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The intensity and connectivity of spontaneous brain activity in a language network relate to aging and language

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ABSTRACT

Neuroimaging studies often either look at functional activation in response to an explicit task, or functional connectivity (i.e., interregional correlations) during resting-state. Few studies have looked at the intensity of brain activity or its relationship with age, behavior, and language. The current study investigated both intensity (i.e., the Amplitude of Low-Frequency Fluctuations, ALFF) and the functional connectivity of spontaneous brain activity during rest and their relationship with age and language. A life-span sample of individuals (N = 152) completed a battery of neuropsychological tests to assess basic cognitive functions and resting-state functional MRI data to assess spontaneous brain activity. Focusing on an extend language network, the mean ALFF and total degree were calculated for this network. We found that increased age was associated with more intense activity (i.e., higher ALFF) but lower within-network connectivity. Additionally, these increases in activity within the language network during resting-state were related to worse language ability, particularly in younger adults, supporting a dedifferentiation account of cognition. Our results support the utility of using resting-state data as an indicator of cognition and support the role of ALFF as a potential biomarker in characterizing the relationships between resting-state brain activity, age, and cognition.

Credit statement

Haoyn Zhang: Conceptualization, Formal analysis, Writing – original draft; Xiaoxiao Bai: Formal analysis, Writing – review & editing; Michele Diaz: Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

1. Introduction

Older adults experience decline in many cognitive functions, including working memory, general processing speed (Park et al., 2002; Park and Reuter-Lorenz, 2009), and cognitive control (Paxton et al., 2008; Schaie, 1996). However, unlike other cognitive functions, language is variably affected by aging. For instance, older adults typically show declines in language production (Burke and Shafto, 2008; Shafto et al., 2007; Zhang et al., 2019). However, language comprehension and vocabulary are well maintained, and sometimes even improve throughout the lifespan (Kavé and Halamish, 2015; Verhaeghen, 2003; For comprehensive reviews of language and aging studies, see Burke and Shafto, 2008).

In addition to age-related behavioral differences, functional neuroimaging studies have also shown that older adults often elicit different patterns of functional activation such as increased bilateral activation and increased activation in prefrontal regions compared to younger adults (Cabeza, 2002; Cabeza and Dennis, 2012; Davis et al., 2008; Grady et al., 2015; Langenecker and Nielson, 2003; Logan et al., 2002; Wierenga et al., 2008). Specific to language, while younger adults typically engage a left-lateralized network, especially during language production (Hickok and Poeppel, 2007; Indefrey and Levelt, 2004; Price, 2010), older adults often show less lateralized patterns of fMRI activation compared to younger adults (Destrieux et al., 2012; Diaz et al., 2014; Diaz et al., 2019; Diaz et al., 2016; Nagels et al., 2012; Rizio et al., 2017; Wierenga et al., 2008; Zhang et al., 2019).

In addition to functional activation during a task, some studies have examined spontaneous brain activity during resting-state, mainly focusing on the patterns of correlated activity in the human brain (i.e., functional connectivity). In general, aging is associated with lower connectivity among brain regions within a functional network (e.g., default mode network; Betzel et al., 2014; Cao et al., 2014; Geerligs et al., 2015; Onoda et al., 2012; Siman-Tov et al., 2017; Song et al.,

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2014; Tomasi and Volkow, 2012). These age-related differences in network characteristics have been associated with worse behavioral performance across several different cognitive domains (King et al., 2018; Onoda et al., 2012; Sala-Llonch et al., 2015; Varangis et al., 2019; L. Wang et al., 2010). To date, only a few studies have investigated age-related differences in a language resting-state network and its relationship with language ability (Ferré et al., 2019; Gertel et al., 2020). For instance, Ferré et al. (2019) reported that increased age was associated with increased connectivity in a language network during language tasks, but decreased connectivity during resting-state. However, they found no relationship between functional connectivity and age-related increases in vocabulary measures, suggesting that the functional networks supporting vocabulary remain intact across the lifespan.

As reviewed above, traditional neuroimaging studies have either looked at functional activation in response to an explicit task, or functional connectivity during resting-state or during a task. However, few studies have looked at the Blood Oxygen Level Dependent (BOLD) *amplitude* during resting-state, which mainly consists of lower frequency brain oscillations (i.e., Amplitude of Low-Frequency Fluctuations, ALFF; Zang et al., 2007). Importantly, these low frequency oscillations are related to brain function (e.g., Achard et al., 2006). Compared to functional connectivity studies that look at the connections among brain regions ("highways"), the ALFF method looks at the regional neural activity ("cities") during resting-state, by measuring BOLD signal power, or amplitude, within the low-frequency range during resting-state, typically between 0.01 and 0.08 HZ (Lv et al., 2018). In other words, ALFF reflects the intensity of brain activity during rest. Because ALFF relies on BOLD signal, it also reflects vascular function (Agarwal et al., 2017; Di et al., 2013). Moreover, other studies have shown that ALFF can reliably detect differences in physiological states (e.g., higher ALFF in bilateral visual cortices during eyes-open resting-state compared to eyes-closed resting-state; Yang et al., 2007). Thus, similar to investigating how brain regions are connected during rest, exploring the amplitude of brain activity at rest and relating it to behavior could also provide insights into individual difference in cognitive abilities.

In addition to linking ALFF to physiological states, it has also been linked to clinical and psychological phenomena. For example, ALFF methods have been used to differentiate neural activation patterns between typical and patient populations such as individuals with amnestic mild cognitive impairment (Han et al., 2011), schizophrenia (Shen et al., 2014; Turner et al., 2012), and idiopathic generalized epilepsy (Z. Wang et al., 2014), providing promising evidence that ALFF can be used to detect disease-related differences in local brain activity. A few studies have also examined the psychological and behavioral correlates of ALFF in younger adults (Mennes et al., 2011; Wei et al., 2012). For instance, Mennes et al. (2011) reported that higher ALFF in midline cingulate regions was associated with better performance during the Flanker task, a task known to be involved in attention and executive function, and Wei et al. (2012) found that higher ALFF in the left posterior middle temporal gyrus was associated with more efficient semantic processing.

In addition to studies focusing on patient populations or younger adults, some studies have also examined ALFF with older adults to understand its relationship with behavior. For instance, Yan et al. (2011) reported that although there were no ALFF differences in the visual cortex between older and younger adults, there were larger ALFF variances in older adults. However, Mather and Nga (2013) reported increased ALFF in the thalamus in older adults compared to younger adults. Relating ALFF to behavior, Hou et al. (2019) found that older adults who played video games had increased ALFF in the left inferior occipital gyrus, left cerebellum and left lingual gyrus relative to their peers who did not play video games. Additionally, these increases in ALFF in the left inferior occipital gyrus and left lingual gyrus were positively associated with overall cognitive status, as measured by the Mini-Mental State Exam (MMSE), even though these regions are not typically thought to be related to higher level cognition. Of particular relevance to the current study, Yin et al. (2015) reported an age-related decrease in ALFF in the precuneus. Additionally, they found that among older adults, better verbal fluency performance was related to lower ALFF in the precuneus. Although the authors argued that the precuneus is involved in language processing, this region has also been recognized as a major hub in the default mode network (e.g., Fransson and Marrelec, 2008; Utevsky et al., 2014). The lower ALFF in the precuneus might reflect a more efficient and segregated network structure during resting-state, which could be related to better off-line behavioral performance.

To summarize, while the majority of resting-state studies have focused on functional connectivity, a few studies have also investigated the amplitude of brain activity during resting-state and its relationship with cognition. Functional connectivity studies often report age-related decreases in within-network connectivity and these reductions are often associated with worse performance. However, the relationship between ALFF and age or cognition is less clear. Additionally, very few studies have focused on a language network and the relationship between network properties and aging or language. Furthermore, the previous literature has primarily relied on the differences between younger and older adults, in which significant differences in cognitive and brain functions are typical. Few studies have included a middle-aged population to investigate age-related differences in cognition and brain functions across the lifespan (but see Chan et al., 2014; Varangis et al., 2019).

To fill the above-mentioned gaps, the current study investigated both the amplitude of spontaneous brain activity (i.e., ALFF) and the functional connectivity (i.e., degree, the number of strong connections among nodes) in a pre-defined language network during resting-state and their relationship with age and language ability across the adult lifespan . Language ability was assessed broadly through several independent language tasks measuring different aspects of language functions (e.g., production, comprehension, vocabulary, and reading). Therefore, we selected a broad, extended language network that was based on a previous meta-analysis (Ferstl et al., 2008). Specifically, this network included bilateral anterior temporal lobe which has been proposed as a semantic hub (e.g., Lambon Ralph, Jefferies, Patterson and Rogers, 2017; Lambon Ralph, Pobric and Jefferies, 2009), bilateral posterior middle temporal gyri which are involved in semantic and lexical processes (e.g., Wilson et al., 2009), bilateral superior temporal gyri which are involved in auditory language processes (e.g., Peramunage et al., 2011; Vaden et al., 2010), left inferior frontal gyrus, which has been implicated in executive aspects of language such as lexical selection (e.g., Thompson-Schill, D'Esposito, Aguirre and Farah, 1997), as well as its right hemisphere homolog. We also included a non-language-related visual network as a control network (Damoiseaux et al., 2006; Power et al., 2011), to test the specificity of the relationship between brain activity in a language network and language ability. We predicted that age would be significantly correlated with both brain activity and functional connectivity in the language network, although the direction of this correlation could not be easily predicted based on the limited literature. Additionally, we hypothesized that both brain activity and functional connectivity in the language network but not in the visual network would show an association with language ability but not other cognitive abilities. Last but not least, age may modulate the relationship between language ability and network characteristics during resting-state.

2. Method

2.1. Participants

One hundred and fifty-four adults participated in the experiment, 1 was removed due to poor performance and a second participant was removed due to the possibility of depression as measured by the GDS (Guerin et al., 2018; Sheikh and Yesavage, 1986), leaving 152 complete data sets (ages: 20–78 years, mean age = 46.9 years, sd = 17.1 years, 91 female, 61 males). All participants were community-dwelling, right-handed, native American English speakers who were not fluent in a second language. All participants had normal or corrected-to-normal vision, and reported no history of neurological, psychological, or major medical conditions (Christensen et al., 1992). Participants were also screened for mild cognitive impairment or dementia (MMSE, Folstein et al., 1975). Prior to the MRI session, each participant completed a battery of psychometric and neuropsychological tests to assess basic cognitive functions such as speed, executive function, memory, and language (For a complete list of tasks, task descriptions, and participants' performance, see: https://osf.io/e2rga/?view_only=89588fb3a6bc489fae6ae40a95c88af7). In this paper, we focused on language assessments which included the WAIS-III vocabulary to assess vocabulary size (Wechsler et al., 1997); phonemic (F, A, S) and categorical (animals) verbal fluency to assess speech fluency, and the author recognition test and a comparative reading habit questionnaire to assess reading habits (Acheson et al., 2008). We also included working memory assessments in our analyses to test the specificity of our findings. These working memory tasks included a reading span task (Conway et al., 2005) and forward and backward digit span. During the MRI session, participants also completed fMRI tasks (either a picture naming task or a word naming task to assess language production) which are reported elsewhere (Diaz et al., 2021) or in progress (Diaz et al., 2020). Demographic characteristics and assessment scores of language and working memory related assessments are reported in Table 1. All participants gave written, informed consent, and all procedures were approved by the Institutional Review Board at The Pennsylvania State University.

Only language-related and working memory-related tasks are reported here. The second column displays the group means, with standard deviations in parentheses. The numbers represent the raw scores of each test. The third column indicates its correlation with age. Statistically significant effects are noted as follows: *p < .05; **p < .01; ***p < .001. [1]ART scores are calculated as the number of correct identifications – the number of incorrect responses.

2.2. Acquisition of MRI data

MRI scanning was completed on a 3T Siemens Prisma Fit MRI scanner with a 64-channel head coil. Sagittal T1 weighted localizer images were collected and used to define a volume for data collection, higher-order shimming, and alignment to the anterior and posterior commissures (AC-PC). Prior to the resting-state scan, T1-weighted anatomical images were collected using a magnetization-prepared, rapid acquisition, gradient echo (MP-RAGE) sequence (repetition time [TR] = 2300 ms; echo time [TE] = 2.28 ms; Inversion Time [TI] = 900 ms; flip angle = 8°; echo spacing = 7 ms; acceleration factor = 2; field of view [FOV] = 256 mm^2; voxel size = 1 × 1 × 1 mm; 160 contiguous slices).

Functional resting-state images were collected using an echoplanar imaging (EPI) sequence (TR = 2000 ms; TE = 25.0 ms; flip angle = 90°; echo spacing = 0.49 ms; FOV = 240 mm^2; voxel size = 3 × 3 × 4 mm; 33 contiguous slices, parallel to the AC-PC; phase encoding = anterior to posterior; fat saturation = on; slice acquisition = sequential, descending; volumes = 180; run duration = ~6 min). Two additional volumes were acquired and deleted at the start of the functional scan to reach steady state equilibrium. During the resting-state run, participants were instructed to relax in the scanner with their eyes open and to look at a fixation cross presented in the center of the screen.

A field map sequence was also collected with a double-echo, spoiled gradient echo sequence (TR = 446 ms; TE = 4.92 ms; flip angle = 60°; FOV = 240 mm^2; voxel size = 3 × 3 × 4 mm; 33 contiguous slices; phase encoding = anterior to posterior, fat saturation = off; duration = 1:12 min) that was used to correct for field inhomogeneites. that was.

Table 1
Participant demographics, neuropsychological testing scores, and its correlation with age.

Demographic information	Mean (SD)	
N	152	
Age	46.9 (17.1)	
Gender (M/F)	61/91	
Participant characteristics	**Mean (SD)**	**Age Correlation**
Education (Years)	16.9 (2.8)	.17*
MMSE	28.8 (1.3)	-.19*
Depression (GDS)	0.8 (1.1)	-.14
Language Assessments		
Verbal Fluency (Number of correct tokens)	66.0 (14.0)	-.14
WAIS Vocabulary (Score out of 66)	54.3 (6.1)	.02
Author Recognition Test (ART)[1]	24.3 (14.3)	.50***
Comparative Reading (Score out of 35)	25.3 (4.8)	.08
Working Memory Assessments		
Digit Span Forward (Score out of 16)	11.2 (2.2)	-.10
Digit Span Backward (Score out of 16)	7.3 (2.1)	-.14
Verbal Working Memory (Score out of 1)	0.4 (0.2)	-.37***

2.3. Behavioral data analyses

As mentioned earlier, participants performed a series of standardized behavioral tests to measure cognitive functions across different domains (i.e., speed, memory, language) and an exploratory factor analysis was conducted to identify the components that reflect different cognitive functions. Before conducting the factor analysis, a data cleaning procedure was conducted as follows. First, all reaction time measures were reverse coded to be consistent with other variables (i.e., higher values = more efficient). In individuals with missing data, the missing values were replaced using the predictive mean matching (PMM) method from the *mice* package in the R environment (Buuren and Groothuis-Oudshoorn, 2010). Outliers in the factor analysis were identified and removed using Mahalanobis Distances (Probability < .001). For all behavioral tasks, only trials with a correct response and a reaction time longer than 200 ms and within 2.5 SDs of that participant's mean were included in further analyses. These data cleaning procedures resulted in the loss of 4 participants, leaving a final sample of 148 individuals to be included in the factor analysis and any analyses including factor analysis scores. There was no multi-collinearity concern among the cognitive variables as assessed by VIFs <4.3 and the data were normally distributed. A Bartlett's test was conducted to determine the correlation adequacy among variables from those cognitive tasks, and a Kaiser-Meyer-Olkin test (KMO, Kaiser, 1974) was then conducted to determine the sampling adequacy. Results suggested that there was a substantial correlation among the cognitive variables (Bartlett test $p <$ .001) and the sample was adequate (KMO = 0.75 greater than the acceptable level of .60, Kaiser, 1974). A factor analysis was conducted using the *psych* package in the R environment (R Core Team, 2014; Revelle, 2015). We used a parallel analysis (i.e., where the actual data and the simulated data cross) to decide how many factors were meaningful. The *oblimin* rotation was used to produce naturally correlated psychological factors. Four latent factors were identified (i.e., Language, Working memory, Recall, and Processing speed). The factor scores for each participant were then calculated. Because we focused on a language brain network, the Language Factor scores were of primary interest. We also incorporated the Working Memory Factor scores to assess the specificity of our results.

2.4. fMRI data analyses

The fBIRN QA tool was used to assess data quality (Glover et al., 2012, https://www.nitrc.org/projects/bxh_xcede_tools/), measuring the number of potentially clipped voxels, mean signal fluctuation to noise ratio (SFNR), and per-slice variation. Additionally, the anatomical and functional images were visually inspected for artifacts and signal drop-out. Preprocessing and first-level analyses were conducted using the CONN functional connectivity toolbox version 18.a (Whitfield-Gabrieli and Nieto-Castanon, 2012). First, functional realignment and unwarping were done to estimate and correct for participant motion. Then, a voxel-displacement map was calculated based on the field map data and applied to the resting-state and task-based data for distortion correction, followed by slice-timing correction, which corrected for maturation of the BOLD signal over time (Huettel et al., 2004). Functional outliers were detected with an ART (Artifact Detection Tools) based identification method in which outliers were defined using a conservative threshold (i.e., data points more extreme than the 97th percentile based on a normative sample were removed). Segmentation was done on all anatomical and functional images to segment images into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) and all images were normalized to standard Montreal Neurological Institute (MNI) space. During registration, functional images were aligned to anatomical images and both were normalized to standard space. A smoothing kernel of 6 mm was used to increase the signal to noise ratio, as well as to reduce spurious activations of single voxels. During denoising, the representative noise signal from WM (5 components) and CSF (5 components) was extracted, and any signal correlated with these components was removed from the BOLD signal. To eliminate frequencies of less interest, a band-pass filter (0.01 Hz, 0.08 Hz) based on the existing ALFF literature was used for the resting-state scan. The following quality assurance parameters were included as second level covariates during data preprocessing: max and mean motion, and max and mean global BOLD signal changes (outlier threshold = global-signal z-value of 3). For the resting-state scan, the total average number of invalid scans was low: 1.45 per participant (SD = 3.03), however there was a significant positive correlation between the number of invalid scans and age ($p = .01$). Similarly, the mean amount of motion was low: 0.20 mm (SD = 0.07 mm), and there was a significant positive correlation between the amount of motion and age ($p < .001$).

2.5. ALFF calculation

The current study investigated spontaneous brain activity during resting-state by examining the Amplitude of Low-Frequency Fluctuations (ALFF), which reflect the average BOLD amplitude or intensity of functional activation. ALFF was calculated using the CONN toolbox. Briefly, for a given voxel, the filtered time course was first converted to the frequency domain using Fast Fourier Transform. The square root of the power spectrum was computed and then averaged across the frequency band (0.01 Hz, 0.08 Hz). The averaged square root was referred as the ALFF (Zang et al., 2007). The normalized ALFF of each participant was used for further statistical analysis.

2.6. Network analysis

To investigate the relationship between ALFF in the language network and language functions, we first identified an extended language network (Ferstl et al., 2008). For this network, 13, 6-mm radius sphere ROIs were created (Fig. 1; Coordinate information can be found in Table 2). Then, the ALFF for each ROI was calculated by averaging across all the voxels in this ROI, and the mean ALFF for each individual was calculated by averaging across all the ROIs in this network. Then, linear regressions were conducted on the mean ALFF for the language network while including Age, the Language Factor scores from the factor analysis, and their interaction as predictors. The Age variable was standardized to z-scores to help with interpretation. The Language Factor scores were already z-scores so there was no need to rescale those. There was no multi-collinearity concern between Age and the Language Factor score as assessed by VIFs <1.7. Additionally, to accommodate variability in the relationship between ALFF, age and language across ROIs, we also conducted a multivariate multiple regression using the ALFF from each language network ROI as the dependent variables, and

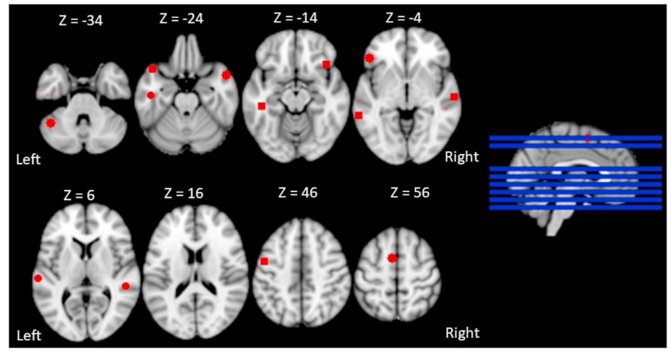

Fig. 1. The 13 Language Network ROIs. Please note that the 6-mm radius sphere ROIs appear to be different shapes and sizes because the axial slices depicted here did not always cross the exact centers of each ROI. The ROIs used in the analyses were identical in size. Slices are depicted in increments of mainly 10 mm, starting at z = −34 and ending at z = 56.

Table 2
MNI coordinates for the Language and Visual Network ROIs. ROIs were created using 6-mm radius sphere around these coordinates.

Language Network				Visual Network			
ROI	x	Y	z	ROI	X	y	z
Left inferior frontal gyrus, pars triangularis	−48	33	−4	Right superior parietal lobule	29	−57	54
Right orbital frontal cortex	39	25	−12	Left superior parietal lobule	−29	−57	54
Left anterior temporal lobe	−44	18	−26	Right intracalcarine cortex	19	−68	13
Right anterior temporal lobe	51	11	−23	Left intracalcarine cortex	−19	−68	13
Left supplementary motor area	−6	3	56	Right lingual gyrus	22	−72	1
Left precentral gyrus	−48	−2	49	Left lingual gyrus	−22	−72	1
Left inferior temporal gyrus	−46	−15	−28	Right superior lateral occipital cortex	29	−80	27
Left posterior inferior temporal gyrus, fusiform gyrus	−44	−29	−15	Left superior lateral occipital cortex	−29	−80	27
Right posterior middle temporal gyrus	62	−17	−6	Right inferior lateral occipital cortex	35	−80	0
Left posterior middle temporal gyrus	−63	−42	−2	Left inferior lateral occipital cortex	−35	−80	0
Left posterior superior temporal gyrus	−63	−23	3				
Right posterior superior temporal gyrus	51	−33	2				
Left cerebellum	−43	−52	−33				

Age and Language Factor score as independent variables.

Additionally, to investigate the specificity of the ALFF results in the language network, additional regressions were conducted on the relationship between the working memory factor scores and the ALFF in the language network, and on the relationship between Language Factor scores and the ALFF in a ‘control’ non-language- related visual network. For the visual network, 10, 6-mm radius sphere ROIs were created based on coordinates obtained from previous studies (Damoiseaux et al., 2006; Power et al., 2011; coordinate information can be found in Table 2).

We were also interested in the functional connectivity in the language network and how it related to language task performance. Therefore, we calculated the un-weighted, within-network connectivity among all the ROIs in the language network. Specifically, for any two ROIs that had a correlation coefficient (i.e., correlation between two ROIs' time series) stronger than 0.2, their connection was included in the analysis. The total degree (i.e., total number of connections among all ROIs in a network) was calculated for each participant and used to reflect the within-network connectivity in the language network. Then, a linear regression was conducted on the total degree for the language network while including Age, Language Factor scores, and their interaction as predictors.

3. Results

3.1. Factor analysis results

We conducted an exploratory factor analysis to assess the data for latent factors. This gave us a four-factor model that accounted for 54% of the variance in the data (TLI: 0.95; CFI: 0.98; RMSR: 0.03; RMSEA: 0.05).[1] Among them, one factor had high positive loadings on the total verbal fluency score (loading = 0.30), WAIS vocabulary score (loading = 0.36), the author recognition task (loading = 0.99), and the comparative reading habit questionnaire (loading = 0.43). All these measurements were related to different aspects of language (e.g., reading, vocabulary), therefore, we referred to this factor as the "Language Factor." Higher factor scores indicated more enhanced language ability in general. Another factor loaded highly on verbal working memory (loading = 0.60), and digit span forwards (loading = 0.72) and backwards (loading = 0.67). This was referred to as the "Working Memory Factor," and higher factor scores were associated with better verbal working memory ability (i.e., more words recalled, longer working memory spans). After identifying the latent factors, individuals' factor scores were calculated. A simple linear regression of age on the factor scores showed that increased age was significantly associated with higher Language Factor scores ($p < .001$), and lower Working Memory Factor scores ($p = .001$), indicating that older adults had enhanced language but decreased working memory abilities.

3.2. ALFF results

To investigate the relationships among age, language task performance, and the intensity of spontaneous brain activity during resting-state, linear regressions were conducted on ALFF (mean = −0.04, sd = 0.13) in the language network while including age, Language Factor scores, and their interaction as predictors. Results showed that increased age was significantly associated with higher ALFF in the language network ($p < .01$, Fig. 2A), indicating that older adults engaged language regions more than younger adults at rest. Additionally, the marginally significant main effect of language score on ALFF indicated that higher Language Factor scores were associated with lower ALFF ($p = .08$, Fig. 2B). The interaction between age and Language Factor score on ALFF in the language network was not significant ($p = .14$).

Moreover, the multivariate regression analysis which accommodates variability in these relationships across different ROIs, showed a similar pattern of results. Specifically, the main effect of age on ALFF was significant ($p < .001$, Fig. 2A), such that increased age was associated with higher ALFF in the language network. The multivariate regression analysis also indicated that the age effects were largest in left temporal regions including superior and inferior temporal gyri, as well as left inferior frontal gyrus, and left cerebellum ($ps < .05$). Although the main effect of the Language Factor score on ALFF was not significant ($p = .44$) in the overall multivariate regression, the language effect was significant in one region: left posterior superior temporal gyrus ($p < .05$). Additionally, the interaction between age and language on ALFF was marginally significant ($p = .09$), which was driven by the significant interactions in left middle temporal gyrus and right superior temporal gyrus ($ps < .05$). To clarify the interaction, participants were further divided into three age groups (51 Younger, 50 Middle-Aged, and 47 Older), and a regression was conducted in each group using the mean ALFF as the dependent variable and Language Factor score as the predictor. Further analysis showed that only in the younger adult group ($p < .05$), but not in the middle-aged ($p = .87$) or the older adult group ($p = .67$), higher Language Factor scores were associated with lower ALFF across all ROIs in the language network (Fig. 2C).

Additionally, to investigate the specificity of the ALFF results in the language network, two additional regressions were conducted. The first one included the Working Memory Factor scores, Age, and their interaction as the predictors and mean ALFF in the language network as the dependent variable. Results showed that although the effect of age on ALFF was significant ($p < .05$), there was no significant relationship between Working Memory Factor scores and the ALFF in the language network ($p = .25$). Furthermore, a regression was conducted on a non-language-related visual network while including Age, Language Factor scores, and their interaction as predictors. The main effect of Age on ALFF in the visual network was significant such that increased age was associated with less intense activity in the visual network at rest ($p = .05$). Critically, the relationship between Language Factor scores and ALFF in the visual network was not significant ($p = .90$). Although these results suggest that the relationship between Language Factor scores and ALFF was specific to the language network, a direct comparison of the regression coefficients showed that these regression coefficients were not significantly different ($Z < 1.96$).[2]

3.3. Functional connectivity

We were also interested in the relationship among functional connectivity within the language network, age, and language performance. Therefore, a regression was conducted on the total degree within the language network while including Age, Language Factor scores, and their interaction as predictors. Only the main effect of Age on total degree was significant, such that increased age was associated with lower degree (i.e., lower within-network connectivity) in the language network ($p < .01$, Fig. 3). Neither the main effect of the Language Factor score nor its interaction with Age was significant ($ps > .1$). Since the relationship between Language Factor scores and degree in the language network was not significant, no further specificity tests were conducted.

4. Discussion

This study examined the amplitude of spontaneous brain activity and functional connectivity during resting-state in a pre-defined language network and their relationships with age and language ability in a lifespan sample. We hypothesized that both the amplitude of resting-state brain activity and functional connectivity would differ as a function of age and language ability. Our results showed that, increased age was associated with higher BOLD amplitude but decreased connectivity

[1] TLI: Tucker-Lewis Index, > 0.95 is considered to be excellent; CFI: Comparative Fix Index, > 0.95 is considered to be excellent; RMSR: Root Mean Square of the Residual, < 0.06 is considered to be excellent; RMSEA: Root Mean Square Error of Approximation, < 0.06 is considered to be excellent.

[2] We directly compared the regression coefficients between the Language Factor and Working Memory Factor scores on ALFF in the language network, and the Language Factor Score effects on ALFF between the language network and the visual network, using the methods suggested by (Clogg et al., 1995) and (Paternoster et al., 1998).

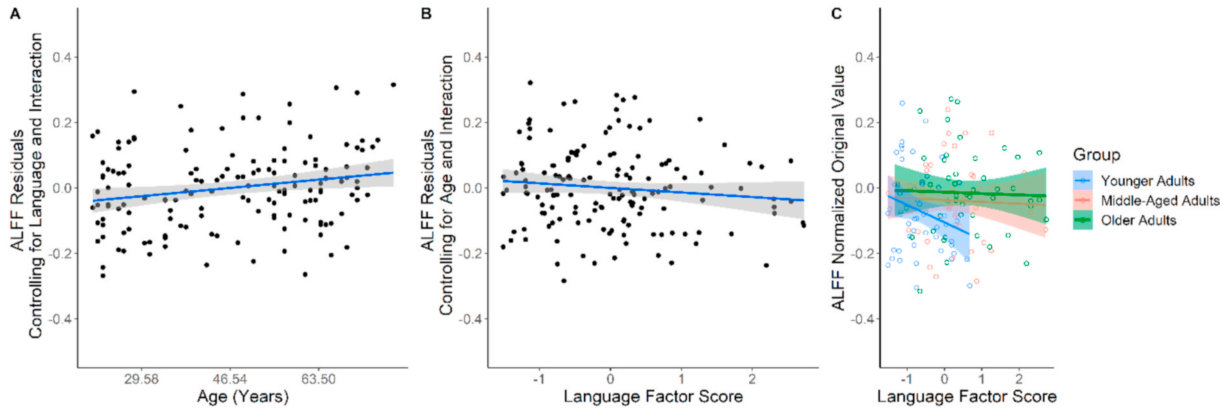

Fig. 2. The relationship between Age, Language Factor scores, and ALFF in the language network. ALFF residuals in A and B are the variances after controlling for the other factors. A) Increased age was associated with higher ALFF, after controlling for the effect of language and its interaction with Age ($p_{regular} < .01$, $p_{multivariate} < .001$). The ages displayed correspond to ± 1 standard deviation and the mean. B) Higher Language Factor scores were marginally significantly associated with lower language network ALFF, after controlling for the effect of Age and its interaction with Language Factor scores ($p_{regular} = .08$, $p_{multivariate} = .44$). C) In the multivariate regression analysis, the interaction between Age and Language Factor score was marginally significant ($p_{multivariate} = .09$). Only in the younger group (YA, $p_{multivariate} < .05$), but not in the middle-aged (MA), or the older group (OA), were higher Language Factor scores associated with lower language network ALFF. We also plotted the effect of Age and Language Factor score on the unadjusted ALFF values, before controlling for other factors. These figures can be found online: https://osf.io/e2rga/?view_only=89588fb3a6bc489fae6ae40a95c88af7.

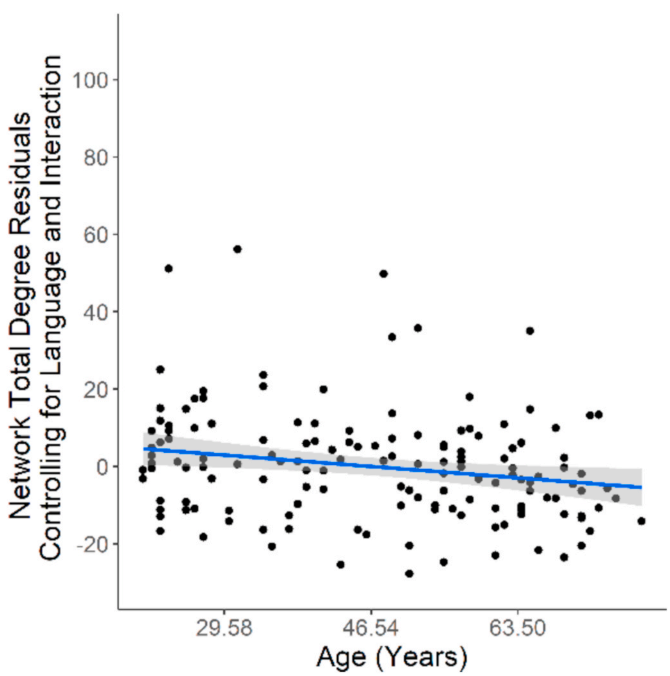

Fig. 3. Increased age was associated with lower within-network connectivity in the language network after controlling for the effect of language and its interaction with age ($p < .01$). ALFF residuals are the variances after controlling for the effect of language and its interaction with age. Ages displayed correspond to ± 1 standard deviation and the mean. We also plotted the effect of Age on the unadjusted network degree values, before controlling for other factors. This figure can be found online: https://osf.io/e2rga/?view_only=89588fb3a6bc489fae6ae40a95c88af7.

within the language network, controlling for the effect of language ability. Additionally, in terms of the brain-behavior relationship, after controlling for the effect of age, higher language abilities were associated with lower ALFF in the left posterior superior temporal gyrus. Finally, the interaction between age and language in the multivariate analysis showed that this language-ALFF relationship was strongest among younger adults.

Looking at the results in more detail, our finding that increased age was related to higher ALFF in the language network indicates that older adults showed more intense functional brain activity in language-related regions during resting-state. Because we used normalized ALFF values for each participant, this age-related difference does not necessarily indicate that the absolute intensity of ALFF was larger for older adults, but still suggests that they utilized their language network to a greater extent compared with younger adults. Although others have reported age-related increases in ALFF in other regions (Mather and Nga, 2013), ours is the first to show this age association in a resting-state language network. This finding of age-related increases in ALFF is also broadly consistent with age-related increases in task-based functional activation that are often reported (Cabeza and Dennis, 2012; Persson et al., 2004; Wierenga et al., 2008; Zhang et al., 2019).

Relating the language network findings to behavioral performance, we found a marginally significant main effect of language on mean ALFF in the language network (regression analyses), with lower ALFF in the language network associated with higher Language Factor scores across all individuals. Although this relationship was only marginally significant, it is consistent with the Yin et al. (2015) study as they also reported a negative correlation between the ALFF in the precuneus and verbal fluency performance. Although we focused on a network analysis rather than individual ROIs in this study, the multivariate regression analysis showed that the effects of language on ALFF were most significant in left posterior superior temporal gyrus.

Though the main effect of language ability on ALFF suggests that this brain-behavior relationship is consistent across the lifespan, we also observed a marginally significant interaction between age and Language Factor scores in the multivariate regression analysis using the ALFFs from each ROI. Further analysis showed that this negative relationship between ALFF and language ability was only significant in the younger adult group, and that the effects were strongest in left middle and right superior temporal gyri. These regions are consistent with where the main effects of Age and Language were localized and are consistent with previous literature highlighting temporal regions as core language regions (e.g., Ferstl et al., 2008; Hickok and Poeppel, 2007; Price, 2010).

The difference in the effect of ALFF on language ability across different age groups could be due to several reasons. First, as shown in Fig. 2C, there were larger Language Factor score variances among older adults compared to younger adults. Therefore, it may have been more challenging to detect a relationship between language and ALFF among older adults. Alternatively, the weaker ALFF-language relationship may suggest a reduced cognitive efficiency among older adults (Ghisletta and

Lindenberger, 2003; Li et al., 2001). Weaker brain-behavior relationships among older adults have been previously observed (Diaz et al., 2014, 2019; Meinzer et al., 2009; Reuter-Lorenz and Cappell, 2008). However, since the relationship between language and ALFF in the language network, and the interaction with age were both only marginally significant, these potential relationships should be interpreted with caution. Nevertheless, our results highlight the general utility of ALFF as a proxy for cognitive ability and are consistent with the idea that increases in ALFF may be associated with less efficient processing.

Although our results suggest that increases in ALFF are related to poorer cognitive performance, the pattern of the language network results are somewhat inconsistent with Hou et al. (2019) who found that increases in ALFF in visual regions as a result of playing video games were related to better MMSE performance. Although they found a positive relationship between ALFF and MMSE, their study was not designed to test for age effects. Since all of their participants were older adults, the increases in ALFF can be most directly linked to the video game experience as opposed to age. Interestingly, our control network, similar to Hou et al. was a visual network. Although it was not the focus of our study, we found that in contrast to the language network, increased age was associated with decreased ALFF in the visual network. Age-related increases in ALFF variability in the visual cortex have previously been reported (Yan et al., 2011). It could be the case that age-related increases in variability led to decreases in our mean values of ALFF. These results also suggest that there may be regional variability in age-related differences in ALFF. However, the functional significance of such differences across networks requires further investigation.

Additionally, although we failed to find a significant relationship between language ability and ALFF in the visual network, these regression coefficients were not significantly different from the significant effects of language ability on ALFF in the language network. This suggests that these effects of language ability on ALFF may be subtle.

In addition to examining resting-state brain activity amplitude, we were also interested in the functional connectivity within the language network and its relationship with age and language ability. We found that increased age was related to decreased within-network connectivity in the language network. This finding is consistent with the few previous studies that have examined the effect of age within the language network (Ferré et al., 2019), and other studies that have shown age-related decreases in whole-brain connectivity (Betzel et al., 2014; Chan et al., 2014; Varangis et al., 2019) or in other resting-state networks such as the default mode or control networks (Geerligs et al., 2015; Siman-Tov et al., 2017; Tomasi and Volkow, 2012). Additionally, although increasing age was associated with lower within-network connectivity, there was no significant relationship between language ability and within-network connectivity, consistent with Ferré et al. (2019). Comparing the ALFF and connectivity results, the relationship with language ability was only significant in resting-state ALFF, but not in connectivity. Although ALFF is related to the amplitude of the BOLD signal, it's important to note that the exact underlying biological mechanisms of ALFF activity are still not clear. However, the difference in the two measures in terms of the relationships between language and ALFF suggests that ALFF might be a more sensitive biomarker than functional connectivity in characterizing resting-state brain activity and its relation to cognition.

In conclusion, focusing on the resting-state language network, we found that increased age was associated with more intense brain activity but lower within-network connectivity. Additionally, these increases in activity within the language network during resting-state were related to worse language ability, particularly among younger adults, supporting a dedifferentiation account of cognition. Our results support the utility of using resting-state data as an indicator of cognition and suggest that brain-behavior relationships are weaker among middle-aged and older adults. Our findings also support the role of ALFF as a potential biomarker in characterizing the relationships between resting-state brain activity, age, and cognition.

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