz), slow-3 (0.073–0.198 Hz), and slow-2 (0.198–0.250 Hz). Compared with the cognitively normal older adults, amnestic MCI patients had widespread ALFF abnormalities in the slow-5 and slow-4 band (Han et al., 2011), AD patients have greater ALFF values in the slow-4 band in the ventral default mode network (i.e., cuneal cortex and lateral occipital cortex) (Veldsman et al., 2017). In comparison to healthy young adults, healthy older individuals had decreased slow-5 ALFF in the default mode network, and increased ALFF in the task-positive networks (the primary visual and sensorimotor networks), while stroke patients of between one to six months post stroke onset demonstrated a global ALFF reductions (La, Mossahebi, et al., 2016). These results indicate inherent neural integrity or adaptive reorganization in aging, stroke, and dementia (La, Nair, et al., 2016; X. Wang et al., 2017). Assessment of multiple frequency bands in resting state ALFF has also been used to investigate brain changes in other diseases, such as schizophrenia (Yu et al., 2014), social anxiety disorder (Y. Zhang et al., 2015), internet gaming disorder (X. Lin, Jia, Zang, & Dong, 2015), obsessive compulsive disorder (Giménez et al., 2017), depression (L. Wang et al., 2016), and psychosis (Gohel et al., 2018).

Recent researches has shown that cognitive changes were associated with ALFF at specific frequency bands (Giménez et al., 2017). For example, a positive linear trend was observed between phonemic verbal fluency score and fractional ALFF values within the slow-5 band in subacute stroke patients (La, Nair, et al., 2016). Greater slow-4 ALFF decline in the right putamen was significantly associated with memory decline in MCI patients (Ren et al., 2016). Poorer episodic memory in AD patients was associated with greater slow-4 band ALFF in the ventral default mode network (Veldsman et al., 2017). Therefore, studying ALFF in different frequency bands in elderly populations can help elucidate cognitive aging processes. Despite the relevance of ALFF to cognitive aging, the relationship between normal cognitive aging and altered patterns of the intrinsic brain activity has not been examined in a longitudinal design.

Based on previous studies, we hypothesized that ALFF changes associated with cognitive decline would show frequency specificity. Thus, we applied the ALFF method to investigate changes of the regional spontaneous brain activity at two-time points scans. Our study was to explore the frequency-specific characteristics of resting state ALFF, including the five specific frequency bands from slow-6 band to slow-2 band, in cognitively normal aging over four years.

Materials And Methods

Participants

Forty-one cognitively normal older individuals (17 M / 24 F, 78.57 ± 3.50 years old) were included from the Sydney Memory and Ageing Study (MAS) (Sachdev et al., 2010). Participants were classified as cognitively normal if the mini-mental state examination (MMSE) score ≥ 24 adjusted for age, education and non-English speaking background (Anderson, Sachdev, Brodaty, Trollor, & Andrews, 2007; Folstein, Folstein, & McHugh, 1975), and performance on all neuropsychological test measures was above -1.5 SDs compared to published normative values (matched for age and education), no subjective complaint of decline in memory or other cognitive function. All participants underwent a neuropsychological test battery and MRI/fMRI scans at baseline, and were retested four years later. Four participants were excluded due to head motion being greater than 3 mm / 3° in either baseline or follow-up scans. Finally, 37 participants were included in the imaging analysis and the subsequent partial correlation analysis (demographic characteristics in Table 1/Table S1).

Table 1
Demographic and cognitive characteristics of the study sample

Variables	Baseline (n=37)	4 years later (n=37)	Paired - *t*	df	P value
	Mean ± SD	Mean ± SD			
Age (years)	78.42 ± 3.48	82.34 ± 3.49	-	-	-
Gender (M/F)	16/21	16/21	-	-	-
Education (years)	12.52 ± 2.81	12.52 ± 2.81	-	-	-
MMSE	29.16 ± 0.96	29.43 ± 0.84	1.434	36	0.160
Attention/processing speed	0.20 ± 1.20	-0.18 ± 1.21	-2.160	36	0.038*
Language	-0.01 ± 0.99	0.09 ± 0.98	0.950	36	0.348
Executive function	0.33 ± 0.96	0.02 ± 1.03	-3.375	35	0.002**
Memory	0.56 ± 0.99	0.48 ± 0.90	-0.654	35	0.517
Visuo-spatial	0.24 ± 1.00	0.11 ± 0.97	-1.198	36	0.239
Global cognition	0.36 ± 0.97	0.14 ± 1.04	-2.767	36	0.009**

F, female; M, male; MMSE, Mini-mental state examination. * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

Neuropsychological assessments

A comprehensive neuropsychological battery was administered to analyze specific cognitive functions (Sachdev et al., 2010). Five cognitive domains were tested, including attention/processing speed, language, executive function, memory, and visuo-spatial (see Table 1/Table S1). Specifically, the digit

symbol coding test (DSCT) (Wechsler, 1997a) and the trail making test-A (TMTA) (Strauss, Sherman, & Spreen, 2006) were measures of attention/processing speed; the Boston naming test (BNT) (Benton, Sivan, & Spreen, 1996) and the semantic fluency test-animals (SFT-animals) (Strauss et al., 2006) as measures of language; the trail making test-B (TMTB) (Strauss et al., 2006) and the controlled oral word association test (FAS) (Strauss et al., 2006) to assess executive function; the WAIS-R block design (Wechsler, 1981) to assess visuospatial function; the Rey auditory verbal learning test (RAVLT) (Strauss et al., 2006), the WAIS-III logical memory story (LM) (Wechsler, 1997b), and the Benton visual retention test (BVRT) (Benton et al., 1996) to measure memory. The signs of *z* scores of TMTA and TMTB were reversed, so the greater positive cognitive domains scores represented better performance.

Raw component test scores were transformed to *z* scores based on the means and standard deviations of the reference group [z = (raw – mean)/SD], and domain composite scores were calculated by averaging *z* scores of component tests. Global cognition score was defined as the average of all composite domain scores, and the final global cognition scores were standardized by transforming to *z* scores.

MRI data acquisition

MRI scans were conducted on a Philips 3T Achieva Quasar Dual scanner (Philips Medical Systems, Best, The Netherlands), at NeuRA (Neuroscience Research Australia), Sydney. All participants were instructed to keep their eyes closed and think nothing when receiving resting state fMRI scans. A T2*-weighted echo planar imaging (EPI) sequence was used, with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 240×130.5×240 mm^3, 29 continuous axial slices, slice thickness = 4.5 mm without inter-slice gap, matrix size = 128×128, resulting in voxel size = 1.9×1.9×4.5 mm^3. During the 7-min scan of fMRI, we required 208 volumes per subject. A 3D T1-weighted structural MRI was acquired during the same scanning session with TR = 6.39 ms, TE = 2.9 ms, flip angle = 8°, FOV = 256×256×190 mm^3, slice thickness = 1.0 without inter-slice gap, resulting an isotropic voxel size = 1×1×1 mm^3.

MRI data preprocessing

The resting-state fMRI data were preprocessed using Statistical Parametric Mapping 12 toolbox (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and Data Processing & Analysis for Brain Imaging (DPABI 4.0, http://rfmri.org/dpabi) (C. G. Yan, Wang, Zuo, & Zang, 2016) on the MATLAB 2017b (Mathworks, Natick, MA, USA) platform. The first 10 volumes were removed to allow for magnetization stabilization and for participants to get used to the scanner noise. The remaining functional images were performed with slice timing for scan time correction and realignment for head motion correction. Participants were excluded if head motion was greater than 3 mm of translation and 3° of angular rotation along any axis. The structural images were co-registered to the mean functional image, and segmented into gray matter, white matter, and cerebrospinal fluid. Three types of nuisance signals were regressed out, including (A) polynomial trend, (B) the Friston 24-motion parameter model: 6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items

(Friston, Williams, Howard, Frackowiak, & Turner, 1996), (C) white matter, cerebrospinal fluid and global mean signal. The obtained functional images were spatially normalized by using EPI templates to the standard Montreal Neurological Institute (MNI) brain space with a resampling resolution of 3 × 3 ×3 mm^3, and smoothed with a Gaussian kernel of 4 mm full width at half maximum.

ALFF calculation in different frequency bands

After data preprocessing, the time series of each voxel was transformed into the frequency domain using the fast Fourier transform to obtain the power spectrum in five frequency bands (i.e., slow-6 [0.01-0.08 Hz], slow-5 band [0.01–0.027 Hz], slow-4 band [0.027–0.073 Hz], slow-3 band [0.073–0.198 Hz], slow-2 band [0.198–0.250 Hz]) (Biswal et al., 1995; Buzsáki & Draguhn, 2004; Zuo et al., 2010). The square root of the power spectrum was calculated at each voxel. The averaged square root was taken as the ALFF value (Zang et al., 2007). For standardization purposes, each individual's ALFF value was transformed to *z* score. The baseline and four-year follow-up zALFF maps of all participants were used for further statistical analysis.

Statistical analysis

Paired *t*-tests were performed to assess differences in cognitive domains between the baseline and four-year follow-up. Analyses were conducted in SPSS 23 (IBM, Armonk, New York, United States).

One-sample *t*-tests were performed on zALFF maps to determine the within-group patterns of LFO amplitude. We then performed a two-way ANOVA (flexible factorial design, 2 × 5) on zALFF maps at voxel-wise level on the whole brain using the SPM12 (Penny, Friston, Ashburner, Kiebel, & Nichols, 2011), for the main effects of the groups (baseline and four-year follow-up), frequency bands (slow-6, slow-5, slow-4. slow-3 and slow-2) and their interactions. The multiple comparison correction was performed by two-tailed Gaussian random field (GRF) correction (voxel-level $P < 0.001$, cluster level $P < 0.05$). The post-hoc paired-sample *t*-tests were further performed on clusters showing significant group and frequency band interactions. The statistical threshold was set by using Bonferroni correction.

Complementary post-hoc paired-sample *t*-tests were also performed to analyze longitudinal differences in voxel-wise zALFF maps for each frequency band, with gray matter density and head-motion parameters (mean frame-wise displacement) as covariates (Jenkinson, Bannister, Brady, & Smith, 2002). Clusters with a voxel-level $P < 0.001$ and a cluster-level $P < 0.05$ was considered to exhibit statistical significance with the use of a GRF correction, as implemented in the DPABI toolbox. The significant clusters were then corrected by Bonferroni correction across five frequency bands, $P < 0.01$ (0.05/5).

Finally, in order to investigate the ALFF and cognition associations in longitudinal settings, partial correlation analyses between ΔzALFF and the change in cognitive domain scores were performed for each frequency band. Age, sex, and years of education at baseline were included as covariates. The changes in zALFF value (ΔzALFF) were defined as follow-up minus baseline. Changes in cognitive domain scores (Δcognition) were also computed as follow-up minus baseline. Multiple comparisons were

carried out by two-tailed GRF correction (voxel-level $P < 0.001$, cluster level $P < 0.05$). Then Bonferroni correction (6 cognitive variables × 5 bands) was applied and only results with $P < 0.0016$ reported.

Results

Sample characteristics and neuropsychological tests

Sample characteristics and neuropsychological tests are presented in Table 1 and Table S1. Significant cognitive declines over four years were found in attention/processing speed (t = -2.160, df = 36, p < 0.05), executive function (t = -3.375, df = 35, p < 0.01), and global cognition (t = -2.767, df = 36, p < 0.01).

Interaction effects of time and frequency band

Spatial ALFF patterns of two time points (baseline and four-year follow-up) at different frequency band (slow-6, slow-5, slow-4. slow-3 and slow-2) are presented in Figure S1. The ANOVA test showed significant interaction effects of time and frequency band in bilateral inferior frontal lobe (IFG), bilateral superior frontal lobe (SFG), right Rolandic operculum, left thalamus, and right putamen (Figure 1, Table 2).

Table 2
Brain regions which had significant time (baseline and 4-year follow-up) and frequency (slow-6 to slow-2) interaction effects on ALFF (voxel-level P□0.001, cluster-level P□0.05, GRF corrected, two tailed)

Brain regions	L/R	Voxels	MNI coordinates			Maximal F value
			x	y	z	
Inferior frontal gyrus, orbital part	L	107	-27	30	-9	15.275
Superior frontal gyrus, orbital part	R	44	21	33	-15	8.225
Rolandic operculum	R	25	42	6	15	10.113
Inferior frontal gyrus, orbital part	R	17	36	33	-12	9.626
Superior frontal gyrus, orbital part	L	14	-12	42	-24	7.704
Inferior frontal gyrus, triangular part	R	13	39	36	9	7.490
Thalamus	L	10	-6	-18	18	8.025
Putamen	R	9	24	18	-6	8.839

Post hoc paired-sample t-tests between groups

Further post hoc paired-sample t-tests were performed based on the clusters from the significant interactions effect (Figure 1). In the left IFG, ALFF values decreased in the slow-5 band, and increased in the slow-2 band after four years. In the right Rolandic operculum, ALFF values decreased in all five frequency bands after four years, and the slow-5 band had the greatest decline. In the right thalamus, ALFF values decreased in the slow-3 and slow-2 band after four years. Further, in the slow-5 band, lower

ALFF was observed in the four-year follow-up than the baseline in the bilateral IFG, right SFG, right Rolandic operculum, and right putamen.

Complementary paired *t*-tests were also performed across the whole brain (Figure 2 and Table 3). The descending pattern of ALFF in the five bands was similar. After four years, our participants showed a significant ALFF decline in the right hemisphere (i.e., frontal lobe, temporal lobe, fusiform, hippocampus, insula, putamen), and the posterior cerebellum at slow-6, slow-5, slow-4, slow-3, and slow-2 bands. Significant ALFF increases were detected at follow-up in the cerebellum at the slow-6, slow-5 and slow-4 bands; left hemisphere and the cerebellum at slow-3 and slow-2 bands.

Table 3

The regions with altered ALFF in 4-years follow-up when compared with the baseline in 5 frequency bands (voxel-level P□0.001, cluster-level P□0.05, GRF corrected, two tailed). Clusters were then corrected by using Bonferroni correction, P□0.01 (0.05/5)

Brain regions		L/R	Voxels	MNI coordinates			Maximal T value
				x	y	z	
Slow-6 (0.01-0.08 Hz)							
Follow-up < baseline							
Cluster 1	Cerebelum_8	R	39	24	-63	-60	-4.503
Cluster 2	Cerebelum_8/9	L	80	3	-36	-63	-5.601
Cluster 3	Fusiform	R	24	27	-30	-18	-4.770
Cluster 4	Putamen	R	52	30	3	-9	-5.182
Cluster 5	Rolandic operculum	R	27	45	3	9	-5.195
Cluster 6	Rolandic operculum	R	36	51	-12	15	-5.724
Follow-up > baseline							
Cluster 1	Cerebelum_Crus1	L	68	-27	-78	-30	5.428
Cluster 2	Cerebelum_6	R	67	15	-63	-24	5.481
Slow-5 (0.01-0.027 Hz)							
Follow-up < baseline							
Cluster 1	Cerebelum_8/9	L	55	3	-36	-63	-4.984
Cluster 2	Inferior temporal gyrus	R	28	39	-3	-45	-4.654
	Fusiform						
Cluster 3	Putamen	R	39	33	6	-18	-5.089
Cluster 4	Rolandic operculum	R	36	45	3	9	-5.947

Brain regions		L/R	Voxels	MNI coordinates			Maximal T value
Follow-up > baseline							
Cluster 1	Cerebelum_6	R	98	15	-66	-24	6.048
Cluster 2	Cerebelum_Crus1	L	73	-15	-69	-30	5.483
Cluster 3	Vermis_8	L/R	21	-3	-66	-33	5.846
Slow 4 (0.027-0.073 Hz)							
Follow-up < baseline							
Cluster 1	Cerebelum_8	R	48	18	-57	-60	-4.839
Cluster 2	Cerebelum_8/9	L	89	3	-36	-63	-5.740
Cluster 3	Fusiform	R	21	30	-30	-18	-4.671
	Parahippocampal gyrus						
Cluster 4	Rolandic operculum	R	25	45	3	9	-4.565
Cluster 5	Rolandic operculum	R	39	48	-12	18	-6.738
Follow-up > baseline							
Cluster 1	Cerebelum_Crus1	L	21	-39	-69	-27	4.520
Cluster 2	Cerebelum_Crus1	R	29	42	-72	-30	5.369
Cluster 3	Cerebelum_Crus1	L	30	-21	-75	-24	5.200
Cluster 4	Caudate	R	24	12	18	-6	4.853
Slow 3 (0.073-0.198 Hz)							
Follow-up < baseline							
Cluster 1	Cerebelum_8	R	307	3	-36	-63	-5.868
	Cerebelum_8/9	L					

Brain regions		L/R	Voxels	MNI coordinates			Maximal T value
Cluster 2	Insula	R	47	39	6	12	-5.467
Follow-up > baseline							
Cluster 1	Cerebelum_Crus1	L	98	-27	-78	-30	5.928
Cluster 2	Superior frontal gyrus, orbital part	L	29	-9	24	-21	5.119
	Rectus						
Cluster 3	Inferior temporal gyrus	L	40	-63	-36	-15	5.979
	Middle temporal gyrus						
Cluster 4	Rectus	R	63	6	21	-24	6.482
Cluster 5	Superior frontal gyrus, medial	L	77	-6	60	21	10.740
Slow 2 (0.198-0.250 Hz)							
Follow-up < baseline							
Cluster 1	Cerebelum_8/9	R	95	24	-66	-60	-5.504
Cluster 2	Cerebelum_8/9	L	151	3	-36	-63	-6.091
Cluster 3	Rolandic operculum	R	17	45	-9	3	-4.804
	Insula						
Cluster 4	Putamen	R	31	33	-6	3	-5.486
Follow-up > baseline							
Cluster 1	Cerebelum_Crus1	L	29	-30	-75	-30	6.127
Cluster 2	Superior frontal gyrus, medial	L	32	-6	60	21	9.130
	Anterior cingulate and paracingulate gyri						

Cognitive correlations with ALFF

At the slow-6 band, ΔzALFF was positively correlated with ΔAttention/processing speed in the left cerebellum posterior lobe (r = 0.723, p < 0.001; Figure 3a) and the left superior parietal gyrus (r = 0.797, p < 0.001; Figure 3a). At the slow-5 band, ΔzALFF was positively correlated with ΔAttention/processing speed in the left superior parietal gyrus (r = 0.796, p < 0.001; Figure 3b), ΔzALFF was negatively correlated with ΔLanguage in the right middle frontal gyrus (r = -0.747, p < 0.001; Figure 3b). At the slow-4 band, ΔzALFF was positively correlated with ΔAttention/processing speed the left cerebellum posterior lobe (r = 0.726, p < 0.001; Figure 3c) and the right cerebellum posterior lobe (r = 0.710, p < 0.001; Figure 3c). At the slow-3 band, ΔzALFF was positively correlated with ΔGlobal cognition in the right middle frontal gyrus (r = 0.681, p < 0.001; Figure 3d). At the slow-2 band, ΔzALFF was positively correlated with ΔAttention/processing speed in the right superior parietal gyrus (r = 0.712, p □ 0.001; Figure 3e). All the relationship were survived after Bonferroni correction (6 cognitive variables × 5 bands), p □ 0.0016 (0.05/30).

Discussion

The current study investigated longitudinal changes in voxel-wise whole brain ALFF at five frequency bands (i.e., slow-6 band, slow-5 band, slow-4 band, slow-3 band, slow-2 band), and correlations between ALFF changes and changes in cognition over four years in normal older adults. Significant interaction effects of time × frequency was distributed over bilateral IFG, bilateral SFG, right Rolandic operculum, left thalamus, and right putamen. Secondly, across all the five frequency bands, the significant ALFF decreases were mainly distributed in the right hemisphere and posterior cerebellum, whereas significant ALFF increases were mainly distributed in the left hemisphere and cerebellum. In addition, the longitudinal cognitive changes showed frequency-specific correlations with ALFF changes. Our results indicated that aging-related ALFF changes was frequency dependent and may be partially underpinning the cognitive decline of normal aging.

Longitudinal ALFF changes in different frequency bands over four years

We found that regional distribution of ALFF reductions was similar in all frequency bands and tended to be lateralized to the right hemisphere and the posterior lobe of cerebellum. Previous studies showed hemispheric shifts in brain activity over time, with decreased activity in right hemispheric regions and increases in left hemispheric regions (Beason-Held, Kraut, & Resnick, 2008). Cerebellar functional activity is also affected by aging. Previous studies have found that older individuals with subjective cognitive decline (SCD) showed higher ALFF than did healthy control subjects in the posterior lobe of the cerebellum (Sun et al., 2016). Cognitively normal older adults showed a longitudinal decline in functional connectivity (FC) between PCC and posterior lobe of the cerebellum (Cao et al., 2016), while aMCI participants showed greater longitudinal FC decline between hippocampus and posterior lobe of the cerebellum (Bai et al., 2011). A PET study reported increased resting regional cerebral blood flow (rCBF) in the cerebellum over eight years, and decreased rCBF during verbal recognition (Beason-Held et al., 2008).

These combined findings suggest that cerebellar activity changes with age in parallel with cognitive changes, especially the posterior lobe of cerebellum.

In contrast, ALFF increases in the current study were mainly localized to the left frontal and left temporal lobes, especially at slow-3 and slow-2 band. In a previous study, frontal regions exhibited the most significant ALFF differences across normal subjects, MCI, and AD patients (Z. Wang et al., 2011). At the 0.01-0.08 Hz band, ALFF values in MCI patients with depressive symptoms were higher than nondepressed MCI patients in the left medial prefrontal cortex (MPFC) and lower in the right precentral gyrus (preCG) (Liu et al., 2018). In MCI patients, abnormal ALFF at slow-5 and slow-4 bands was observed in the MPFC, posterior cingulate cortex/precuneus (PCC/PCu), basal ganglia, and hippocampus/parahippocampal gyrus (PHG) (Han et al., 2011). Our results, combined with previous research, show that the frontal and temporal lobes are sensitive to both normal and abnormal aging. Previous studies have demonstrated that intrinsic brain activity patterns are sensitive to specific frequency bands (Han et al., 2011). Our results further suggest that this is especially true with increased ALFF during normal aging.

Frequency-specific associations between longitudinal cognitive decline and ALFF changes

Our results showed that a normal aging population had significant longitudinal cognitive decline over four years in executive function, attention/processing speed, and the global cognition, which is consistent with previous studies (Diamond, 2013; Lipnicki et al., 2017; Tombaugh, 2004). For example, longitudinal studies showed a decline in executive function in elderly individuals (Shea & Remington, 2018). Across the lifespan, performance on processing-intensive tasks also decreases (Denise C Park et al., 2002). Working memory and long-term memory performance also decrease with age (D. C. Park et al., 2002; Park & Reuter-Lorenz, 2009). In the current study, no significant decreases in memory, visuo-spatial ability, and language were detected. This may be due to the participants having normal cognitive function. A previous study showed that memory performance remained stable over 8 years in cognitively normal older adults (Beason-Held et al., 2008).

The declined domain of attention/processing speed was positively correlated with the changed ALFF values in the left CPL and the left SPG at slow-6 band, the left SPG at slow-5 band, the bilateral CPL at the slow-4 band, and the right SFG at the slow-2 band. These findings illustrate three important points. First, declines in attention/processing speed were frequency specific in relation to local brain activity. Second, in slow-6 band (0.01-0.08 Hz), it was correlated with left CPL and left SPG, and further differentiated into left SPG in slow-5 (0.01-0.027 Hz) and left SPG in slow-4 (0.027-0.073 Hz). It is demonstrated that the use of multifrequency bands has refined the understanding of brain activity associated with cognitive change.

Third, our results demonstrate the contribution of CPL to cognitive function. In addition to being associated with sensory and motor processing, the cerebellum is also associated with working memory, executive function, linguistic processing, visual movement learning, emotional modulation, timing, and

balance (Habas et al., 2009; Jeremy D Schmahmann, 2004; J. D. Schmahmann & Sherman, 1998; Catherine J Stoodley, Valera, & Schmahmann, 2012). The anterior cerebellum is involved in motor task performance, while the posterior cerebellum is involved in higher-level language, spatial processing, and working memory tasks (Bernard et al., 2012). The cerebellum is functionally impacted with advanced age (Bernard & Seidler, 2014; Jacobs et al., 2018). Previous studies demonstrated that fronto-cerebellar connectivity mediate cognitive processing speed (Wong et al., 2020), and cerebellar degeneration was associated with decreased verbal fluency (C. J. Stoodley & Schmahmann, 2009). Our results further confirm the involvement of the posterior cerebellum in cognitive function, suggesting that the posterior cerebellum activity in the typical slow-6 band (0.01-0.08 Hz), especially the slow-4 band (0.027-0.073 Hz) is associated with attentional decline.

Our results also showed that ALFF changes in the right MFG were positively correlated with changes in global cognition at the slow-3 band, and negatively correlated with changes in the domain of language at slow-5 band. It has been suggested that MFG is sensitive to the differentiation of preclinical Alzheimer's disease (SCD, naMCI, and aMCI) (S. Wang et al., 2021). The ALFF in right MFG was positively correlated with general cognition (defined by MMSE) for non-demented old participants (Wu et al., 2021). Reduced local neural activity in the right MFG at the slow-3 band could partially account for the decrease of global cognition. The posterior MFG is an important integration cortical hub for both dorsal and ventral streams of language (Hazem et al., 2021). Higher ALFF within the language network during resting-state were related to worse language ability for a life-span sample of individuals (H. Zhang, Bai, & Diaz, 2021). Our results also confirm this negative correlation, that is the reduced local neural activity in the right MFG at the slow-5 band could partially account for the maintenance of the language.

Additionally, Li et al. (2020) used the same batch of data to explore functional connectivity strength (FCS) in the typical 0.01-0.08 Hz frequency band. FCS is a measure computed by summing the weights of all the connections of a given voxel that exceed a predefined optimized threshold, which is also known as weighted degree centrality. The authors found decreased FCS in right medial frontal and bilateral superior parietal lobes, and increased FCS in left supplementary motor area and left insula (Li et al., 2020). ALFF is a measure based on regional intensity of spontaneous fluctuations in the BOLD signal, represent local changes in resting state brain activity. Combining the current results with the previous study, we can confirm that changes in local brain activity are consistent with changes in long-distance functional connectivity strength. FCS changes in the left precuneus were associated with an age-related decline in global cognition (Li et al., 2020). Our results provided further evidence that longitudinal cognitive decline shows a frequency-specific correlation with ALFF changes.

Limitation and future direction

Several limitations should be noted. First, the sample size in the current study is relatively small, so caution is necessary when inferring the cognitive aging results to the general population, and the results need to be verified in a larger sample. Next, all participants were over 70 years old, so the results may not be replicable in young older people. Third, the elderly individuals included in the present study all had a relatively high level of education. Previous evidences indicated that high education was one of strongest

marker of cognitive reserve which may shape cognitive aging trajectories (Durrani et al., 2021; Farfel et al., 2013; Singh-Manoux et al., 2011). Therefore, future studies would be profit from a larger adult sample with wide levels of education. Finally, cerebral small vessel disease such as white matter hyperintensity was commonly observed in the elderly people, and regarded as one of primary neural pathological cause of cognitive decline in older age (Hamilton et al., 2021). The present study did not consider the potential impact of these pathological factors on the relationship between ALFF changes and longitudinal cognitive declines. Future studies need to explore the casual relationship between the ALFF change, pathological changes, and cognitive aging using mediation effect model and / or structural equation model.

Conclusion

In this study, cognitively normal participants exhibited cognitive decline with increasing age in attention/processing speed, executive function, and the global cognition. Longitudinal ALFF changes in older adults showed frequency and regional specificity. Similarities were also found in that the ALFF decreases tended to be lateralized to the right hemisphere and the posterior cerebellum lobe across the five frequency bands. In addition, these changes showed frequency-specific associations with specific cognitive functions. The increased ALFF value does not simply imply functional compensation, and may indicate that aging leads to a shift in the balance between left and right hemispheric activity. Thus, the neural mechanisms underlying potential cognitive changes could not be fully explained with a single frequency band. The resting state functional brain oscillations in multiple frequency bands can be a novel marker of normal aging and explain possible mechanisms of cognitive decline in normal aging.

Declarations

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Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate: Written informed consent has been received from all participants in this study.

Consent to Publish: Not applicable.

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Figures

Figure 1

The significant time (baseline and 4-year follow-up) and frequency (slow-6 to slow-2) interaction effects on ALFF (voxel-level P□0.001, cluster-level P□0.05, GRF corrected, two tailed). The red-yellow regions represent significant interaction between time and frequency. For the bar maps, * illustrated significance in post hoc paired-sample t-test after Bonferroni correction (8 clusters × 5 bands), P□0.00125 (0.05/40). IFG, inferior frontal gyrus; SFG, superior frontal gyrus; ROL, Rolandic operculum.

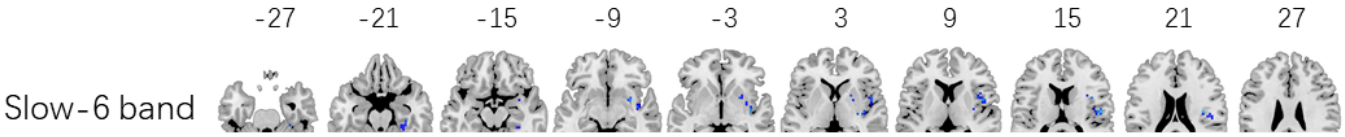

Figure 2

Brain regions with significant ALFF differences over four years at different frequency bands. Significant changes in resting state ALFF were observed at (A) slow-6 band, (B) slow-5 band, (C) slow-4 band, (D) slow-3 band, and (E) slow-2 band. Two-tailed, voxel-level P□0.001, cluster-level P□0.05, GRF corrected. All the clusters were survived after Bonferroni correction, P□0.01 (0.05/5).

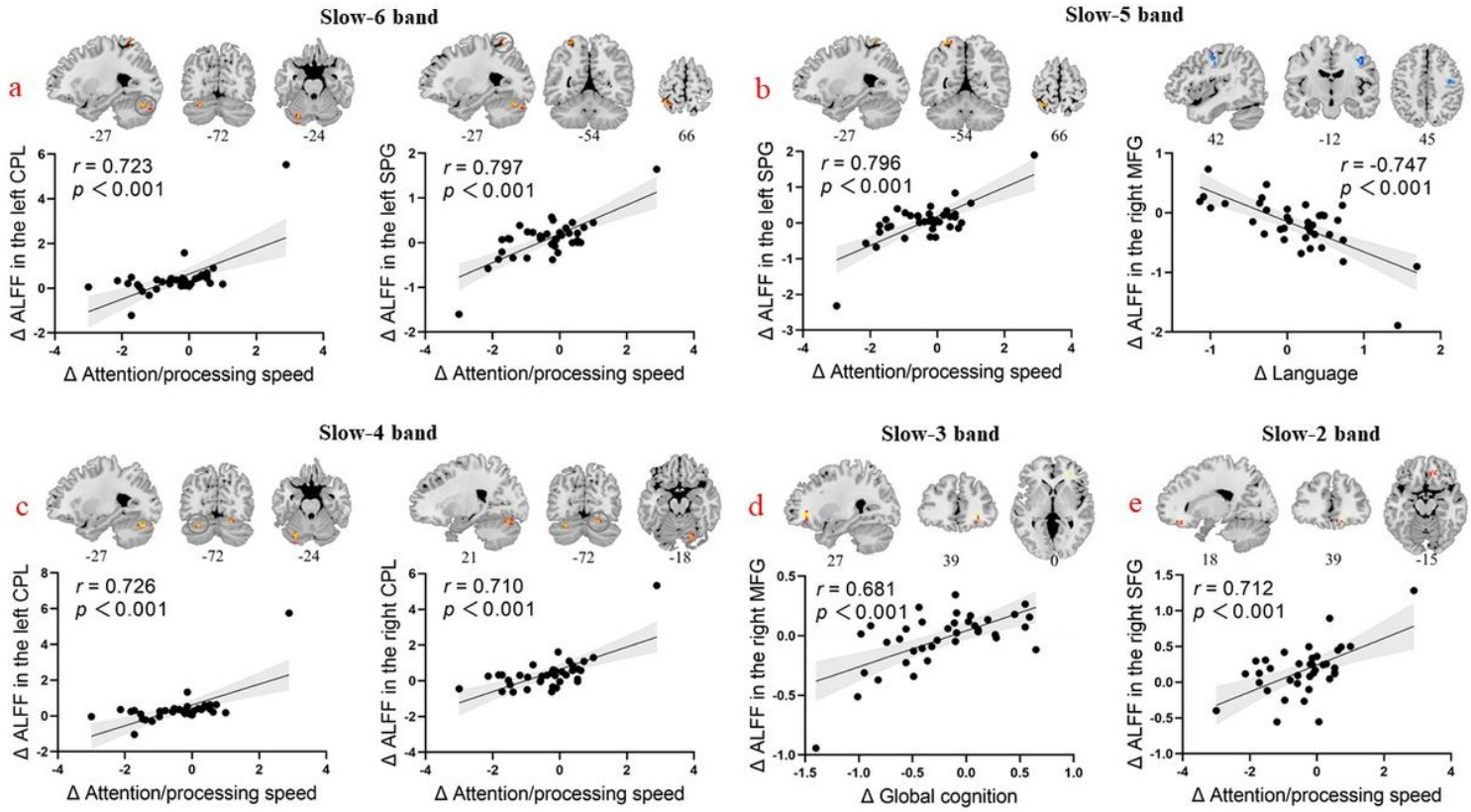

Figure 3

Correlations between the changed cognition and changed ALFF values. The scatter plot shows the correlation between ΔAttention/processing speed and ΔzALFF in the (a) left CPL, the left SPG at slow-6 band, (b) the left SPG at slow-5 band, (c) the left and right CPL at slow-4 band, (e) the right SFG at slow-2 band; the correlation between ΔLanguage and ΔzALFF in the (b) right MFG at slow-5 band; the correlation between ΔGlobal cognition and ΔzALFF in the (d) right MFG at slow-3 band. Δ, post-test minus pre-test for the zALFF value or the component cognitive domain value. CPL, cerebellum posterior lobe, SPG, superior parietal gyrus, MFG, middle frontal gyrus, SFG, superior frontal gyrus. Two-tailed, voxel-level P□ 0.001, cluster-level P□0.05, GRF corrected. All the relationship were survived after Bonferroni correction (6 cognitive variables × 5 bands), P□0.0016 (0.05/30).

Supplementary Files

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- SupplementaryMaterials.docx