Fronto-Parietal Network Segregation Predicts Maintained Processing Speed in the Cognitively Healthy Oldest-old

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Abstract

Evaluating brain network interactions in cognitively healthy older adults can help us understand how brain characteristics vary with age and how these variations affect cognitive functioning. Functional connections among groups of brain areas give insight into the brain's organization, and the cognitive effects of aging may relate to this large-scale organization. We investigated functional network properties in 146 cognitively healthy participants aged 85+ in the McKnight Brain Aging Registry. We found that the segregation of both the cortical association system and the segregation of the fronto-parietal network (FPN) were strong predictors of cognition and processing speed. We also provide a healthy oldest-old (85+) cortical parcellation that can be used in future work in this age group. This study shows that network segregation of the oldest-old brain is closely linked with cognitive performance. In particular, segregation of the FPN plays an important role in supporting overall cognition and processing speed in this aging cohort. This work adds to the growing body of knowledge about age-related dedifferentiation by demonstrating that cognitive ability is associated with differentiated functional networks even in very old individuals experiencing successful cognitive aging.

Keywords: oldest-old, cognitive aging, networks, segregation, FPN, CON, DMN, dedifferentiation, processing speed

1. Introduction

Slowing age related cognitive decline is an important societal goal. Understanding the factors contributing to optimal cognitive function throughout the aging process is essential to developing effective cognitive rehabilitation interventions. To better understand successful cognitive aging, we recruited participants who have reached oldest-old age (i.e., 85+ years) with documented excellent cognitive health and examined the variability in behavior within this cohort to measures of their brain network segregation, large-scale patterns of functional connectivity measured with fMRI. Prior work has mostly been done in younger-old samples (largely 65-85 years old). Studying the younger-old can be confounded by including pre-symptomatic disease, since it is unknown which individuals may be experiencing undetectable, pre-clinical cognitive disorders and which will continue to be cognitively healthy for another decade. The cognitively unimpaired oldest-old have lived into late ages, and we can be more confident in determining their status as successful agers. A further benefit of studying these successful cognitive agers is that because of their advanced age and the normal aging and plasticity processes associated with it, there is greater variance in both their performance on neurocognitive tasks, and in brain connectivity measures than there is in younger cohorts (Christensen et al., 1994). This increased variance makes it easier to observe across-subject relationships of cognition and brain networks. We provide new insight into the relationship between the segregation of networks and cognition by investigating this relationship in an oldest old cohort of healthy individuals.

Some cognitive domains are particularly susceptible to decline with age, including processing speed, executive function, and memory (Reuter-Lorenz, Festini, & Jantz, 2016; Spaan, 2015). Processing speed refers to the speed with which cognitive processes, such as reasoning and memory, can be executed (Sliwinski & Buschke, 1997). (Salthouse, 1996) proposed that cognitive aging is associated with impairment in processing speed, which in turn may lead to a cascade of age-associated deficits in other cognitive abilities. Because processing speed is so strongly associated with a wide array of cognitive functions, it is crucial to understand how it can be maintained in an aging population. Executive functioning is a broad collection of cognitive capacities encompassing sustained attention, updating, inhibition, switching, and set-shifting (Fisk & Sharp, 2004; Lamar, Zonderman, & Resnick, 2002; McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010; Rabinovici, Stephens, & Possin, 2015; Sorel & Pennequin, 2008). With normal aging, executive functioning performance reliably declines (Fisk & Sharp, 2004; Harada, Natelson Love, & Triebel, 2013; Reuter-Lorenz et al., 2016; Salthouse, Atkinson, & Berish, 2003; Spaan, 2015), and this decline is faster in older ages (Zaninotto, Batty, Allerhand, & Deary, 2018). Memory is another well-studied cognitive domain that encompasses multiple processes, such as encoding, consolidation, and retrieval of information (Huo, Li, Wang, Zheng, & Li, 2018; Zlotnik & Vansintjan, 2019). Age-related decline in memory is reported subjectively by most older adults (Craik, 2008), with episodic memory being the most impacted by aging compared to other memory systems (Luo & Craik, 2008). Working memory and language function cognitive domains are known to be vulnerable to the aging process as well. Working memory refers to the simultaneous temporary storage and active manipulation of information (Stanley et al., 2015). There is reliable evidence across studies that working memory gradually declines from early to late adulthood (Kidder, Park, Hertzog, & Morrell, 1997; Salthouse & Babcock, 1991; Stanley et al., 2015; Vaqué-Alcázar et al., 2020). Language function, particularly language production, also undergoes age-related decline and is related to

other cognitive functions affected by aging, including working memory and executive function (Rizio & Diaz, 2016).

Brain networks play a crucial role in aging, and older adults exhibit differences in brain structural and functional network integrity that impact network dynamics (Marstaller, Williams, Rich, Savage, & Burianová, 2015). Because of their correlation to cognitive performance, brain network dynamics have emerged as a major avenue to study aging and cognitive decline (Andrews-Hanna et al., 2007; Antonenko & Flöel, 2014; Chan, Park, Savalia, Petersen, & Wig, 2014; Cohen & D'Esposito, 2016; Ng, Lo, Lim, Chee, & Zhou, 2016; Shine et al., 2016; Wen et al., 2011). Many properties of networks can be quantified (Bullmore & Sporns, 2009; Damoiseaux, 2017; van den Heuvel & Hulshoff Pol, 2010). Network integration describes how much the network's regions interact and can be quantified as the mean connectivity of nodes within a given network (within network connectivity). The network participation coefficient describes the variety of connections of a given node. A low participation coefficient indicates a node is more selectively connected to its network, and high participation coefficient indicates a node is widely connected to other networks (Rubinov & Sporns, 2010). Modularity describes how separable a system is into parts (Rubinov & Sporns, 2010). Lastly, segregation describes the balance of within and between network connectivity. Very high segregation indicates isolated networks, and very low segregation indicates the networks are no longer separable (Wig, 2017).

A neural system's functional specialization and segregation is determined by the network's balance of connections between and within the network and is indicative of organizational integrity (Chan, Alhazmi, Park, Savalia, & Wig, 2017; Damoiseaux, 2017; Iordan et al., 2017; Koen, Srokova, & Rugg, 2020; Varangis, Habeck, Razlighi, & Stern, 2019). In older adults, functional networks have increased between-network connectivity and decreased within-network connectivity (Chan et al., 2017; Damoiseaux, 2017; Iordan et al., 2017; Koen et al., 2020; Varangis et al., 2019). Prior research suggests differing hypotheses about the origin of age-related cognitive decline, including the compensation hypothesis, which refers to the over-recruitment of brain regions within a network, and the dedifferentiation hypothesis, which refers to the loss of functional specialization and segregation in brain network activity, which has received greater support; however, these hypotheses are not mutually exclusive (Chan et al., 2014; Daselaar et al., 2015; Seider, Porges, Woods, & Cohen, 2021; Siman-Tov et al., 2016).

Previous studies have found that dedifferentiation of higher-order cognitive networks of the association system —the fronto-parietal network (FPN), cingulo-opercular network (CON), and default mode network (DMN)—are related to poorer performance in many cognitive abilities, including episodic memory, processing speed, attention, and executive function (Chan et al., 2017; Damoiseaux, 2017; Goh, 2011; Hausman et al., 2020; Iordan et al., 2017; Koen et al., 2020; Nashiro, Sakaki, Braskie, & Mather, 2017; Ng et al., 2016; Varangis et al., 2019). The FPN is associated with complex attention and directing cognitive control (Avelar-Pereira, Bäckman, Wåhlin, Nyberg, & Salami, 2017; Malagurski, Liem, Oschwald, Mérillat, & Jäncke, 2020; Oschmann & Gawryluk, 2020; Ray et al., 2019). The CON is associated with sustained executive control and perceptual and attentional task maintenance (Coste & Kleinschmidt, 2016; Hausman et al., 2020; Sadaghiani & D'Esposito, 2015). The DMN is activated during rest, internally focused tasks and memory processing, but is suppressed during cognitively demanding, externally focused tasks (Avelar-Pereira et al., 2017; Hampson, Driesen, Skudlarski, Gore, & Constable, 2006; Hellyer et al., 2014; Ng et al., 2016; Sambataro et al., 2010; Sestieri, Corbetta, Romani, & Shulman, 2011). Processing speed has been shown to be related to all of these networks (Ruiz-Rizzo et al., 2019; Sheffield et al., 2015; Staffaroni et al., 2018; Vatansever,

Menon, & Stamatakis, 2017). In longitudinal studies, the rate of change in functional segregation of the FPN (Malagurski et al., 2020), and DMN (Ng et al., 2016), has been associated with the rate of change in processing speed.

The purpose of this study is to understand the underlying neural mechanisms associated with preserved cognition. In particular, we focused on the functional network architecture and, specifically, examined how FPN, CON, and DMN segregation relate to executive function, processing speed, working memory, language, and episodic memory. We expand on prior methods of studying functional networks and cognition by using an older, 85+ cohort and a brain parcellation derived from our healthy oldest-old sample. Here we address the hypothesis that maintaining higher levels of cognitive function into healthy aging relies on greater segregation of the association system and its sub-networks: FPN, CON, and DMN. We predicted that decreases in segregation within the Association System, FPN, CON, and DMN would be related to poorer overall cognition and cognitive domain performance in oldest-old adults. We used multiple regression and forward selection hierarchical regressions between cognitive measures and network properties to test their association in this oldest-old aged cohort.

2. Results

2.1 A priori power analysis

An a priori power analysis was conducted using a sample size of 146 in hierarchical multiple regression with one variable in block one and five variables in block two, and a hierarchical multiple regression with one variable in block one and ten variables in block two (See section 4.2). Using the sample size of 146, all analyses can detect small effect sizes with an alpha of .05 and a power of .80. The smallest detectable effect for a correlation was r=.23, similar to the effect size found by Chan et al. (2014). The smallest detectable effect for hierarchical multiple regression with two variables in block one and four variables in block two was .085, and the hierarchical multiple regression with two variables in block one and three variables in block two was .078.

2.2 Exploratory Factor Analysis

EFA revealed five factors: 1) Processing Speed, 2) Episodic Memory, and 3) Executive Functioning, 4) Working Memory, and 5) Language. (See Supplemental Table 1 for variable factor loadings). Overall cognition was calculated as the average of an individual's factor scores across the 5 factors.

2.3 Functional Connectivity of Network Nodes

We created network nodes based on methods developed by Chan et al. (2014) and Han et al. (2018) for our oldest-old sample (Figure 1).

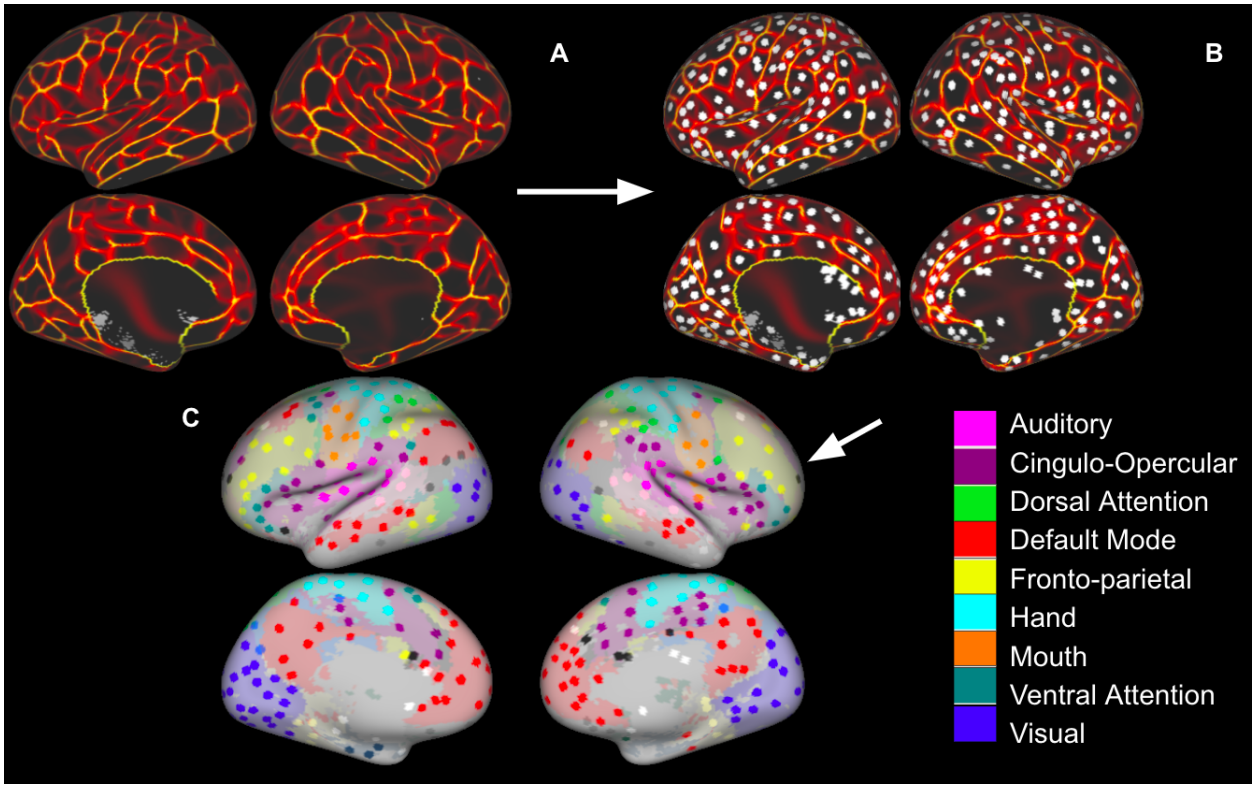

Figure 1. Regions of Interest Identification. *A: Functional connectivity boundary maps based on methods used by (Han et al., 2018); B: Local minima ROIs (3mm discs) based on methods used by (Chan et al., 2014); C: Local minima ROIs with the color of Network Membership of ROIs based on parcellation colors that are shown underneath ROIs (Power et al., 2011). White ROIs indicate nodes that do not belong to any labeled network.*

Using the ROIs we created (Figure 1), we generated a group average of Fisher's z-transformed correlation matrix grouped by network and system membership (Figure 2).

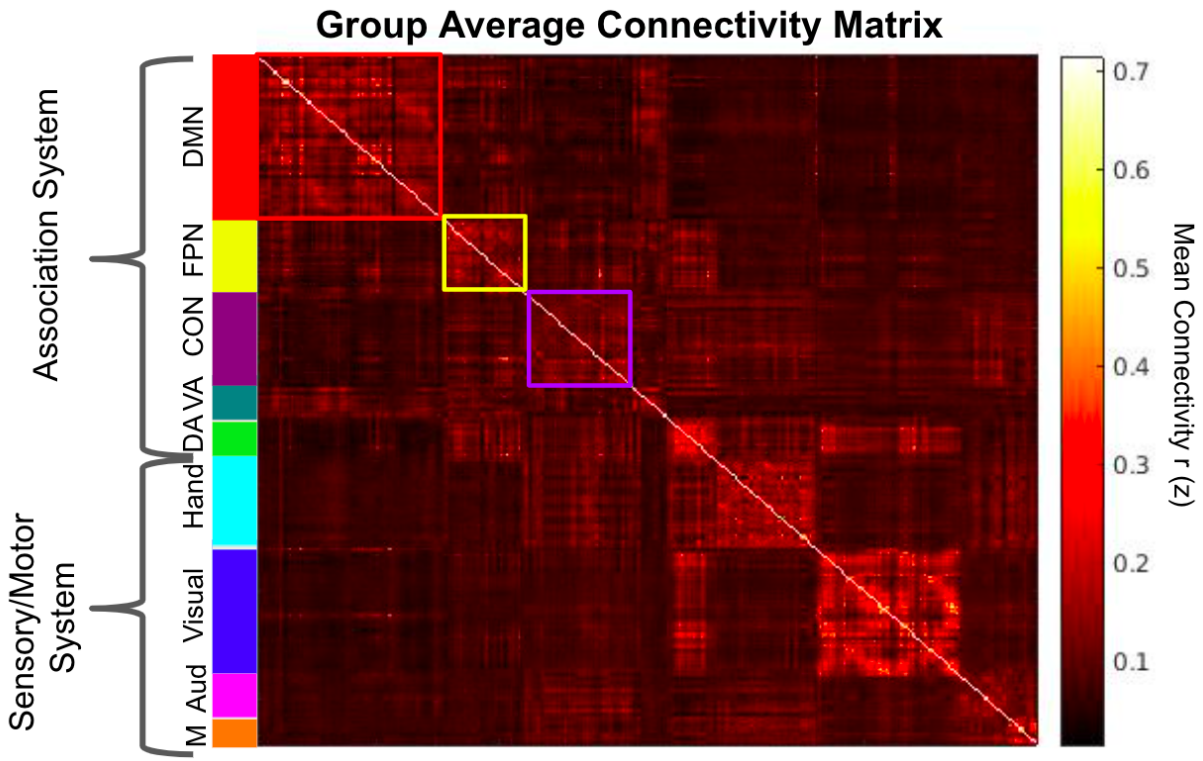

Figure 2. Group average Fisher's z- transformed correlation matrix of 321 nodes. The Association system consists of the Default mode (red), Fronto-parietal control (yellow), Ventral attention (teal), Cingulo-opercular control (purple), and Dorsal attention (green). The Sensory-Motor system consists of the Hand somato-motor (light blue), Visual (blue), Mouth somato-motor (orange), and Auditory networks (pink).

2.4 Association System metrics & Overall Cognition

Table 1. **Association System and Overall Cognition Metrics**	**Mean**	**SD**	**Range**
Segregation	0.4205	0.1071	0.0929–0.6463
Mean Within-Network Connectivity	0.0833	0.0246	0.0162–0.1522
Participation Coefficient	0.4356	0.0235	0.3675–0.4746
Modularity	0.2561	0.0374	0.1321–0.3501
Overall Cognition Factor Score	0.00989	0.4428	-0.96-1.4

We then generated descriptive statistics of association system metrics and the overall cognition metric (Table 1; methods section 4.3). Overall cognition was related to association system segregation (r=.243, p=.003), modularity (r=.266, p=.001), and mean within-network connectivity (r=.193, p=.019), but not participation coefficient (r=-.122, p=.14) (Figure 3). These relationships remainded significant after multiple comparisons correction using FDR (Benjamini & Hochberg, 1995), partial correlation with site as a covariate and partial correlation with cortical thickness as a covariate. Additionally, the effect size of the correlations remained largely unchanged with partial correlations. There was a strong, significant relationship between association system segregation and modularity (r=.575, p<.001).

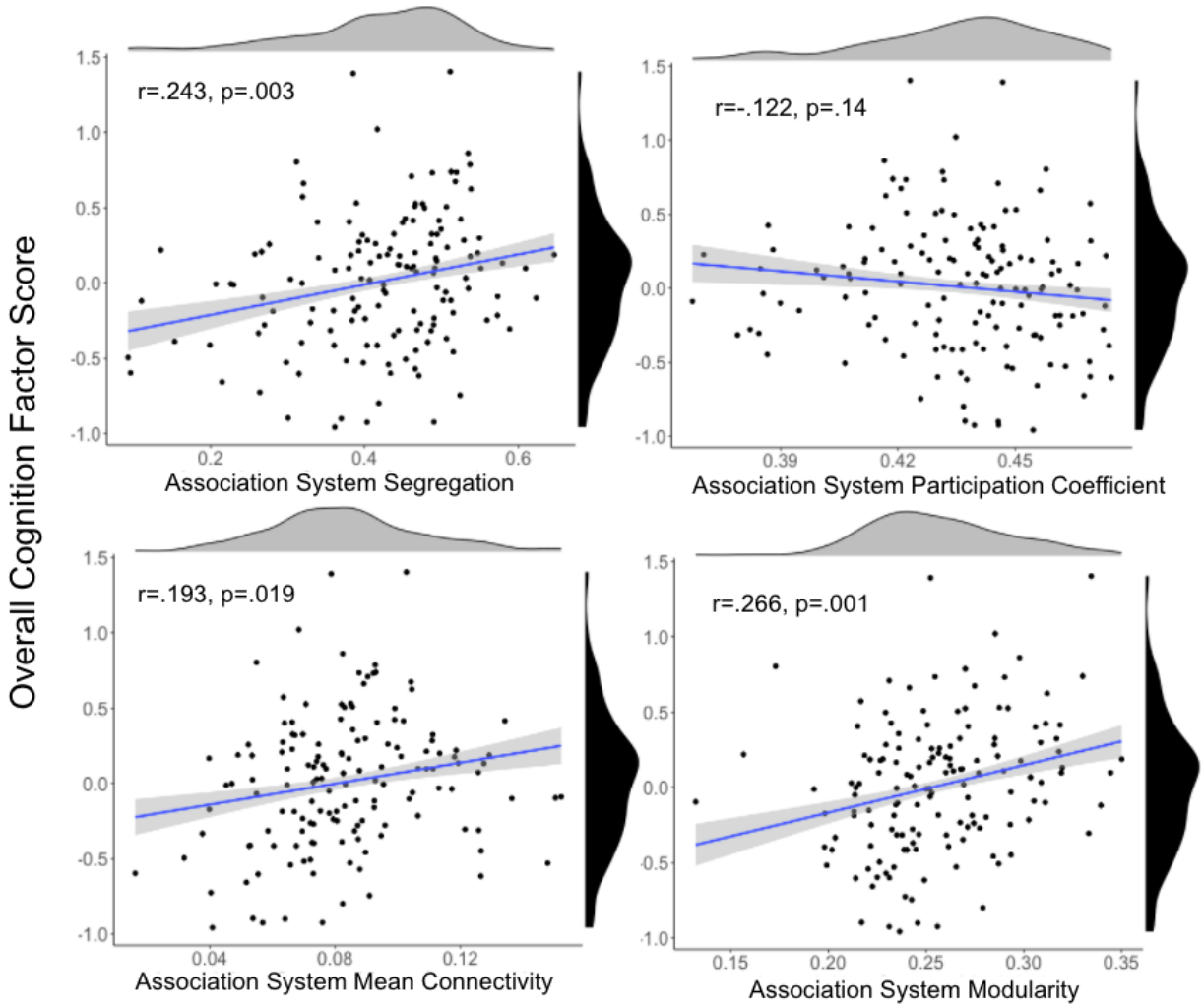

Figure 3. Scatter plots between Association System metrics and overall cognitive performance. Density plots for the variables are presented for each variable on the edge of the scatter plot. Overall cognition score is shown in black and association system metrics are shown in grey.

The hierarchical multiple regression of overall cognition showed that there were no significant predictors of overall cognition among the association system metrics: segregation (β = .137, p=.25), modularity (β = .175, p=.075), participation coefficient (β = .071, p=.501), and mean connectivity (β = .088, p=.358). There was a significant R^2-change of .082 (F(4,139)=3.26, p=.014) between the first block of the covariates (site and cortical thickness) and the second block with association system metrics.

2.5 Network metrics and Overall Cognition

Table 2. **Network Segregation**	**Mean**	**SD**	**Range**
DMN	0.4517	0.1495	0.0628–0.7209
FPN	0.3279	0.1385	-0.0482–0.5989
CON	0.2784	0.1848	-0.2677–0.7439

We then investigated the relationship of overall cognition with the network segregation of three networks that belong to the Association System: FPN, CON, and DMN (Table 2).

The forward selection hierarchical regression of overall cognition showed that FPN segregation was the best predictor of overall cognition among the networks. There was a significant R^2-change of .08 ($F(1, 142)=12.987$, $p<.001$) between the first block of the covariates (site and cortical thickness) and the second block with FPN segregation, which was also a significant predictor ($\beta = .284$, $p<.001$).

To further describe specific relationships between overall cognition and network metrics, are shown in Figure 4. Of note, these relationships remainder significant after correction for multiple comparisons using FDR and partial correlation with site as a covariate. Partial correlation showed that the addition of cortical thickness as a covariate did not impact the relationship between overall cognition and FPN and DMN, however the correlation between CON segregation and overall cognition was no longer significant after adding cortical thickness as a covariate ($r=.159$, $p=.055$).

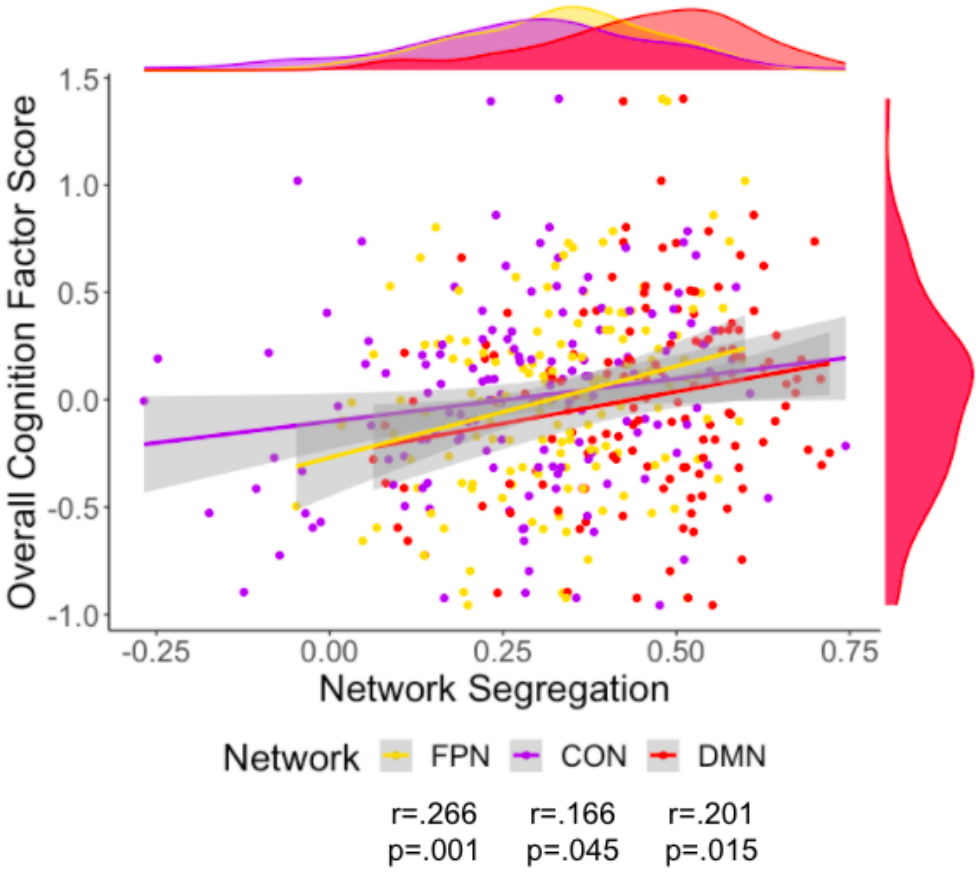

Figure 4. Scatter plot of Overall Cognition and FPN (yellow), CON (purple), and DMN (red) network segregation, mean connectivity, and participation coefficient. Density plots for the variables are presented for each variable on the edge of the scatter plot. The colors on these plots match the network color in Figure 1. Only segregation for FPN and DMN were still significant after adding a covariate of cortical thickness.

2.6 Network metrics and cognitive domains

To further break down overall cognition into cognitive domains, we investigated the relationship between the segregation of the FPN, CON, and DMN and five domains of cognition:

Processing Speed, Executive Functioning, Episodic Memory, Working Memory, and Language (Table 3). To replicate prior findings we analyzed the relationship between association system segregation and memory, which was not correlated as had been previously found in work by Chan and colleagues (2017) (r=.061, p=.467).

Table 3. **Cognitive Domain Factor Scores**	**Mean**	**SD**	**Range**
Processing Speed	0.05	0.86	-2.49-2.74
Executive Functioning	0.05	0.83	-2.36-2.34
Episodic Memory	0.05	0.84	-1.82-1.69
Working Memory	-0.02	0.87	-2.4-2.53
Language	-0.08	0.79	-1.77-2.54

The forward selection hierarchical regression of processing speed showed that FPN segregation was the best predictor of processing speed among the networks. There was a significant R^2-change of .09 ($F(1, 142)=15.519$, $p<.001$) between the first block of the covariates (site and cortical thickness) and the second block with FPN segregation which was a significant predictor ($\beta = .301$, $p<.001$). Processing speed was related to all networks' segregation (Figure 5). These relationships were still significant after correction for multiple comparisons using FDR, partial correlation with site as a covariate and partial correlation with cortical thickness as a covariate.

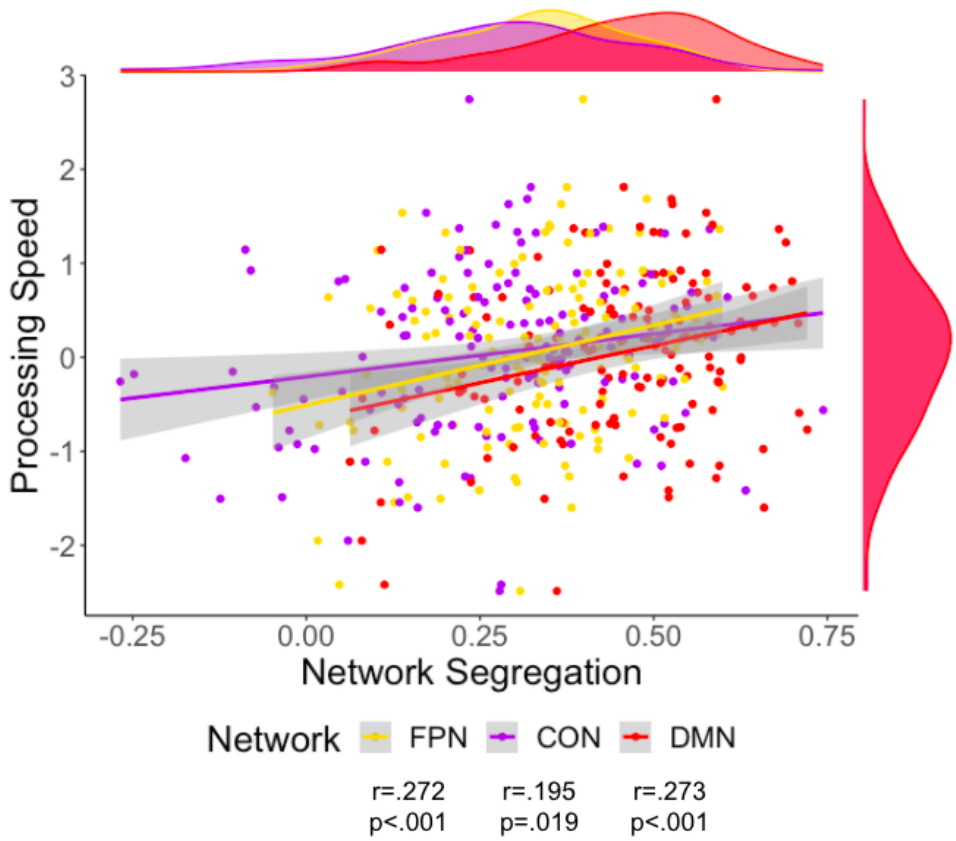

Figure 5. Scatter plot of Overall Cognition and FPN (yellow), CON (purple), and DMN (red) network segregation, mean connectivity, and participation coefficient. Density plots for the variables are presented for each variable on the edge of the scatter plot. The colors on these plots match the network color in Figure 1.

The forward selection hierarchical regression of executive functioning showed that FPN segregation was the best predictor of executive functioning among the networks; there was strong trend in R^2-change of .025 ($F(1, 142)=3.921$, $p=.050$) between the first block of the covariates (site and cortical thickness) and the second block with FPN segregation, which was not a significant predictor ($\beta = .157$, $p=.050$). Executive functioning was only significantly related to FPN segregation (Figure 6). However, this relationship was no longer significant after multiple comparison corrections ($p=.132$).

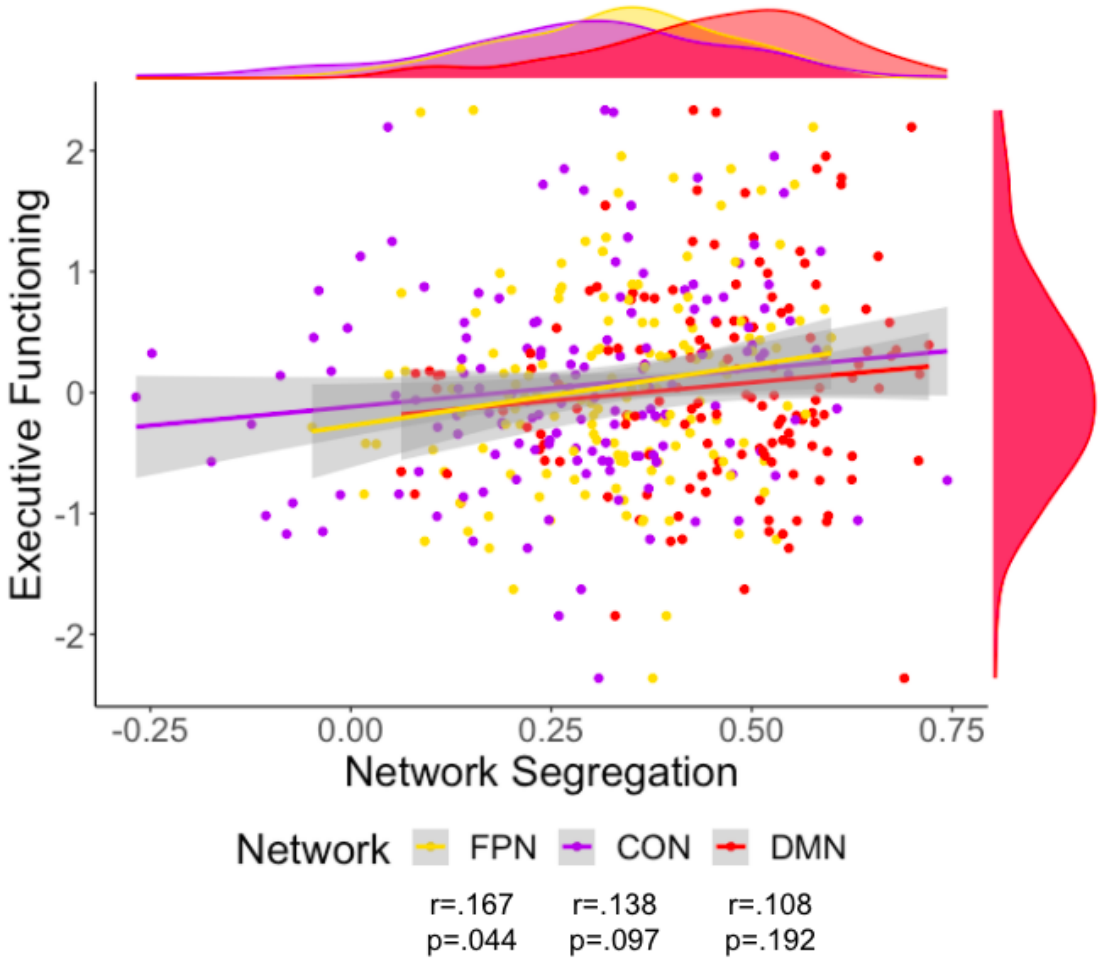

Figure 6. Scatter plot of Overall Cognition and FPN (yellow), CON (purple), and DMN (red) network segregation, mean connectivity, and participation coefficient. Density plots for the variables are presented for each variable on the edge of the scatter plot. The colors on these plots match the network color in Figure 1. No relationships were significant after multiple comparisons correction.

The forward selection hierarchical regression for memory, working memory, and language did not identify a predictor. Additionally, correlations between these cognitive domains and the FPN, DMN, and CON segregation were very weak and not significant (Supplemental Table 3).

3. Discussion

First, we created a set of parcels for oldest-old adults based on functional connectivity boundary-based mapping. We then showed that association system segregation, modularity, and mean connectivity were related to overall cognition. We found that compared to segregation of the CON and DMN, FPN segregation was the best predictor of overall cognition, processing speed, and executive functioning. These results demonstrate that the oldest-old brain is segregated within the association system and association networks, and that the FPN may be important in supporting cognitive function and processing speed as we age. Prior studies have largely examined young-older adults when studying network dynamics (under age 85), thereby excluding an ever-growing portion of the older adult population. In this study, we expanded on prior methods of studying network functioning by using an older, healthy 85+ cohort to better understand how aspects of cognition are related to brain networks in the context of healthy aging.

3.1 Healthy Oldest-old network parcellation

It is important to understand how a healthy aging cortex is subdivided, especially since brain network organization can change across the lifespan (Bagarinao et al., 2019). Previous work has measured brain organization in younger age ranges by creating boundaries between brain regions using shifts in functional connectivity patterns, boundary-based mapping, and then identifying nodes within those boundaries (Chan et al., 2014; Han et al., 2018). With the sample from the McKnight Brain Aging Registry, we had the opportunity to apply the same methods to a sample with an older age range and larger sample size than previous work for the oldest-old portion of the sample. We provide a healthy oldest-old (85+) parcellation that can be used in future work in this age group and can be used to compare to disease populations in this age range. An age-appropriate parcellation may more accurately identify cortical mapping of networks. Future work will analyze the organization of the nodes in this parcellation and identify networks without younger-adult-based network descriptors.

3.2 Age-related functional dedifferentiation

Models of dedifferentiation and compensation are used to explain changes in the selectivity of functional activity of brain regions that occurs in the aging context (Koen et al., 2020; Li, Lindenberger, & Sikström, 2001; Rakesh, Fernando, & Mansour L, 2020; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz, Stanczak, & Miller, 1999). The neural dedifferentiation hypothesis posits that functional networks are not as selectively recruited (Goh, 2011; Koen et al., 2020). On the other hand, the compensation hypothesis posits that functional networks must recruit more regions or “over-activate” to complete the intended task (Reuter-Lorenz & Cappell, 2008). These two models may be compatible (Burianová, Lee, Grady, & Moscovitch, 2013). The study of the association system and association networks across the lifespan has indicated that dedifferentiation is related to age and a co-occurring decrease in cognitive functioning (Chan et al., 2014; Geerligs, Renken, Saliasi, Maurits, & Lorist, 2015; Han et al., 2018). Longitudinal work on association system networks has indicated that segregation of association system networks decreases with age (Chong et al., 2019), and this rate of decline corresponds to declining cognitive functioning in the elderly (Malagurski et al., 2020; Ng et al., 2016). However, the mean age of participants in prior work was well below that of the current study and the study sample size for the oldest-old was smaller than that of the current study. Therefore, it was unknown how far in the aging process dedifferentiation can continue while cognitive functions are maintained and to what degree different networks are sensitive to dedifferentiation in the oldest-old brain.

The goal of this study was to further investigate cognition and brain network dedifferentiation in the context of successful brain aging in the oldest-old cohort by examining dedifferentiation of the association system metrics of segregation, participation coefficient, modularity, and within-network connectivity and network segregation.

3.3 Dedifferentiation predicts preserved cognition in the cognitively healthy elderly

We found that association system segregation and modularity had positive, significant relationships with overall cognition while mean-connectivity had a relatively weaker relationship and participation coefficient did not have a significant relationship. Additionally, modularity and segregation were tightly related. The findings of our study support the dedifferentiation hypothesis, since the association system cannot function as well when it is not differentiated adequately. However, this finding does not exclude the compensation hypothesis. Overall cognition is modestly correlated with mean connectivity, which shows that within-system connectivity is an important aspect of overall system structure, but measures like segregation and modularity go beyond measurement of network strength and provide insight into how the system is organized.

When we analyzed specific networks within the association system, we found that among the networks (FPN, CON, and DMN), the network segregation of the FPN was the greatest predictor of overall cognition. Additionally, only the FPN and DMN segregation were significantly correlated with overall cognition. Although all networks' segregation were correlated to processing speed performance and the effect size of correlations between processing speed and FPN and DMN segregation were similar, FPN segregation was the best predictor. Additionally, FPN was the best predictor of executive functioning though it was not a significant predictor on its own and the association did not survive multiple comparison correction. We have shown that FPN segregation is related to overall cognitive abilities and one of the key cognitive functions affected by aging — processing speed.

Prior studies have shown that FPN and DMN properties relate to processing speed task performance (Madden et al., 2010; Malagurski et al., 2020; Reineberg, Andrews-Hanna, Depue, Friedman, & Banich, 2015; Rieck, Baracchini, Nichol, Abdi, & Grady, 2021). Recent research indicates that the FPN regulates other brain networks to support cognitive functioning (Avelar-Pereira et al., 2017; Marstaller et al., 2015). The FPN and DMN interact less efficiently in older adults compared to younger adults; the networks are coupled during rest and across tasks in older adults, suggesting that aging causes the FPN to have more difficulty flexibly engaging and disengaging networks (Avelar-Pereira et al., 2017; Grady, Sarraf, Saverino, & Campbell, 2016; Spreng & Schacter, 2012). Age-related within-network structural changes and between-network functional dedifferentiation may disrupt the FPN's ability to control other networks, like the DMN (Avelar-Pereira et al., 2017; Geerligs et al., 2015; Grady et al., 2016; Marstaller et al., 2015; Romero-Garcia, Atienza, & Cantero, 2014; Zhang et al., 2014). Because of the FPN's function as a control network, age-related disruptions in FPN connectivity may explain the initial and most noticeable difference in cognition, processing speed (Ng et al., 2016; Oschmann & Gawryluk, 2020; Rieck, Baracchini, & Grady, 2021).

The findings from this work support prior research by demonstrating that while dedifferentiation may occur in aging populations, processing speed can be maintained in old age and this may be due to co-occurring maintained segregation of the DMN and especially the FPN. Therefore, sustainable healthy cognitive aging may be marked by maintaining segregated network organization. Further research will need to investigate the mechanisms of maintenance of network organization in healthy agers.

While segregation is not the only metric that can detect dedifferentiation, our findings indicate that it reliably relates to cognitive abilities. With segregation's predictive ability, it may serve as a more sensitive metric than other network metrics when assessing cognitive decline in aging populations. Additionally, our work helps inform other research that has indicated that segregation may be a marker of potential cognitive resilience in Alzheimer's Disease (Ewers et al., 2021) and prior work has begun to investigate its usage as a marker for future cognitive status (Chan et al., 2021). Studies have shown that learning-induced plasticity through cognitive training and exercise could be an avenue for changing network dynamics to improve cognitive performance (Iordan et al., 2017; Voss et al., 2010). Future research could target network dynamics in the older adult population to preserve cognitive functioning.

3.4 Limitations and Future Directions

This study has several limitations. Since this work is based on data collected across multiple sites, the data collection site was used as a covariate in partial correlation analysis and entered in the first block of hierarchical regression analyses. Across analyses, inclusion of site as a covariate had little to no effect on statistical tests. However, we recognize that this may not completely address site differences, such as different test administrators, different populations, scanner inhomogeneities, etc. We also included cortical thickness values as a covariate to account for the potential confounding of fMRI signal due to atrophy in this oldest-old sample. We did not find that cortical thickness had a significant impact across most of our analysis, except for one correlation between CON segregation and overall cognition. We performed post-collection data quality assessment methods, including visual inspection of MRI and cognitive data, strict fMRI preprocessing steps, visual inspection of all generated surfaces and motion parameters, and double data entry for all cognitive data.

We also recognize that the generalizability of our findings is limited due to the limited diversity of our sample which is mostly non-Hispanic, Caucasian, and highly educated individuals. Prior work has shown that these factors can influence association system segregation (Chan et al., 2021). Future work should be focused on broadening the diversity of oldest-old samples.

Given the cross-sectional nature of this work, we have limited information about our participants' state of health and cognitive performance earlier in life or what their cognitive health will be later in life. Thus, we are not able to investigate whether an individual's current functioning is a decline from prior functioning or if they will go on to develop cognitive impairment. The scope of this work is focused on healthy oldest-old and not the developmental process of aging. Therefore, inferences from this study focus on what we can learn from individuals who survived to 85+ and are cognitively healthy in their oldest-old years. Future work should investigate longitudinal changes in cognition and functional networks to evaluate differences in rates of decline among the oldest-old.

3.5 Conclusions

This work provides novel insight into the healthy oldest-old brain and intact cognition in the aging process. We add to the literature on age-related dedifferentiation, showing that even in a very old and cognitively healthy sample, dedifferentiation is related to cognition. This suggests that previously observed relationships are not due to inclusion of participants with early stage disease. Our results demonstrate that the association system of the oldest-old brain is segregated, and that the FPN is important to supporting cognitive function and processing speed as we age. These results are consistent with the idea that the segregated organization of association

networks is needed to allow the FPN to serve as a central player for manipulating other networks efficiently.

4. Materials and Methods

4.1 Participants

Data were collected as part of the McKnight Brain Aging Registry (MBAR), funded by the Evelyn F. McKnight Brain Foundation. Data were collected from the four McKnight Institutes: the University of Alabama at Birmingham, the University of Florida, the University of Miami, and the University of Arizona. The study sample includes 197 individuals with cognitive data and 146 with cognitive and MRI data, after excluding ten participants due to high head movement in MRI, six due to anatomical incompatibility with Freesurfer surface rendering, and one due to outlier network segregation values. Participants were community-dwelling, cognitively unimpaired older adults, 85 to 99 years of age. We performed a multi-step screening process including exclusions for memory disorders, neurological disorders, and psychiatric disorders. Details of the screening process are shown in Supplemental Figure 1. In the first stage of screening, trained study coordinators administered the Telephone Interview for Cognitive Status modified (TICS-M) (Cook, Marsiske, & McCoy, 2009) and conducted an interview to determine whether the patient met major exclusion criteria, which included individuals under age 85, severe psychiatric conditions, neurological conditions, and cognitive impairment. The telephone screening was followed by an in-person screening visit at which eligible participants were evaluated by a neurologist, a comprehensive medical history was obtained to ascertain health status and eligibility, and the Montreal Cognitive Assessment (MoCA) was administered (Nasreddine et al., 2005). Participants were recruited through mailings, flyers, physician referrals, and community-based recruitment. Participant characteristics are shown in Table 4. Participant characteristics of the full sample of 197 participants used in the cognitive data analysis can be found in supplemental Table 1 broken down by data collection site. Approval for the study was received from the Institutional Review Boards at each of the data collection sites including University of Alabama at Birmingham, University of Florida, University of Miami, and University of Arizona.

Table 4. **Participant Characteristics**	**Total Sample, N=146**
Age (years), *mean ± SD (range)*	88.4 ± 3.18 (85-99)
Education (years), *mean ± SD (range)*	16.1 ± 3.03 (9-26)
Sex, N(%)	
Female	79 (54.11%)
Male	67 (45.89%)
Race, N(%)	
Non-Hispanic Caucasian	134 (91.78%)
African American	6 (4.11%)
Hispanic Caucasian	5 (3.42%)
Asian	1 (0.69%)
Marital Status, N(%)	
Widowed	74 (50.69%)
Married	54 (36.99%)
Divorced	13 (8.90%)
Living as Married/Domestic Partnership	3 (2.06%)
Never Married	2 (1.37%)
Dominant Hand, N(%)	
Right	131 (89.73%)
Left	15 (10.27%)

4.2 Cognitive Measures

Multiple imputation is a statistical technique to estimate missing values in a dataset (Murray, 2018; Nassiri, Lovik, Molenberghs, & Verbeke, 2018). In our multiple imputation analysis, all variables used in the subsequent exploratory factor analysis (EFA) were used in multiple imputations to address missingness in Stroop interference score (10 missing values), Trails B score (3 missing values), and Stroop word trial score (6 missing values). Missingness was due to administrator error, participant's inability to correctly perceive the stimuli due to low visual acuity or color blindness, or the participant not finishing a task in the allotted time. We obtained a similar mean and range of the variables when the dataset was restricted to only complete cases. Imputed data from 5 iterations were then pooled by the average of the imputed value across iterations.

An exploratory factor analysis (EFA) with varimax rotation was performed on 18 variables to identify cognitive domains. The EFA used all available cognitive data (n=196). The number of factors was determined by eigenvalue greater than 1, analysis of scree plot, and parallel analysis, which indicated five factors (Humphreys & Montanelli Jr., 1975; O'Connor, 2000; Zwick & Velicer, 1986). Factor scores were then calculated using the regression method

(Thomson, 1939). Cognitive measures used for this EFA can be found in supplemental Table 2. Overall cognition was calculated as the average of the factor scores for each individual.

Quality control was performed on behavioral data through Redcap double data entry, wherein data are entered twice, and discrepancies are identified and corrected (Harris et al., 2019, 2009). Data were also visually inspected for errors.

4.3 Network Analysis

4.3.1 Imaging Acquisition

For all subjects, an anatomical scan was collected (T1-weighted; repetition time (TR) = 2530ms; echo time (TE) = 3.37ms; field of view [FOV (ap,fh,rl)] = 240 X 256 X 176 mm; slice gap=, 0; voxel size=1.0 X 1.0 X 1.0 mm; flip angle (FA) = 7º). After the anatomical scan, a resting-state functional scan was collected (T2*-weighted, TE/TR 30/2400 ms; FOV = 140 X 5 X 140; FA = 70º; voxel size = 3.0 X 3.0 X 3.0 mm; interleaved order of acquisition). Before the functional scan, participants were instructed to try to be as still as possible, stay awake, keep their eyes open, and let their minds wander without thinking of anything in particular. A central fixation cross was presented during the scan, which participants were told they could choose to look at during the scan.

4.3.2 Preprocessing

Anatomical images were preprocessed through Freesurfer (version 6.0) to render cortical surfaces (Fischl, 2012). Generated surfaces were then visually inspected for errors.

Before functional connectivity analysis, data were preprocessed with rigorous quality control methods for motion censoring (Carp, 2013; Gratton et al., 2020; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Power, Schlaggar, & Petersen, 2015; Siegel et al., 2014), implemented by XCPEngine (Ciric et al., 2018) and fMRIPrep (Esteban et al., 2019). Nuisance regressors included global signal, cerebral spinal fluid (CSF), white matter (WM), the six motion parameters, their temporal derivatives, and their first order and quadratic expansion. Censoring included a framewise displacement threshold of 0.5mm, a DVARS threshold of 5, a high pass filter of 0.01, and a low pass filter of 0.08. Spatial smoothing of 4 mm was applied.

4.3.3 Network Nodes

We build upon Chan et al. (2014) and Han et al. (2018) by creating nodes from our oldest-old sample. Since our sample of oldest-old adults was larger and included more fMRI data per participant than Han et al. (2018) or Chan et al. (2014), we generated nodes from our sample using the same methods. Han et al. (2018) showed that while functional connectivity boundary-based parcellation of the human cortex was generally consistent across the lifespan, the boundaries become less similar to the younger adult boundaries as cohorts get older. However, the relationship between increasing age and decreasing system segregation was still intact even with older adult nodes (Han et al., 2018). This difference between young and oldest-old adult parcellations led us to use the same methods of boundary-based parcellation as Han et al. (2018) (Figure 1, Part A), the method of detection of local minima ROIs and creation of 3-mm radius discs as Chan et al. (2014) (Figure 1, Part B), and network membership identification from the parcellation by Power et al. (2011) (Figure 1, Part C) to assess system and network segregation.

4.3.4 Calculation of Network Properties

In each participant, a mean time course was computed for each node from the atlas. A node-to-node correlation matrix was formed by correlating each node's time course with every node (Figure 2). The matrix of Pearson's r values was then transformed into Fisher's z. Only positive correlations were retained for all metrics except the within-network mean connectivity

for which both negative and positive values were incorporated. Within-network connectivity was calculated as the mean node-to-node z-value of all the nodes within that network. Segregation was calculated as within-network connectivity minus between-network connectivity, divided by within-network connectivity (Chan et al., 2014; Wig, 2017). Participation coefficient and modularity were calculated using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010).

4.3.5 Cortical Thickness Covariate

Cortical thickness data was derived from Freesurfer's cortical surfaces. Cortical thickness values were averaged across all ROIs (Figure 1) for each individual. This variable was then used as a covariate in subsequent analyses in order to account for potential confounding effects of atrophy.

4.3.6 Relating Cognition to Network metrics

Multiple regression was performed to assess association system metrics (modularity, participation coefficient, segregation, and mean connectivity) as predictors of overall cognition. Site and cortical thickness were entered in block one and association system metrics were entered in block two. We also performed correlation analysis between overall cognition and each association system metric including site and cortical thickness as covariates in partial correlations. Correlations were corrected for multiple comparisons using false discovery rate (FDR) correction. We also examined the relationship between modularity and segregation with a correlational analysis.

Five forward selection hierarchical regressions were performed to assess the predictors of each of the cognitive domains identified in the EFA (processing speed, executive functioning, episodic memory, working memory, and language). For each forward selection hierarchical regression, the data collection site and cortical thickness were entered as the first block, and segregation of the FPN, DMN, and CON were entered as the second block. Partial correlations with the site and cortical thickness as a covariate were assessed for variables within each regression, and FDR correction was used for multiple comparison correction.

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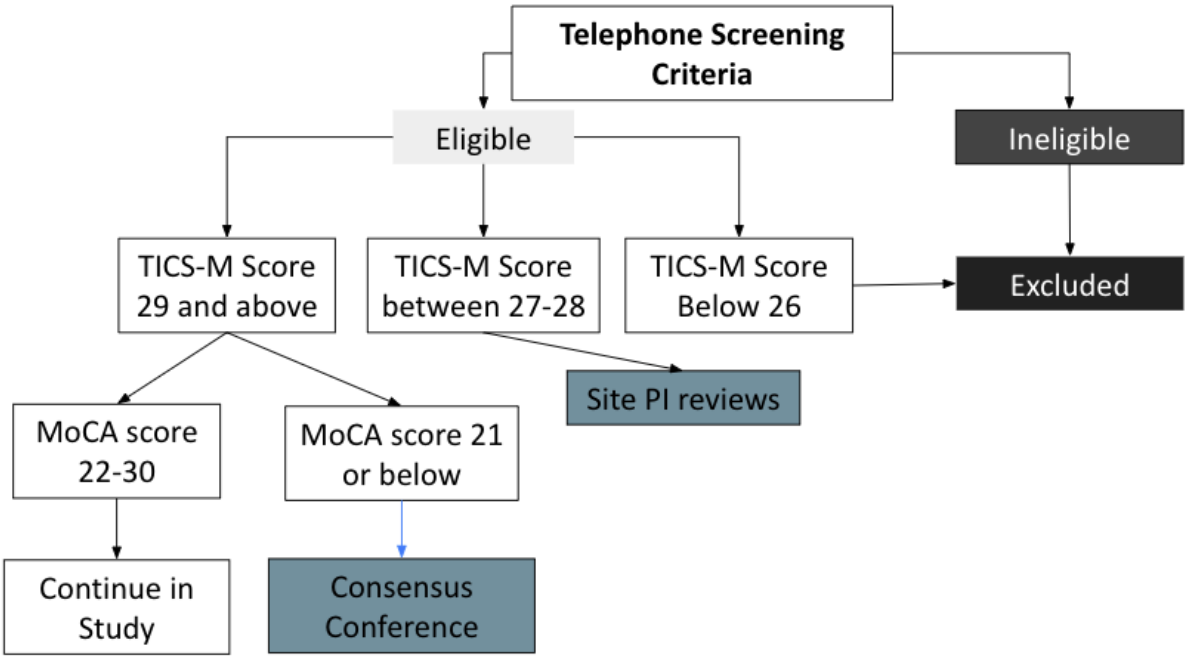
Data and code availability statement
Data are available through the McKnight Brain Aging Registry.
Code is available for node creation at https://github.com/Visscher-Lab/MBAR_oldestold_nodes and for statistical analysis and figures at https://github.com/Visscher-Lab/FPN_segregation_paper

Supplemental Materials
Supplemental Figure 1



Telephone screening criteria included exclusion for major physical disabilities, MRI contraindications, dependence in instrumental activities of daily living or basic activities of daily living, uncontrolled medical conditions that would limit life expectancy or interfere with participation in the study, severe psychiatric conditions, neurological conditions (i.e., major vessel stroke, Parkinson's Disease, dementia), active substance abuse or alcohol dependence, less than 6th-grade reading level, vision or hearing deficits that would cause impediment to cognitive test administration, and inability to follow study protocol and task instructions due to cognitive impairment. TICS-M was administered over the phone. If the TICS-M score falls within range for Site PI review, the Site PI would then decide if the participant should be deemed ineligible and excluded from the study or if the participant should continue on with the screening process. MoCA was performed at the in-person screening visit. An additional evaluation was included in the initial in person visit, including examination by a neurologist, geriatric depression scale, and detailed medical history.

Supplemental Table 1. **Participant Characteristics**	**Total, N=146**	**UAB[1], N= 48 (32.9%)**	**UA[2], N= 35 (24.0%)**	**UF[3], N= 35 (24.0%)**	**UM[4], N= 28 (19.2%)**
Age (years), *mean ± SD (range)*	88.4 ± 3.18 (85-99)	88.4 ± 3.47 (85-98)	88.7 ± 2.98 (85-95)	89.1 ± 3.65 (85-99)	87.1 ± 1.70 (85-91)
Education (years), *mean ± SD (range)*	16.1 ± 3.03 (9-26)	15.7 ± 2.62 (12-22)	15.9 ± 2.89 (9-22)	16.5 ± 3.30 (10-22)	16.5 ± 3.52 (12-26)
Sex, N(%)					
Female	79 (54.11%)	24 (50.00%)	18 (51.43%)	20 (57.14%)	17 (60.71%)
Male	67 (45.89%)	24 (50.00%)	17 (48.57%)	15 (42.86%)	11 (39.29%)
Race, N(%)					
Non-Hispanic Caucasian	134 (91.78%)	44 (91.67%)	33 (94.29%)	35 (100.00%)	22 (78.57%)
African American	6 (4.11%)	4 (8.33%)	0 (0.00%)	0 (0.00%)	2 (7.14%)
Hispanic Caucasian	5 (3.42%)	0 (0.00%)	2 (5.71%)	0 (0.00%)	3 (10.71%)
Asian	1 (0.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.57%)
Marital Status, N(%)					
Widowed	74 (50.69%)	27 (56.25%)	16 (45.71%)	19 (54.29%)	12 (42.86%)
Married	54 (36.99%)	17 (35.42%)	12 (34.29%)	13 (37.14%)	12 (42.86%)
Divorced	13 (8.90%)	4 (8.33%)	3 (8.57%)	3 (8.57%)	3 (10.71%)
Living as Married/Domestic Partnership	3 (2.06%)	0 (0.00%)	3 (8.57%)	0 (0.00%)	0 (0.00%)
Never Married	2 (1.37%)	0 (0.00%)	1 (2.86%)	0 (0.00%)	1 (3.57%)
Dominant Hand, N(%)					
Right	131 (89.73%)	45 (93.75%)	29 (82.86%)	33 (94.29%)	24 (85.71%)
Left	15 (10.27%)	3 (6.25%)	6 (17.14%)	2 (5.71%)	4 (14.29%)

[1]UAB, University of Alabama at Birmingham; [2]UA, University of Arizona; [3]UF, University of Florida; [4]UM, University of Miami

Supplemental Table 2. **Factor Loadings for Cognitive Domains**	**Processing Speed**	**Memory**	**Executive Functioning**	**Working Memory**	**Language**
WAIS-IV Coding[1]	.785				
Stroop Color-Word Reading Trial[2]	.678				
Trail Making Test A (lines/sec)[3]	-.670				
WAIS-IV Symbol Search[1]	.593		.364		
CVLT II Long Delay Recall[4]		.749			
FNAME Total Score[5]		.709			
Craft Story Paraphrase Delay Recall[6]		.599			
WAIS-IV Block Design[1]			.704		
WAIS-IV Matrix Reasoning[1]			.552		
Benson Figure Test Delay Recall[6]		.362	.376		
Stroop Color Word-Inhibition Test Interference[2]			.367		
Trail Making Test B (lines/sec) (minus Trail Making Test A (lines/sec))[3]			-.328		
Digit Span Forward[6]				.745	
Digit Span Backward[6]				.714	
WAIS-IV Letter-Number Sequencing[1]				.362	
Letter Verbal Fluency (F & L)[7]					.661
WAIS-IV Similarities[1]					.430
Semantic Fluency (Animals)[8]		.409			.421

1 (Weschler, 2008)
2 (MacLeod, 1992)
3 (Gaudino, Geisler, & Squires, 1995)
4 (Delis, Kramer, Kaplan, & Ober, 1987)
5 (Amariglio et al., 2012)
6 (Beekly et al., 2007)
7 (Newcombe, 1969)
8 (Benton, 1968)

Supplemental Table 3. **Correlations between Cognitive**	**Memory**	**Working Memory**	**Language**

Domains and Network Segregation			
FPN Segregation	r=.073 p=.382	r=.124 p=.135	r=.06 p=.473
DMN Segregation	r=-.017 p=.84	r=.092 p=.729	r=.137 p=.098
CON Segregation	r=-.024 p=.777	r=.097 p=.242	r=.025 p=.762

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