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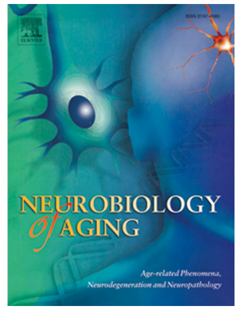

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Age-related differences in resting-state and task-based network characteristics and cognition: A lifespan sample

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Abstract

Aging is often associated with cognitive and neural decline, but how these factors interact is still not fully understood. Recently, functional connectivity, or the degree to which brain regions are concurrently active, has provided insight into age-related differences. However, functional connectivities during task and rest differ and few studies have examined how these relate to a broad range of cognitive functions. The present study investigated the effect of age on cognition, whole-brain functional connectivity during resting-state and task, and their relationships across the adult lifespan. Cognition was broadly assessed using a battery of cognitive assessments and mean network characteristics were calculated across the whole brain. Behaviorally, increased age was associated with worse recall, executive function, and verbal working memory abilities, but better language performance. Neurally, increased age was associated with lower overall within- and between-network functional connectivities during both rest and task, and these age—connectivity relationships were stronger during task performance. Connectivity was also related to cognition, and for all participants, these relationships were strongest during rest. Specifically, higher resting-state between-network functional connectivity was associated with poorer cognition for all adults, and poorer language ability among older adults. Collectively, these findings demonstrate that while age effects were strongest during task, resting-state functional connectivity was most closely tied to cognition. Moreover, these results are theoretically consistent with dedifferentiation accounts of cognition and aging and show that less differentiated functional connectivities are associated with cognitive costs for both older and younger adults.

Keywords: Functional connectivity; Resting-state; Task-based; Aging; Cogniti**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), language production (Burke and Shafto, 2008; Shafto et al., 2007), and cognitive control (Paxton et al., 2008; Schaie, 1996). Concurrent with age-related cognitive decline, older adults often experience neural decline and many studies have focused on the patterns of correlated activity in the human brain (i.e., functional connectivity). However, previous studies have largely focused on either task-based data or resting-state data. The difference between task-based and resting-state data may be of particular importance in the study of aging as age-related cognitive and neural differences may be more pronounced during a task (e.g., Davis et al., 2014). Moreover, aging studies most commonly focus on younger and older adults, leaving out middle-aged participants who represent a significant portion of the adult lifespan. Lastly, most previous studies have focused on brain–behavior relationships within a single cognitive domain (e.g., King et al., 2018) or a single network (e.g., Andrews-Hanna et al., 2007), instead of a whole-brain level across multiple cognitive domains. To address these issues, we examined task-based and resting-state data collected from a large sample of individuals from across the lifespan and relate these neural measures to a broad assessment of cognitive abilities including executive function, recall, working memory, and language.

Functional connectivity analyses directly measure the temporal correlation of functional activations across the brain, and one hypothesis is that this coordinated pattern of activations may reflect how functionally specialized brain regions work together and interact (Friston, 1994). When brain regions have coordinated patterns of activation, they are said to form functional networks such as the default mode network (DMN) or the executive control network (ECN, Power et al., 2011), among others. Studies of functional connectivity are often based on “resting-state” fMRI data, which is collected while participants are not performing an explicit task (Biswal et al., 1995), and reflects a default state of overall brain organization which may be related to task performance (Raichle and Gusnard, 2005; Raichle et al., 2001). In such resting-state studies older adults often show lower within-network connectivity, and this has primarily been demonstrated in the DMN (Betzel et al., 2014; Cao et al., 2014; Geerligs et al., 2015; Onoda et al., 2012; Siman-Tov et al., 2017; Song et al., 2014; Tomasi and Volkow, 2012). These reduced connectivities in network characteristics have often been associated with worse behavioral performance across different cognitive domains (King et al., 2018; Onoda et al., 2012; Sala-Llonch et al., 2015; Varangis et al., 2019a; Wang et al., 2010).

Although there have been many functional connectivity studies during resting-state, these typically focus on connectivity within a specific functional network in isolation. However, networks often interact with one another, so examining the relationships between networks across the whole brain is important in understanding overall brain functioning. Yet, only a few studies have examined how functional networks work together, and how this relates to age and cognition (Chan et al., 2018; Chan et al., 2014; Varangis et al., 2019a). In looking at network segregation, a measure that combines both within- and between-network connectivities to provide a measure of the degree to which different networks share connections, older age was associated with lower network segregation during resting-state (Chan et al., 2014; Varangis et al., 2019a). Additionally, less segregated networks, such as the DMN and dorsal attentional network (DAN), were associated with worse episodic memory scores (Chan et al., 2014) and with worse performance on speed, fluid intelligence, and memory tasks (Varangis et al., 2019a). Interestingly, these network segregation–cognition relationships were independent of age, indicating that less differentiated brain networks are associated with lower cognitive functioning across the lifespan.

In addition to examining whole-brain network characteristics, the type of data one examines is also relevant. Studies have demonstrated that brain connectivity patterns are different when engaged in a task, compared to connectivity patterns observed during resting-state (e.g., within and between network connectivity, reorganization of communication hubs; Cole et al., 2014; Gonzalez-Castillo and Bandettini, 2018). This may be particularly relevant for aging research, as older adults often show larger age-related differences during laboratory-based tasks compared to more naturalistic tasks (e.g., Davis et al., 2014). Several studies have looked at task-based connectivity and its relationship with age and cognition when participants were engaged in certain tasks. They found that increased age was associated with decreased task-based, within-network connections in the DMN, as well as other networks such as supplementary motor regions, and the DAN-somatomotor network (Andrews-Hanna et al., 2007; Geerligs et al., 2014; Steffener et al., 2012). Additionally, reduced task-based, within-network connectivity reported in these studies were associated with poorer cognitive performance in domains such as executive function, memory, and processing speed. Additionally, studies also reported that older adults showed different between-network connectivity patterns compared to younger adults (Geerligs et al., 2014; Varangis et al., 2019b). For instance, Varangis et al. (2019b) found that age may particularly affect between-network connectivity with the DMN, memory, and salience networks, however the age-effects were variable, with older adults showing higher between network connectivities between the fronto-parietal network and the salience and memory networks, and younger adults showing higher between-network connectivities between the DMN and the salience and memory networks. Collectively, these studies suggest that the effects of age on functional connectivities were similar between resting-state and task performance, such that older adults typically show weaker within-network connectivity, and sometimes weaker between-network connectivity.

In sum, many existing studies have examined age-related differences in functional connectivity during rest or a task, consistently finding that older adults showed lower within-network connectivity compared to younger adults. Additionally, lower within-network connectivity has been associated with worse behavioral performance across several different cognitive domains. However, the findings for age-related differences in between-network connectivity are less consistent. To date, very few studies have investigated both resting-state and task-based connectivity and their relationship with age and cognition (but see a study comparing adults and children, Hutchison and Morton, 2015). Moreover, the previous literature examining the relationships between age, cognition, and the brain 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 and investigated age-related differences in cognitive and brain functions across the lifespan (Chan et al., 2014; Varangis et al., 2019a). Therefore, examining differences between resting-state and task-based functional connectivity within-subjects across the lifespan is essential to further our understanding of how brain–behavior relations differ with age, as well as with task demand. Additionally, individual differences in cognition may also play a role in these relationships, highlighting the importance of considering such factors. The current study used a whole-brain network approach to investigate the effect of age on resting-state and task-based functional connectivity and its relationship with cognition across the adult lifespan (i.e., 20-75 years). Additionally, given the potential effect of education and socioeconomic status on cognition and neurodevelopment (Braveman and Gottlieb, 2014; Chan et al., 2018; Hackman et al., 2010; Hurst et al., 2013; Wang and Geng, 2019), education was controlled for in all analyses. We predicted that increased age would be associated with lower within-network connectivity. However, given the inconsistent literature on age-related differences in between-network connectivity, either a positive or negative relationship between age and between-network connectivity could be possible. We were also interested in the relationship between these network measures and cognition to better understand if age-related differences in these metrics are compensatory or reflect decreased neural efficiency. For instance, higher between-network connectivity or lower within-network connectivity in older adults that relates to worse cognitive performance would reflect dedifferentiation, in which increases in functional connectivity are interpreted as decreases in neural efficiency (Ghisletta and Lindenberger, 2003; Li et al., 2001). However, higher between-network connectivity or lower within-network connectivity in older adults that relates to enhanced behavioral performance can be interpreted as a potential compensatory mechanism for weakened efficiency (Cabeza and Dennis, 2012). Furthermore, given the increased cognitive demands of engaging in a task, we expected task-based connectivity to be more sensitive to age and cognitive performance compared to resting-state connectivity (i.e., Compensation-Related Utilization of Neural Circuits Hypothesis, CRUNCH, Reuter-Lorenz and Cappell, 2008).

2. Method

2.1 Participants

Ninety-one adults (ages: 20-75 years, mean age = 47.4 years, sd = 17.4 years, 54 female) participated in the experiment. All participants were community-dwelling, right-handed, native 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).

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. First, participants completed the Mini-Mental State Exam to screen for mild cognitive impairment or dementia (MMSE, Folstein et al., 1975), and the Geriatric Depression Score (GDS) short version to screen for depression[1] (Guerin et al., 2018; Sheikh and Yesavage, 1986). Participants also completed several cognitive assessments that were either standardized or adapted from standardized neuropsychological assessments including WAIS-III vocabulary to assess vocabulary size (starting from item 13 “Remorse”), forward and backward digit span to

[1] While the GDS was designed for use in an older adult population, studies have shown that it has good diagnostic sensitivity and specificity for adults aged 18 and older, particularly when using the short-form which is what we incorporated here (Guerin, Copersino, Schretlen, 2018).

assess working memory, and a computerized adaptation of the digit-symbol subtests to assess processing speed (Wechsler et al., 1997); simple (i.e., respond to a black square as quickly as possible) and choice (i.e., identify the direction of left/right arrows as quickly as possible) reaction time tests to assess processing speed; a computerized Stroop task to assess executive function (i.e., make a response to the color of the ink when it is consistent/inconsistent with the word meaning, MacLeod, 1991; Stroop, 1935); the California Verbal Learning Test to assess immediate and delayed memory (i.e., one learning trial, 16 word list in 4 categories, one immediate recall assessment, one delayed recall assessment, and one delayed recognition, Woods et al., 2006); a reading span task to assess verbal working memory (Conway et al., 2005); phonemic (F, A, S) and categorical (animals) verbal fluency to assess speech fluency (Patterson, 2011), and the author recognition test and a comparative reading habit questionnaire to assess reading habits (Acheson et al., 2008). During the MRI session, participants completed a functional neuroimaging picture naming task to assess language production, which is reported elsewhere (Diaz et al., under review). In this task, participants were presented with pictures of objects and were asked to overtly name each picture as quickly and accurately as possible. Detailed descriptions of each of these above-mentioned tasks can be found in the Supplementary Materials. Demographic characteristics and assessment scores 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.

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

Demographic information	**Mean (SD)**	
N	91	
Age (Years)	47.4 (17.4)	
Gender (M/F)	37/54	
Participant characteristics	**Mean (SD)**	**Age regression**
Education (Years)	16.9 (2.5)	0.24*
MMSE (Score out of 30)	28.9 (1.0)	-0.19
Depression (GDS) (Score out of 15)	0.8 (1.2)	-0.13
Cognitive Assessments		
Simple RT (Box, ms)	297.2 (83.5)	0.18
Choice RT (Arrow, ms)	323.8 (55.7)	0.56***
Recognition RT (ms)	1262.0 (301.2)	0.29**
Digit Symbol RT (ms)	1622.2 (385.6)	0.67***
Digit Span Forward (Score out of 16)	11.4 (2.2)	-0.21*
Digit Span Backward (Score out of 16)	7.3 (2.1)	-0.25*
Stroop Effect RT (Incongruent-Congruent, ms)	69.3 (85.0)	0.38***
Verbal Working Memory (Score out of 1)	0.4 (0.2)	-0.37***
Immediate Recall (Score out of 16)	11.0 (2.6)	-0.25*
Delayed Recall (Score out of 16)	9.5 (3.1)	-0.26*
Verbal Fluency (Number of correct responses) †	68.0 (14.7)	-0.16
Phonemic Fluency (F, A, S)	44.6 (11.6)	-0.05
Category Fluency (Animal)	23.4 (5.4)	-0.08**
WAIS Vocabulary (Score out of 66)	54.5 (6.6)	0.09
Author Recognition Test (ART)† (Score out of 76)	24.7 (14.6)	0.52***
Comparative Reading (Score out of 35)	24.8 (5.1)	0.07

*The second column displays means, with standard deviation in parentheses. The numbers represent the raw scores of each test. The third column indicates its correlation coefficient with age. *Denotes a statistically significant difference, * p < .05; ** p < .01; *** p < .001. †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 commissure and posterior commissure (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 minutes). Two additional volumes were acquired and deleted at the start of the 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. Four task-based runs using the same parameters as the resting-state run were also collected after the resting-state run (task run duration = ~5.6 minutes). During the task runs, participants were presented with pictures and were asked to name each picture as quickly and accurately as possible. Here we focus on functional connectivity analyses of resting and task-based runs.

Finally, a field map sequence was performed 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 minutes) that generated 2 magnitude images and 1 phase image.

2.3 Behavioral Data Analyses

As mentioned earlier, participants performed a series of standardized behavioral tests to measure cognitive functions across different domains (See Table 1 for the list of Cognitive Assessments). To better capture the relationship between age and an individual's cognitive ability, a factor analysis was conducted to identify shared components that reflect different cognitive functions. Before conducting the factor analysis, a data cleaning procedure was conducted as follows. First, 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. Additionally, for individuals with missing data (one participant had 35.7% missing data, and 6 participants had 7.1% 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, N = 1), leaving a final sample of 90 individuals to be included in the factor analysis.[2] We examined the residuals to confirm that the assumptions for a parametric test were met. Results showed that there was no

[2] One participant was excluded after the factor analysis data cleaning procedure. Thus, any analyses that involved the factor analysis scores included 90 participants' data. However, the complete sample of 91 participants was included in the age-network connectivity analysis.

multi-collinearity concern among the cognitive variables (VIFs < 5) and the residuals 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 = .70 > .60, Kaiser, 1974), which motivated our use of factor analysis. The *psych* package in the R environment was used for the factor analysis (Revelle, 2015). Cognitive variables that were not normally distributed were log transformed to better approximate a normal distribution (mean skewness after transformation = 0.14). All cognitive variables were standardized using the *scale* function in the R environment ((score-mean)/sd). We used a parallel analysis (i.e., where the actual data and the simulated data intersect) to decide how many factors were meaningful. The *oblimin* rotation was used to produce oblique psychological factors.

After the latent factors were identified, factor scores for each participant were then calculated. Then regressions were conducted on each factor while including age as the independent variable and years of education as a control variable. Because the relationship between age and cognitive functions across the lifespan may not always be linear, we first fit a linear regression of age on each factor, then added a quadratic age term to see if the model fit was significantly improved.

As with the behavioral factor analysis, the same normalization and standardization processes were conducted on all variables in the regression analyses.[3] After the transformation, there was no multi-collinearity concern among the independent variables (VIFs < 5). Furthermore, subject-level random effects were also included in the regression models to accommodate potential individual level effects.

2.4 fMRI Data Preprocessing

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. One participant's data was excluded from the task-based connectivity analysis due to missing data from one run. 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.,

[3] Age was not normally distributed in the current sample, because we explicitly recruited sub-samples from each decade (ages 20 – 79) to achieve a lifespan sample. Although the sampling was not perfectly balanced across decades, this recruitment approach resulted in a largely rectangular distribution (see Figure 1 in supplementary materials).

data points more extreme than the 97th percentile based on a normative sample). All anatomical and functional images were normalized into standard MNI space. The anatomical images were segmented into grey matter, white matter, and CSF tissue classes using SPM12 unified segmentation and normalization procedure, then these masks were applied to the functional images (Ashburner and Friston, 2005). 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 (0.008, 0.09) was used for the resting-state scan (Davey et al., 2013; Gohel and Biswal, 2015; Hallquist et al., 2013) and a high-pass filter (0.008, infinite) was used for task-based scans (Gonzalez-Castillo and Bandettini, 2018). The effects of the following quality assurance parameters were controlled for during data analysis: number of outlier and non-outlier scans (outlier threshold = 0.5 mm), 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 1.55 out of 180 scans/volumes (0.9%, SD = 3.06), and there was a marginally significant positive correlation between number of invalid scans and age (p = .06, β = .60, 95% CI = [-.03, 1.23], R^2 = .03). The mean amount of motion was 0.20 mm (SD = 0.08 mm), and there was a significant positive correlation between the amount of motion and age (p < .001, β = .04, 95% CI = [.02, .05], R^2 = .20).

For the task-based scans, the total average number of invalid scans across all runs was 24.02 out of 708 scans/volumes across four runs (3.4%, SD = 43.21), and the effect of age was not significant (p = .14, β = 6.75, 95% CI = [-2.30, 15.79], R^2 = .01). The mean amount of motion during the task runs was 0.27 mm (SD = 0.10 mm), and there was a significant positive correlation between the amount of motion and age (p < .005, β = .03, 95% CI = [.01, .05], R^2 = .10). The analyses removing variance associated with all of the variables described above occurred in a single linear regression step, and the residualized BOLD signal was used for further statistical analyses.

2.5 Node definition

Chan et al. (2014) identified 441 coordinates in the brain and created fixed-radius disks (3 mm geodesic radius) around those locations. We used the same 441 locations and created 4 mm non-overlapping fixed-radius disks using the MNI152, 2mm brain as the reference (The ROI size increased to 4 mm fixed-radius disks due to the reference image resolution). All nodes were further divided into 10 networks (Hand somatomotor, Mouth somatomotor, Visual, Salience, Auditory, Cingulo-opercular control, Fronto-parietal control, Ventral attention, Dorsal attention, and Default) according to Power et al. (2011) and 108 nodes were excluded from the analysis due to poor classification fit with the Power networks. Therefore, the final set included 333 nonoverlapping nodes.

2.6 fMRI Data Analysis

For each participant, the resting-state and task-based fMRI time series of each node was extracted, then a cross-correlation of each node's time course with every other node's time course was calculated, forming a 333 × 333 correlation matrix for each scan type. Correlation coefficients were then converted to Z-values using Fisher's equation. Negative correlations were not included in further analysis due to uncertainty regarding the meaning of negative correlations (Hallquist and Hillary, 2018).[4] The final matrix for each scan type for each participant was a 333 × 333 weighted Z-matrix with the diagonal and negative values set to zeros.

Using the same methods as Chan et al. (2014), we also calculated within-network connectivity, between-network connectivity for each network for each scan type. We did not use the segregation measure because it is derived from within- and between-network connectivities, making it inter-dependent with those measures. Within-network connectivity was calculated as the mean node-to-node correlation of all nodes in that network. Between-network connectivity was calculated as the mean correlation value between each node in one network and the rest of the nodes outside of that network. Furthermore, for each scan type of each participant, mean within-network connectivity, and mean between-network connectivity were calculated by averaging those measurements across all networks. Since we were interested in the relationship between age and each network measurement, and the difference between resting-state and task-based status, mixed effect regression models were conducted.[5] For each regression, one network measurement was used as the dependent variable, while age,

[4] Negative correlations may be related to statistical artifacts and global signal regression, or N-methyl-D-aspartate (NMDA) action in cortical inhibition. Moreover, others have also adopted a similar strategy, for example, Chan et al., 2014 set all negative nodes to 0. To be comparable to their findings, we adopted the same analysis strategy. For a full discussion about the meaning of negative correlations see Hallquist & Hillary, 2018.

[5] The main focus of the paper was on overall brain network characteristics. Therefore, only the mean network properties across all networks are reported in the main body of the paper. We also conducted analyses on selected individual networks, which are reported in supplementary materials.

scan type and their interaction were included as independent variables, and years of education was included as a control variable.

Additionally, previous studies have used the partial correlation to explore the relationship between network measures and cognition controlling for the effect of age on both variables (Andrews-Hanna et al., 2007; Chan et al., 2014; Geerligs et al., 2014). Although this type of analysis examines the age-invariant brain–behavior relationship, it cannot provide information about the interaction between age and either factor. Since we were interested in how age affects the relationship between network measures and cognition, we conducted regression analyses on cognitive factor scores while including age, scan type, network characteristics (i.e., within- and between-network connectivities), and their interactions in the models while including years of education as a control variable. For cases where the interactions were significant, further analyses were conducted to investigate the direction of the interactions. Since these models were testing a similar hypothesis (i.e., the effect of age and network measures on cognition), and the dependent variables from the behavioral factor analysis of these models are not entirely independent from each other, multiple comparisons were corrected using the False Discovery Rate (FDR) method.

In addition to the regression analyses we were also interested in testing the mediation effect of the network measures on the relationship between age and cognition. Therefore, additional mediation analyses were conducted, while controlling for the effect of years of education.

3. Results

3.1 Behavioral Factor Analysis and Effect of Age

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: 0.99; CFI: 1.00; RMSR: .04; RMSEA: .04).[6] The first factor had high positive loadings from immediate recall (loading = 1.00) and delayed recall (loading = .81), therefore, we named it the "Recall Factor." Higher scores on the Recall Factor suggested better Recall. The second factor had high positive loadings on the total verbal fluency score (loading = .31), WAIS vocabulary score (loading = .46), the author recognition task (loading = .98), and the comparative reading habit questionnaire (loading = .56). All these measurements were related to different aspects of language (e.g., reading, vocabulary), therefore, we referred to this factor as the "Language Factor." The third factor loaded positively on reaction time measurements of executive functions, including the recognition task (loading = .50), simple speed task (loading = .56), choice speed task (loading = .91), digit symbol task (loading = .56), and the Stroop effect (loading = .38). Therefore, we named it the "Executive Factor." Because the tasks loading on the Executive Factor reflect speed of response as well as amount of interference, higher Executive Factor scores were associated with worse executive function ability. Lastly, the fourth factor loaded highly on the reading span task score (loading = .69), digit span forwards (loading = .75) and backwards (loading = .65).[7] This was referred to as the

[6] TLI: Tucker-Lewis Index, > .95 is considered to be excellent; CFI: Comparative Fix Index, > .95 is considered to be excellent; RMSR: Root Mean Square of the Residual, < .06 is considered to be excellent; RMSEA: Root Mean Square Error of Approximation, < .06 is considered to be excellent.

[7] Note that Verbal Fluency also loaded relatively highly on the Verbal Working Memory factor (loading = .41). This may be because verbal fluency taps into both language as well as memory aspects (as participants are asked to generate only novel items, and so must keep track of what responses they have already provided). Because Phonemic and Semantic verbal fluency may tap into different aspects of

"Verbal Working Memory Factor," and higher factor scores were associated with better verbal working memory ability (i.e., more words recalled, longer working memory spans).

Individuals' factor scores were also calculated for each latent factor. Then regression analyses were conducted for each factor while including participant age as the independent variable and years of education as a control variable. Results showed that increasing age was associated with higher factor scores on the Language (p < .001, β = .40, 95% CI = [.22, .59], R^2 = .29) and Executive Factors (p < .001, β = .27, 95% CI = [.21, .32], R^2 = .51), and lower scores on the Recall (p < .05, β = -.27, 95% CI = [-.48, -.06], R^2 = .08), and Verbal Working Memory Factors (p < .001, β = -.40, 95% CI = [-.57, -.22], R^2 = .18), indicating that increasing age was related to enhanced language abilities, and worse executive function, recall, and verbal working memory abilities. Higher education was only significantly associated with higher language scores (p < .01, β = .27, 95% CI = [.09, .46], R^2 = .29). Additionally, to better capture age-related differences in cognitive measurements, a quadratic regression was also conducted between age and the latent factors. We found that adding a quadratic term of age significantly improved the model fit of the Language Factor (p < .05, β = -1.73, 95% CI = [-3.39, -.07], R^2 = .31), such that although language scores increased with age, as age increased, increases in language ability were smaller.

3.2 The Effect of Age and Scan Type on Network Characteristics

language production and cognition, we also ran a factor analysis with these measures separated. The results showed that the phonetic fluency loaded highly and similarly on the Language and Verbal Working Memory Factors, but the semantic fluency load similarly but not highly on the Language and the Verbal Working Memory Factors. This suggests that the loading of the total Verbal Fluency score was driven by phonemic (FAS) fluency.

The mean node-to-node correlation matrix (10 networks) during resting-state and task-based data can be found as Supplementary Figures 2 and 3. In order to test the effect of age on network characteristics and also compare resting-state and task-based network characteristics, analyses were conducted on each network characteristic while including age, scan type, and their interaction as independent variables, and years of education as a control variable. These effects were displayed in Figure 1.

First, across both scan types, increased age was significantly associated with lower overall within-network connectivity (p < .001, β = -.01, 95% CI = [-.02, -.007], R^2 = .55, see Figure 1). The main effect of scan type on within-network connectivity was also significant, such that the resting-state within-network connectivity was significantly higher than the task-based within-network connectivity (p < .001, β = -.07, 95% CI = [-.074, -.068], R^2 = .55). Additionally, the interaction between age and scan type on within-network connectivity was also significant (p < .001, β = -.01, 95% CI = [-.02, -.005], R^2 = .55). To further analyze this interaction, we examined the data by scan type. Although the relationship between age and within-network connectivity was significant for both task-based and resting-state scans, the significant interaction indicated that the effect of age on within-network connectivity was significantly stronger in the task-based scan (p < .001, β = -.02, 95% CI = [-.03, -.01], R^2 = .29) compared to the resting-state scan (p = .049, β = -.01, 95% CI = [-.02, -.00002], R^2 = .04).

For between-network connectivity, increased age was associated with lower connectivity (p < .05, β = -.02, 95% CI = [-.05, -.003], R^2 = .66). There was also a main effect of scan type such that, between-network connectivity was significantly higher during resting-state compared to the task (p < .001, β = -.35, 95% CI = [-.38, -.31], R^2

= .66). The interaction between age and scan type was also significant ($p < .05$, $\beta = -.04$, 95% CI = [-.07, -.009], $R^2 = .66$), indicating that the effect of age on between-network connectivity differed between scan types. Further analyses breaking down the data into different scan types showed that the effect of age on between-network connectivity was only significant during the task ($p < .01$, $\beta = -.05$, 95% CI = [-.07, -.02], $R^2 = .11$), but not during the resting state ($p > .1$, $\beta = -.004$, 95% CI = [-.03, .02], $R^2 = .01$).

In summary, overall the resting-state scan had higher within- and between-network connectivities compared to the task-based scan. Moreover, increased age was associated with lower within-network connectivity and lower between-network connectivity in general, although the effect of age on within- and between-network connectivities seemed to be driven by the task-based scan.

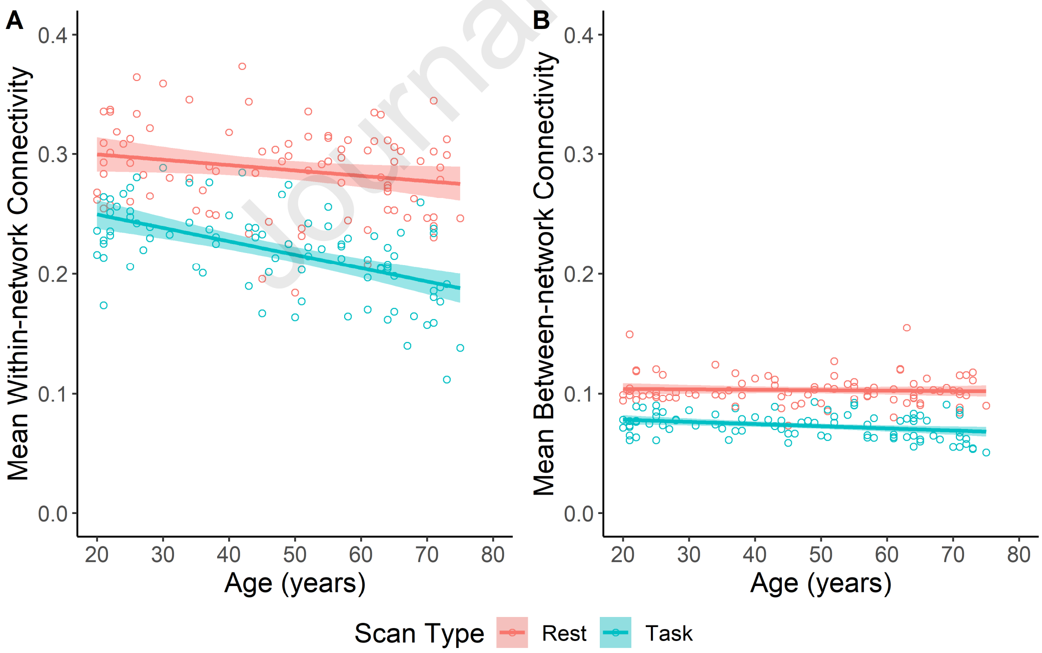

Figure 1. Effect of age and scan type on network characteristics: (a) Increased age was associated with lower within-network connectivity in both resting-state and task-based scans (i.e., main effect of age, $p < .001$), and this relationship was stronger during the task (i.e., interaction between scan type and age, $p < .001$; Task $p < .001$ vs. Rest $p = .049$); (b)

Increased age was associated with lower between-network connectivity across both scan types (i.e., main effect of age, $p < .05$), and this was driven by the task, but not resting-state (i.e., interaction between age and scan type, $p < .05$; Task $p < .01$ vs. Rest $p > .1$). Red dots represent resting-state data points. Blue dots represent task-based data points. Higher within- and between-network connectivities were observed during resting-state scans compared to during the task (i.e., main effect of scan type, *p*s < .001).

3.3 Contribution of Brain Network Characteristics and Age to Cognition

To investigate how the interaction between network characteristics and age contribute to behavioral measurements of cognitive abilities, we performed a regression on each cognitive factor including the within- and between-network connectivities, age, scan type, and their interactions. Additionally, years of education was also included in the model as a control variable. An FDR correction was used to correct for multiple comparisons (the reported *p* values and 95% confidence intervals below were after correction).

To summarize, consistent with our behavioral models (Section 3.1), increased age was significantly associated with higher Language Factor scores (i.e., better language performance, $p < .001$, $\beta = .64$, 95% CI = [.33, .95], $R^2 = .33$), higher Executive Factor scores (i.e., worse executive function, $p < .001$, $\beta = .35$, 95% CI = [.26, .44], $R^2 = .60$), and lower Verbal Working Memory scores (i.e., worse verbal working memory, $p < .001$, $\beta = -.38$, 95% CI = [-.67, -.09], $R^2 = .24$). Unlike the behavioral model, the relationship between age and the Recall Factor scores was no longer significant ($p > .1$, $\beta = -.12$, 95% CI = [-.46, .22], $R^2 = .16$) when including network characteristics.

Furthermore, for the Recall Factor, higher overall between-network connectivity ($p < .05$, $\beta = -.46$, 95% CI = [-.92, -.0008], $R^2 = .16$), and lower overall within-network connectivity (p = .07, β = .36, 95% CI = [-.04, .77], R^2 = .16) were associated with lower Recall Factor scores, independent of age (Figure 2). The interaction between scan type and between-network connectivity was marginally significant at all ages (p = .09, β = .76, 95% CI = [-.16, 1.68], R^2 = .16). Further analyses of the different scan types showed that higher between-network connectivity was only associated with worse recall during the resting-state scan (p < .01, β = -.84, 95% CI = [-1.35, -.35], R^2 = .20), but not the task-based scan (p > .1, β = -.08, 95% CI = [-.58, .41], R^2 = .13). Other interactions, including the three-way interactions among age, scan type, and within- and between-network connectivities, on the Recall Factor were not significant (ps > .1, 95% CIs of β include 0).

For the Executive Factor, although there were no significant main effects of connectivity measures on Executive Factor scores (ps > .1, 95% CIs of β include 0), the interaction between scan type and between-network connectivity was significant (p < .05, β = -.27, 95% CI = [-.50, -.03], R^2 = .60, Figure 3). Further analyses of the different scan types showed that higher between-network connectivity was associated with higher (worse) Executive Factor scores during the resting-state scan (p < .05, β = .13, 95% CI = [.005, .25], R^2 = .64), but lower (better) Executive Factor scores during the task scan across all ages (p < .05, β = -.14, 95% CI = [-.26, -.009], R^2 = .57). In general, these results indicated that higher between-network connectivity during resting-state was associated with worse executive function, consistent with the results on the recall ability. However, during the task, higher between-network connectivity was associated with better executive function. Other interactions, including the interaction between scan type and within-network connectivity, and the three-way interactions on the Executive Factor were not significant (*ps* > .1, 95% CIs of β include 0).

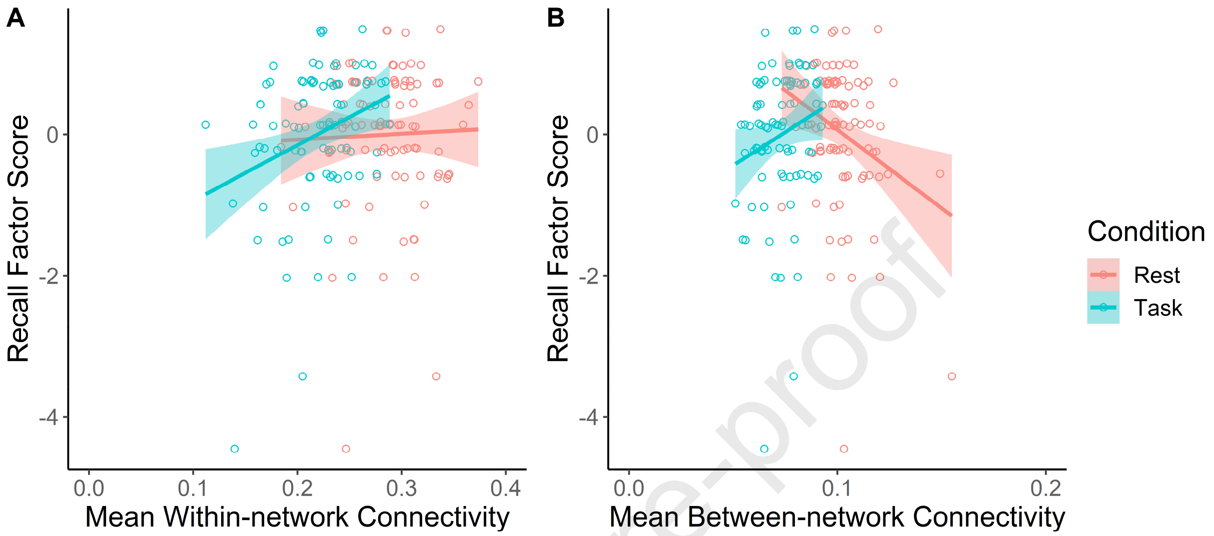

Figure 2. Relationship between network measures and Recall Factor scores across both scan types: (a) The main effect of within-network connectivity on Recall Factor Scores was marginally significant ($p = .07$), such that lower within-network connectivity was associated with worse recall across both scan types, (b) The main effect of between-network connectivity ($p < .05$), and its interaction with scan type ($p = .09$) on Recall Factor Scores were (marginally) significant, such that higher between-network connectivity was associated with worse recall but this was driven by the resting-state ($p < .01$), not the task-based data ($p > .1$).

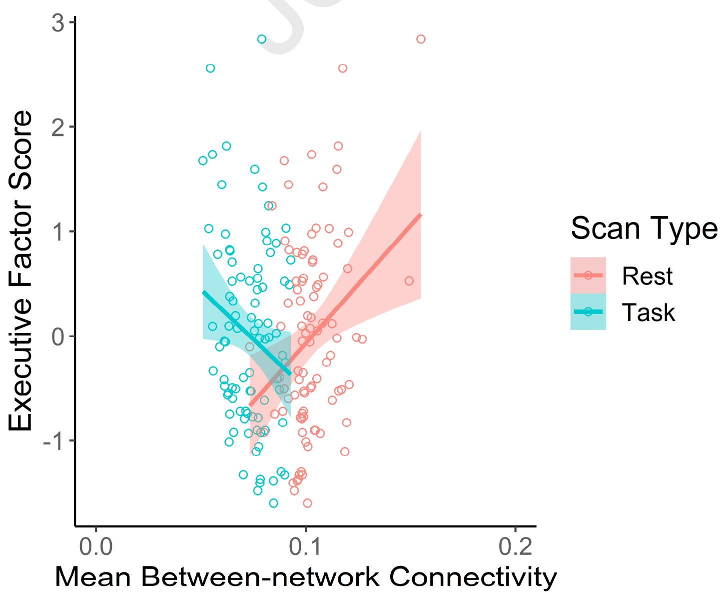

Figure 3. The interaction between scan type and between-network connectivity on Executive Factor scores ($p < .05$). Higher between-network connectivity during rest ($p < .05$) and lower between-network connectivity during task ($p < .05$) were associated with worse executive function (higher executive function factor score). The interaction between scan type and within-network connectivity was not significant on Executive Factor scores ($p > .1$), therefore, was not plotted.

Finally, on the Language Factor, while there were no significant main effects (*p*s > .1, 95% CIs of β include 0), there was a marginally significant three-way interaction among age, scan type, and between-network connectivity ($p = .07$, $\beta = .72$, 95% CI = [-.10, 1.55], $R^2 = .33$, Figure 4). Further analyses showed that the interaction between age and between-network connectivity was significant during the resting-state scan ($p < .05$, $\beta = -.53$, 95% CI = [-1.00, -.08], $R^2 = .35$) but not during the task-based scan ($p > .1$, $\beta = .19$, 95% CI = [-.24, .63], $R^2 = .31$). To better understand this interaction in the resting-state data, we conducted a Johnson-Neyman test to investigate at what age the relationship between the resting-state between-network connectivity and the Language Factor score became significant (Esarey and Sumner, 2018; Johnson and Fay, 1950). Results showed that the relationship between higher resting-state between-network connectivity and lower Language Factor scores became significant at the age of 57.99 (FDR corrected $p < .05$, Figure 4). These results suggest that a less specialized functional network structure during resting-state in older adults was associated with worse language ability. Other interactions on the Language Factor were not significant (*p*s > .1, 95% CIs of β include 0). There were no significant effects of network measures on verbal working memory.

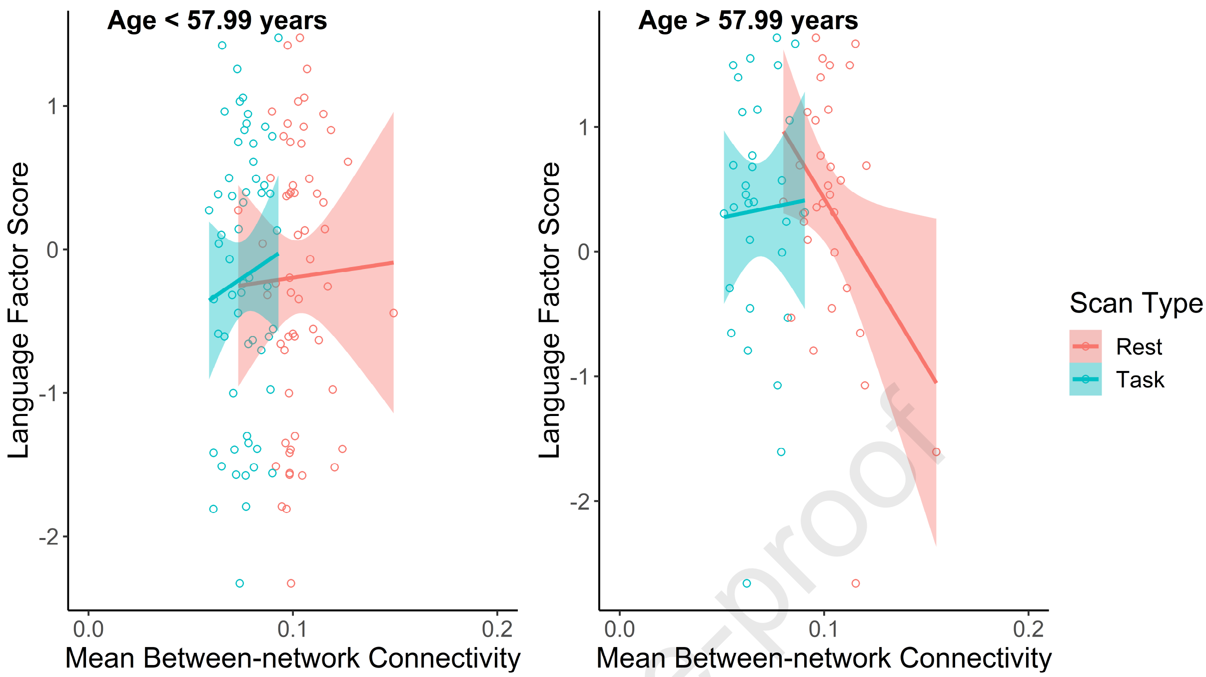

Figure 4. The interaction among age, scan type, and between-network connectivity on Language Factor scores (p = .07). Only during the resting-state scan (p < .05), but not the task-based scan (p > .1), older adults (red, right panel), but not younger adults (red, left panel), showed a significant relationship between higher resting-state between-network connectivity and lower Language Factor score (Johnson-Neyman test, p < .05).

3.4 Mediation Effect of Network Characteristics of Age and Cognition

Mediation analyses were conducted to further investigate the effect of network measures on the relationship between age and cognitive factors, controlling for the effect of education. Results showed that the overall within-network connectivity partially mediated the relationship between age and the Executive Factor score (Average Causal Mediation Effect, ACME p < .05; Average Direct Effects, ADE p < .001). Separating resting-state and task-based connectivities, we found similar trends in the mediation results such that both the resting-state (ACME p < .05; ADE p < .001) and the task-based (ACME p = .08; ADE p < .001) within-network connectivities partially mediated the relationship between age and the Executive Factor score. This result suggested that although increasing age was significantly related to worse executive function ability, this relationship was partially explained by individual differences in within-network connectivity. The relationships between age and other cognitive factors were not significantly mediated by within-network connectivity (ACME *p*s > .1).

Because there was also a significant main effect of age on between-network connectivity, we conducted a mediation analysis on between-network connectivity. However, the between-network connectivity did not significantly mediate any relationships between age and cognitive factor scores (ACME *p*s > .1). Because the main effect of age on between-network connectivity was largely driven by the task-based data, we also examined the resting-state and task-based data separately for mediation effects. However, there were no significant mediation effects in the individual data sets (ACME *p*s > .1), indicating that the between-network connectivity in general did not mediate the age-behavior relationships.

4. Discussion

Older adults often exhibit decline across cognitive domains, such as language production, memory, and executive function; however, how these age-related behavioral differences relate to whole-brain functional organization is not entirely understood. Additionally, how brain–behavior relationships can be altered by task demands is not clear either. In the current study, we analyzed 333 brain regions organized into 10 functional networks and examined within- and between-network functional connectivities in a lifespan sample. Both resting-state and task-based fMRI data were examined and directly compared. We also investigated the relationships between whole-brain network organization and behavior across numerous cognitive domains, including recall, language, executive function, and verbal working memory. We expected that older individuals would exhibit worse cognitive performance on fluid abilities, have lower within-network connectivity, and that age-related differences in network connectivities may be related to cognitive performance. We also expected that the brain–behavior relationships may vary as a function of whether participants were engaged in a task and as a function of the participants' age.

Consistent with prior results (Park et al., 2002; Park and Reuter-Lorenz, 2009), we found that older individuals performed worse on recall, executive function and verbal working memory tasks, after controlling for years of education. On the other hand, language abilities, as measured by reading and vocabulary tests, were enhanced with age, and higher education was associated with better language performance (Kavé and Halamish, 2015; Verhaeghen, 2003). Interestingly, there was also a significant quadratic relationship between age and language, suggesting that as age increased, age-related performance improvements in language were smaller. This is in line with the literature showing crystallized intelligence increases during the lifespan through the acquisition of different life experiences (e.g., education, occupation) and is resistant to cognitive decline (Anstey and Low, 2004; Gordon et al., 2016; Park, 2002; Park et al., 2002).

In terms of the effect of age on network measures, the fMRI results demonstrated that increases in age were significantly associated with overall lower within-network connectivity. This is consistent with the prior resting-state literature showing lower within-network connectivity for older adults (Betzel et al., 2014; Cao et al., 2014; Chan et al., 2018; Chan et al., 2014; Geerligs et al., 2015; Onoda et al., 2012; Siman-Tov et al., 2017; Song et al., 2014; Tomasi and Volkow, 2012). We also observed a significant interaction between age and scan type on within-network connectivity, such that the age effect was stronger during the task-based scan compared to the resting-state scan. This interaction indicates that age-related neural differences are most pronounced when individuals were engaged in a task. There was also a significant main effect of age on between-network connectivity, with lower between-network connectivities associated with increasing age. This result appears to be consistent with some studies that showed lower between-network connectivity with aging (Onoda et al., 2012) but inconsistent with others that showed higher between-network connectivity with increased age (Chan et al., 2014; King et al., 2018). However, it is important to note that we also observed a significant interaction between age and scan type on between-network connectivity. As with the within-network connectivity, we found that the age effect on whole-brain between-network connectivity was stronger during the task scans than the resting-state scans. The stronger age effects on network connectivities during task scans are consistent with the idea that network connectivity might be affected not only by age, but also the specific demands of the situation (Varangis et al., 2019b). Although participants in this study were engaged in a picture naming task, which is a minimally demanding task, this increased task demand compared to resting-state highlighted age differences in network characteristics. The stronger age effects on network connectivities during the task compared to the resting-state are also consistent with prior literature showing that older adults' performance declines are most pronounced when task demands are high (Reuter-Lorenz and Cappell, 2008).

To determine how these age-related differences in brain functional connectivity relate to cognition, regression and mediation analyses were conducted on the cognitive variables to examine the effects of age, and the modulation of network connectivity, while controlling for years of education. There are four aspects to these results. First, the main effects of overall within- and between- network connectivities on recall ability were significant (or nearly significant) across both scan types, such that higher overall within-network connectivity and lower overall between-network connectivity were associated with better recall ability. Moreover, these relationships were independent of age and education, suggesting that having a more optimal and separated network organization in general is associated with better recall ability across the lifespan. These results are consistent with prior studies that have demonstrated that higher within-network connectivity and lower between-network connectivity were associated with better cognitive performance (Andrews-Hanna et al., 2007; Geerligs et al., 2014; Geerligs et al., 2015; Hampson et al., 2010; Onoda et al., 2012; Sala-Llonch et al., 2015; Varangis et al., 2019b; Wang et al., 2010).

Second, there were significant or nearly significant interactions between scan type and between-network connectivities on the recall ability (p = .09) and executive function measures (p < .05), irrespective of age and education. Further analyses showed that higher between-network connectivity was associated with worse recall and executive function abilities, but only during resting-state (ps < .05) and not when participants were engaged in a task. Very few studies have examined the relationship between cognition and between-network connectivity on a whole-brain level. But among them, King et al. (2018) also reported that stronger age-related between-network resting-state connectivity was significantly related to worse motor performance. Although we did not find age differences, our results are consistent with increasing between-network resting-state connectivity being associated with worse cognitive performance. The stronger cognition-brain relationships we observed during resting-state may be because resting-state scans measure a default state of brain organization. As suggested by Chan et al. (2014), differences in network connectivities during resting-state might be a marker of individual differences in cognitive ability across the lifespan. Having stronger between-network connectivity during resting-state might reflect a decline in optimal network organization across the lifespan. However, in the task-based data, higher between-network connectivity was unexpectedly associated with better executive function ($p < .05$), opposite to the pattern found in the resting-state data. This might be because the brain is in a more dynamic mode during the task, so higher between-network coordination was associated with better behavioral performance. However, the lack of significant relationships between higher task-based between-network connectivity and the other cognitive measures indicates that this relationship needs to be interpreted tentatively.

Third, although there was no significant main effect on the language measures, we found an interaction between age, between-network connectivity, and scan type ($p = .07$). Specifically, the interaction between age and between-network connectivity on the language measures was only significant during the resting-state scan ($p < .05$), and not the task-based scan ($p > .1$). Further analysis showed that only among older adults (> 57.99 years), higher resting-state between-network connectivity significantly correlated with worse language performance. These results are consistent with the findings on the recall and executive function measures such that higher resting-state between-network connectivity was associated with worse cognitive performance. More critically, for language measures, the significant interaction between age and resting-state between-network connectivity indicated that although language abilities were well-maintained and even improved with age, older adults with higher between-network connectivities had lower language performance. This age-related difference in between-network connectivity and language supports a dedifferentiation account of aging, such that higher connectivities among different brain networks are interpreted as decreases in neural efficiency in older adults (Ghisletta and Lindenberger, 2003; Li et al., 2001). While we only found this specific age effect for language, these results are consistent with the overall trend of higher between-network connectivity during resting-state being associated with poorer cognitive function. It is also worthwhile to mention that we observed these relationships in the resting-state, but not in the task-based data, indicating that resting-state network characteristics might be better general indexes for cognitive function, across the lifespan.

Finally, across both resting-state and task-based scans, the overall within-network connectivity partially mediated the relationship between age and executive function. This relationship was not found with between-network connectivity. Previous studies have consistently found age-related differences in within-network connectivity during resting-state as being related to differences in cognitive performance (King et al., 2018; Onoda et al., 2012; Sala-Llonch et al., 2015; Varangis et al., 2019a; Wang et al., 2010). This finding reinforces the idea that within-network functional connectivity overall is a robust measure for examining age-related differences in cognitive abilities, perhaps more so for fluid intelligence measures, such as executive function, which often show larger declines with age. Additionally, the lack of between-network connectivity mediation was surprising since resting-state between-network connectivities were linked to cognitive performance. However, given the conflicting results in prior studies regarding the relationship between between-network connectivity, age, and cognitive performance, our results are not inconsistent with the existing literature. These variabilities in between-network connectivity results may reflect variability in these relationships across individuals, and future studies could consider examining broader populations of older adults.

5. Conclusion

To summarize, the present study investigated the effect of age on cognition, whole-brain functional connectivity during resting-state and during a task, and their relationships across the adult lifespan. We found that increased age was associated with worse recall, executive function, and verbal working memory, but better language ability, although these improvements lessened as age increased. We also found consistency across both resting-state and task-based data, in that increased age was associated with lower within- and between- network functional connectivities, and age effects were stronger during the task than the resting-state. In terms of the relationships among age, network characteristics, and cognition, we consistently found that higher resting-state between-network functional connectivity was associated with poorer recall, executive function. Additionally, higher resting-state between-network connectivity was associated with worse language ability in older adults, supporting the dedifferentiation account of cognition and aging. We also found that within-network connectivity partially mediated the relationship between age and executive function, highlighting the importance of the integrity of within-network connectivity for cognition. Overall, these findings demonstrate that although age effects on network characteristics were most pronounced during the task, resting-state functional connectivities may be more reliable indicators of cognitive function across the lifespan.

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Highlights

1) Increased age related to worse recall, working memory, executive function.

2) Increased age related to lower within- and between- network connectivities.

3) Higher between-network connectivity at rest related to worse cognition at all ages.

4) Older adults with higher between-network at rest connectivity had worse language.

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April 21, 2020

Dear Dr. Rapp,

Thank you for your consideration of our research article: *Age-related differences in resting-state and task-based network characteristics and cognition: A lifespan sample*.

The authors are in full agreement that this paper be submitted to *Neurobiology of Aging*. We have no conflicts of interest, financial or otherwise, that would preclude a fair review or publication of this manuscript. This manuscript is not being considered for publication elsewhere. Approval to conduct this study was obtained from The Pennsylvania State University Institutional Review Board and informed consent was obtained from all of our participants. We thank you for your consideration of our manuscript.

Sincerely,

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