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Cognition and the Brain of the Healthy Oldest-Old

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COGNITION AND THE BRAIN OF THE HEALTHY OLDEST-OLD

by

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A DISSERTATION

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MEDICAL/CLINICAL PSYCHOLOGY

ABSTRACT

There is an increasing number of people aged 65 and older, particularly in the oldest old cohort (aged 85 and older). Aging is characterized by significant changes in the brain including disruptions to white matter and functional connectivity. While cognition is impacted in many age related diseases, like Alzheimer's Disease or Parkinson's Disease, an understanding of the healthy aging brain is important for informing research on successful aging.

My dissertation consists of three aims: (1) For the first aim, my overall objective was to determine the validity of the NIH toolbox in the oldest old cohort. I used other standard measures of cognition and compared performance on the NIH toolbox measures of cognition in order to determine validity of the toolbox. (2) For the second aim, I created a brain parcellation based on an oldest-old sample so that I could use age appropriate network node locations when studying network dynamic measures in Aim 3. (3) For the third aim, my overall objective was to identify the degree to which brain networks are segregated in healthy oldest-old adults and whether network properties explain variance in cognitive performance. To address these aims, I used The McKnight Brain Aging Registry (MBAR), which is a multisite study across the McKnight Brain Research Foundation institutes. The dataset consists of cognition and MRI data from 200 individuals who were screened for neurological disorders and cognitive impairment.

I have expanded the field's current knowledge of cognition of successful agers by investigating the relationship between brain functional network dynamics and cognitive performance in the healthy oldest old as well as the validity of new measures of cognition in this cohort. I add to the literature on age-related dedifferentiation, showing that even in a very old and cognitively healthy sample, cognitive dedifferentiation may impact executive functioning abilities and functional network dedifferentiation is related to cognitive abilities.

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

DEDICATION

To my Peter- may you never stop being curious, asking questions, and learning.

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Thank you to my mentor and committee chair, Dr. Kristina Visscher. Thank you for giving me the space to grow and the guidance to keep me growing. I would also like to thank my committee members for taking the time to serve on my dissertation committee and their valuable feedback and support. I would like to thank my fellow lab members for their unwavering assistance, without whom this project would not have been possible. I would also like to thank the Evelyn F. McKnight Foundation for funding this work and our MBAR collaborators who have not only worked with us to collect these data, but also who have revised many manuscript drafts along the way. As part of this project, I have had the opportunity to meet so many wonderful, lively 85+ year olds and I am grateful for their participation in our study. Finally, I would like to thank my family for their constant love, support, and patience.

TABLE OF CONTENTS

Page

LIST OF TABLES

Table *Page*

VALIDITY OF THE NIH TOOLBOX COGNITIVE BATTERY IN A HEALTHY OLDEST-OLD 85+ SAMPLE

FRONTO-PARIETAL NETWORK SEGREGATION PREDICTS MAINTAINED PROCESSING SPEED IN THE COGNITIVELY HEALTHY OLDEST-OLD

LIST OF FIGURES

Figures *Page*

INTRODUCTION

VALIDITY OF THE NIH TOOLBOX COGNITIVE BATTERY IN A HEALTHY OLDEST-OLD 85+ SAMPLE

FRONTO-PARIETAL NETWORK SEGREGATION PREDICTS MAINTAINED PROCESSING SPEED IN THE COGNITIVELY HEALTHY OLDEST-OLD

LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
CFI	Comparative Fit Index
CON	Cingulo-opercular Network
CVLT II	California Verbal Learning Test 2nd edition
DCCS	Dimensional Change Card Sort
DMN	Default Mode Network
DVARS	spatial standard deviation of successive difference images
EFA	Exploratory Factor Analysis
FDR	False Discovery Rate
fMRI	functional magnetic resonance imaging
FPN	Fronto-parietal Network
LNS	Letter Number Sequencing
MBAR	McKnight Brain Aging Registry
MCI	Mild Cognitive Impairment
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NIH TB-CB	NIH Toolbox Cognitive Battery
RMSEA	Root Mean Square Error of Approximation
ROI	Region of Interest
SD	Standard Deviation

SRMR	Standard Root Mean Square Residual
TICS-M	Telephone Interview Cognitive Screening- Modified
TLI	Tucker Lewis Index
TMT	Trail Making Test
WAIS IV	Wechsler Adult Intelligence Scale 4th edition
WM	Working Memory

INTRODUCTION

An increasing number of people are reaching the age of 65 and older, with rapid growth of the 85 and older cohort (Vincent & Velkoff, 2010). It is estimated that by 2050, people aged 85 and over will make up more than 21% of the older adult population (Vincent & Velkoff, 2010). The oldest-old cohort is of particular research interest because these individuals have undergone healthy cognitive aging - a goal for most older adults. Since successful brain aging is important to quality of life, the goal of aging research is no longer to promote survival to old age, but thriving in older adulthood, and these studies focus on a thriving older adults sample.

The first step to understanding cognitive aging is studying successful agers. Studying healthy agers is impactful because it enables examination of brain and behavior relationships of individuals who have lived into the oldest-old age range without being affected by diseases common to aging populations. Studies of the younger-old (65-85 years old) can be confounded by the inclusion of individuals with pre-symptomatic disease, since it is not known which individuals may be experiencing undetectable, pre-clinical cognitive disorders and which individuals will go on to be healthy for another decade. However, the oldest-old have lived into late ages and we can therefore be more confident of their status as successful agers. Additionally, these successfully aged individuals allow for measurement of the upper-end of the spectrum of aging: what we all hope to achieve in the aging process.

While our work exclusively examines individuals who are cognitively healthy, the general trend is that variance in cognitive performance and brain metrics increases with age. More variance in the variables of interest helps us better understand the relationship between the brain and preserved cognition (Gratton, Nelson, & Gordon, 2022).

With age, the ability to think and reason declines, with executive functioning and processing speed being particularly affected by aging (Reuter-Lorenz, Festini, & Jantz, 2016; Spaan, 2015). Dedifferentiation has been used to help explain cognitive and brain changes in aging individuals. Dedifferentiation describes how previously the process of previously separable entities becoming less distinct; this concept can be used to describe cognitive abilities (Baltes et al., 1980) as well as network organization (Goh et al., 2011). However, relatively little work has examined cognition and brain relationships in oldest-old individuals (Wettstein, Wahl, & Heyl, 2015).

An important societal goal is an intervention to slow or stop age-related cognitive decline; essentially to develop strategies to make all oldest-old adults more like the rarer cognitively healthy oldest-old adults. Thus, understanding the aspects of healthy oldest-old brains which contribute to healthy cognitive performance is essential to developing cognitive rehabilitation interventions for aging individuals. The experiments performed in Paper 1 addressed: 1) the capacity and validity of measuring cognitive domains in oldest-old adults, and in Paper 2 addressed: 1) creating oldest-old specific brain network parcellation, and 2) relating cognitive measures to brain functional network dynamics.

NIH Toolbox Cognitive Battery

The NIH Toolbox Cognitive assessment battery (NIH TB-CB) was developed as a way to strive toward brevity, portability, and homogeneity in neurobehavioral assessment research through the use of short tasks that can be administered via iPad (Gershon et al., 2013). The NIH TB-CB covers a wide range of cognitive domains including executive functioning, episodic memory, language, processing speed, attention, and working memory (Gershon et al., 2013). Factor analysis of the NIH TB-CB measures with "gold standard" measures of the same domains of cognition has revealed convergent and discriminant validity of these measures (Mungas et al., 2014). Mungas and colleagues (2014) tested the validity of the NIH TB-CB in a younger age range (20-85) by generating a series of factor models and then comparing the models based on model fit indices. They found that the 5 factors of Vocabulary, Reading, Episodic Memory, Working Memory, and Executive Function/Processing Speed best described the relationship between the NIH TB and the gold standard measures. This factor structure did not vary across their younger adult (20-60) and older adult (60-85) age groups. The factor loadings also supported convergent and discriminant validity. However, normative data for the NIH TB-CB was only collected for adults up to age 85, leaving out an ever-growing percentage of the older adult population.

In order to better understand the utility of the NIH TB-CB in the oldest-old population, the current study used confirmatory factor analysis to investigate (1) whether the NIH TB-CB factor structure differs in the oldest-old adults compared to what was previously reported for younger older adults (Mungas et al., 2014) and (2) if there is convergent and discriminant validity among the NIH TB-CB and validated measures in the oldest-old. I was also interested in the impact of an individual's experience with

technology on NIH TB-CB composite scores. I hypothesized that the factor structure of the NIH Toolbox is consistent across the lifespan, therefore the 5-factor model, derived from a younger adult sample (Mungas et al., 2014) would have a better model fit than alternative factor models.

Based on the methods of previous work (Mungas et al., 2014), in this study, I assessed the degree to which the original conceptual model, which was created during the production of the NIH TB-CB, aligns with the factor structure created from an oldest-old sample. This approach established the reproducibility of previous findings (Mungas et al., 2014) while extending it into the oldest-old cohort.

Brain Network Parcellation for the Oldest-Old

When studying interactions among brain networks, it is important to know that the individual elements (nodes) in the network are correctly identified in the cerebral cortex. Some literature suggests that these network elements may be different in older vs. younger adults (Han et al., 2018). Therefore, it is important to use an age-specific cortical parcellation that most accurately represents the brain organization of the sample. Although there is evidence that increasing age is associated with decreasing segregation of brain systems and functional brain networks, such observations are limited by having only been found in younger age ranges using younger adult nodes (Han et al. 2018; Geerligs et al. 2015; Chan et al. 2014; Wig 2017). Han et al. (2018) found that while the spatial organization of large-scale brain networks is relatively maintained throughout aging, the boundaries of resting-state functional connectivity-defined area parcellation become more dissimilar from the younger adult map with increasing age, with the largest distinction between parcellations in the younger-adults and oldest-old adults.

Additionally, cohort-specific parcellations were more homogenous and provided better estimates of functionally distinct areas compared to parcellations defined by younger-adult nodes (Han et al., 2018). Based on these findings, I created a cortical parcellation with nodes that would best fit our cognitively healthy oldest-old sample using similar methods as Han et al. (2018) and Chan et al. (2014).

Cognition and Brain Network Segregation in the Healthy Oldest-Old

Next, I aimed to understand how measures of cognition relate to brain network dynamics. There are some cognitive domains that are especially susceptible to age-related decline, including processing speed, executive function, and memory (Reuter-Lorenz et al., 2016; Spaan, 2015). Brain networks are an important avenue of aging and cognitive research since network infrastructure, including network integration and segregation, have been shown to be related to cognition (Chan, Park, Savalia, Petersen, & Wig, 2014; Cohen & D'Esposito, 2016; Shine et al., 2016). The term segregation refers to the balance of connectivity within and among networks, with very high segregation indicating isolated networks and very low segregation indicating networks are no longer separable ((Wig, 2017); Figure 1).

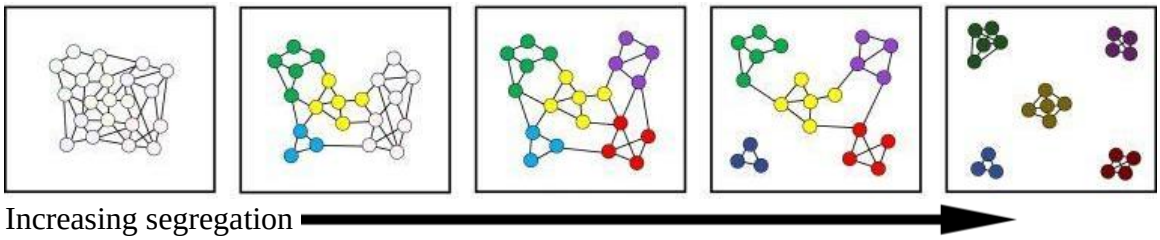

Figure 1. Spectrum of network segregation. The circles represent network nodes or regions of the network, and the lines represent connections between the nodes. Each color in the circles represents a distinct network. The middle panel depicts balanced networks with integration (connections within the network) and segregation (the distinction between networks with fewer connections between networks than within a network). To the right of the middle panel, networks become increasingly isolated with increasing segregation. To the left of the middle panel, networks become decreasingly distinguishable with decreasing segregation. Images adapted from Wig 2017.

Recent studies have shown that the network properties of brain connectivity change over the lifespan (20-89 years old) and that older adults have less well-segregated networks (Chan et al., 2014). Previous work has shown that many brain factors contribute to preserving cognition in aging populations. Such factors include improved efficiency of network structure and intact white and gray matter structure, which both relate to relatively better cognitive performance (Vaqué-Alcázar et al., 2020). We know that brain networks also play a key role in aging since older adults exhibit changes in brain structural and functional network integrity as part of the aging process (Marstaller, Williams, Rich, Savage, & Burianová, 2015). For example, relative to younger adults, older adults have weaker connections within functional networks, including the fronto-parietal, salience, and default mode networks (Marstaller et al., 2015). Also, older adults exhibit an overall decline in gray matter thickness and white matter integrity related to declining functional network engagement (Marstaller et al., 2015). In addition, brain

structure and function are impacted by many of the diseases that are common in the aging population including cognitive disorders such as Alzheimer's Disease and mild cognitive impairment (MCI) (Birdsill et al., 2014; Chhatwal et al., 2018; Pichet Binette et al., 2020; Taylor et al., 2017).

The association system consists of higher-order cognition networks such as the frontoparietal network (FPN), cingulo-opercular network (CON), and default mode network (DMN). These networks are associated with poorer performance on measures of episodic memory, processing speed, attention, and executive functions (Chan, Alhazmi, Park, Savalia, & Wig, 2017; Damoiseaux, 2017; Goh, 2011; Hausman et al., 2020; Iordan et al., 2017; Koen, Srokova, & Rugg, 2020; Nashiro, Sakaki, Braskie, & Mather, 2017; Ng, Lo, Lim, Chee, & Zhou, 2016; Varangis, Habeck, Razlighi, & Stern, 2019). However, Chan et al. (2014) only reported the relationship between the segregation of the association system as a whole to measures of cognitive performance. Here, I focused on not only the association system but the networks that comprise that system including the FPN, CON, and DMN in order to look at specific network segregation relationships to cognitive domains. I used the network nodes created from the MBAR sample of oldest-old individuals which were created as part of Aim 2.

My objectives were to 1) identify the degree to which the association system and functional networks are segregated in healthy oldest-old adults and 2) determine if network segregation explains variance in cognitive performance. I hypothesized that maintaining cognition at age 85+ requires segregated association networks.

Much previous research on aging has focused on age-related diseases and disease-related brain changes. Other studies have examined differences between younger and

older adults in a relatively small age range. Thus the functioning of a healthy aging brain in the oldest-old age group (85 and older) is largely understudied. In these studies, I have expanded on prior methods of studying the functional networks and cognition by using an older, 85+ population. The goal of this study was to further investigate cognition in the context of successful brain aging in the oldest-old cohort by examining new cognitive measures and how functional network dynamics are associated with cognitive performance.

My dissertation is innovative in addressing the validity of the NIH TB in adults over 85, which has not been done before. Technology use in the testing environment is emerging and so ensuring the validity of using these new methods of neuropsychological testing in the aging population is essential. Research in this area is novel in that it applies network dynamics to an oldest-old cohort and looks at the relationship between network dynamics and cognition within that cohort.

An understanding of the healthy aging brain's functional networks and cognitive performance will help define the goal of becoming a healthy ager for studies assessing cognitive rehabilitation interventions for aging-related cognitive disorders. Although research in the 85+ age group is increasing, a lack of data has hindered research in the oldest-old, especially individuals who have successfully aged to 85 years and older (Bennett et al., 2017; Giulioli & Amieva, 2016; Rogalski et al., 2019). In particular, some widely-used methods from research on younger people have not been validated in this population. Further, while some aspects of brain function have been shown to change with age and with age-related changes in behavior, a thorough investigation of the complex relationship between cognitive abilities and functional network dynamics has yet to be done in the oldest-old.

VALIDITY OF THE NIH TOOLBOX COGNITIVE BATTERY IN A HEALTHY OLDEST-OLD 85+ SAMPLE

by

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Abstract

Objective

To evaluate the construct validity of the NIH Toolbox Cognitive Battery (NIH TB-CB) in the healthy oldest-old (85+ years old).

Method

Our sample from the McKnight-Brain-Aging-Registry consists of 179 individuals, 85 to 99 years of age, screened for memory, neurological, and psychiatric disorders. Using previous research methods on a sample of 85+ y/o adults, we conducted confirmatory factor analyses on models of NIH TB-CB and same domain standard neuropsychological measures. We hypothesized the five-factor model (Reading, Vocabulary, Memory, Working-Memory, and Executive/Speed) would have the best fit, consistent with younger populations. We assessed confirmatory and discriminant validity. We also evaluated demographic and computer use predictors of NIH TB-CB composite scores.

Results

Findings suggest the six-factor model (Vocabulary, Reading, Memory, Working Memory, Executive, and Processing Speed) had a better fit than alternative models. NIH TB-CB tests had good convergent and discriminant validity, though tests in the executive functioning domain had high inter-correlations with other cognitive domains. Computer use was strongly associated with higher NIH TB-CB overall and fluid cognition composite scores.

Conclusion

The NIH TB-CB is a valid assessment for the oldest-old samples, with relatively weak validity in the domain of executive functioning. Computer use's impact on composite scores could be due to the executive demands of learning to use a tablet. Strong

relationships of executive function with other cognitive domains could be due to cognitive dedifferentiation. Overall, the NIH TB-CB could be useful for testing cognition in the oldest-old and the impact of aging on cognition in older populations.

Keywords: Aged 85 and over, neuropsychological tests, cognition, confirmatory factor analysis, construct validity, test development

Introduction

The population of individuals within the oldest-old age range (85 years and older) is rapidly growing (Vincent & Velkoff, 2010). However, the lack of available data with a comprehensive assessment of cognitive functions in healthy agers over age 85 limits research in this age cohort. The developers of the NIH Toolbox- Cognitive Battery (NIH TB-CB) limited their collection of normative data to those ages 3-85. Technology use in the cognitive testing environment is emerging, so ensuring the validity of using these new neuropsychological testing methods in the aging population is essential - especially since this oldest-old population may be less likely than other age groups to be comfortable with technology usage. Results of this study inform the use of the NIH TB-CB in future research in the oldest-old population.

The NIH Toolbox Cognitive Battery (NIH-CB) strives towards brevity, portability, and homogeneity in neurobehavioral assessment research through short tasks performed on an iPad (Gershon et al., 2013). The Cognitive Battery covers a wide range of cognitive domains, including executive functioning, episodic memory, language, processing speed, attention, and working memory (Gershon et al., 2013). The NIH Toolbox is valid in diverse samples of varying age, language, race, ethnicity, gender,

education, developmental disability, and neurological conditions (N E Carlozzi et al., 2017; Flores et al., 2017; Hackett et al., 2018; Heaton et al., 2014; Hessl et al., 2016; Ma et al., 2021; Mungas et al., 2013; Tulsky et al., 2017; Weintraub, Dikmen, et al., 2013; Weintraub et al., 2014). For example, Mungas and colleagues (2014) examined younger and older age groups but only up to age 85. While the NIH TB-CB has been used in older adult samples (O'Shea et al., 2018), to our knowledge, no findings have been reported on the effectiveness of the NIH TB-CB as a battery to measure cognitive functions in healthy individuals over age 85.

Factor analysis of the NIH Toolbox cognitive measures with standard neuropsychological tests of the same domains of cognition revealed good construct validity (Mungas et al., 2014). Meaning, there was support for correspondence between a given domain and a test used to measure it, which was indicated by the individual tests showing both strong associations with the hypothesized cognitive domains (i.e., convergent validity); as well as, weak relationships between each of the tests and other domains (i.e., discriminant validity). In this case, Mungas and colleagues (2014) tested the validity of the NIH TB-CB in a cohort of adults, 20 to 85 years of age using confirmatory factor analysis. Although the NIH Toolbox assesses six specific domains (working memory, executive function, episodic memory, processing speed, vocabulary, and reading), they found that a five-factor model best describes the relationship between the NIH Toolbox Cognitive Battery and standard neuropsychological measures: Vocabulary, Reading, Episodic Memory, Working Memory, and Executive Function/Processing Speed with the NIH TB-CB tests falling largely within expected domains (Mungas et al., 2014). This factor structure did not vary across younger (ages 20-60) and older adults (ages 60-85), supporting the use of the NIH TB-CB as a measure

of cognitive health across the adult age range from 20 to 85. Investigating the factor structure of the NIH TB-CB in individuals older than age 85 provides an important opportunity to evaluate its utility for assessing cognitive functions in the fastest growing age group within the population of healthy older adults.

This study examines the validity of the NIH TB-CB cognitive domains in cognitively healthy older adults over age 85, which, to our knowledge, has yet to be reported. We employed a series of confirmatory factor analyses to investigate the convergent and discriminant validity, as well as the dimensional structure underlying the NIHTB-CHB and other validated measures of cognition in healthy older adults aged 85 years old and over. We hypothesized that the factor structure of the NIH Toolbox would be consistent across the lifespan, and thus the 5-factor model, derived from a younger adult sample (Mungas et al., 2014), would have a better model fit than alternative factor models. We also sought to evaluate the influence of demographic characteristics and computer use in this oldest-old age cohort on NIH TB-CB Composite scores.

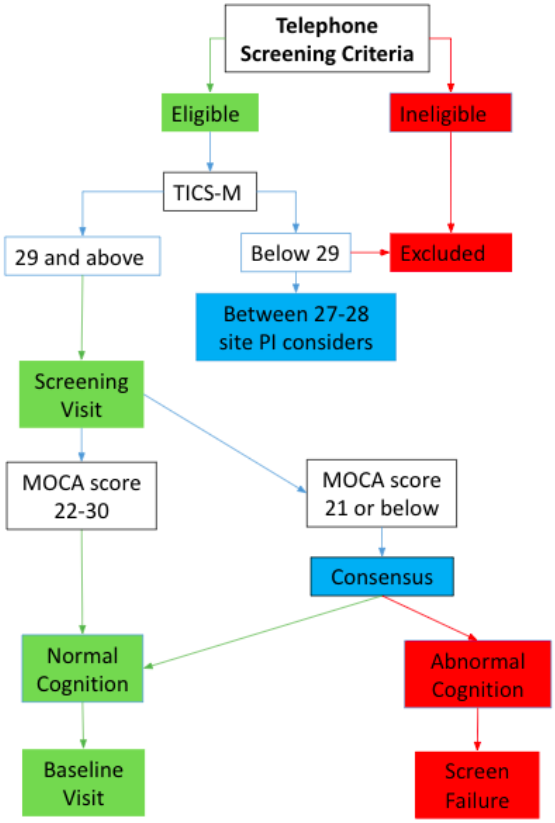
Method

Participants

We analyzed data collected from the McKnight Brain Aging Registry, a cohort of community-dwelling, cognitively unimpaired older adults, 85 to 99 years of age. Figure 1 shows the extensive participant screening process. During initial screening over the phone, trained study coordinators administered the Telephone Interview for Cognitive Status modified (TICS-M) (Cook, Marsiske, & McCoy, 2009) and an interview to assess for major exclusion criteria, which included individuals under age 85, severe psychiatric conditions, and neurological conditions, and cognitive impairment. Following the

telephone screening, eligible participants underwent an in-person screening visit during which they were evaluated by a neurologist, a detailed medical history was obtained to assess health status and eligibility, and the Montreal Cognitive Assessment (MoCA) was administered (Nasreddine et al., 2005). An additional point was added for adjustment of the MoCA score to account for non-white race and/or education equal to or below 12th grade. This adjustment was for the purpose of fairly screening individuals of lower education or non-white backgrounds and this adjustment is not based on normative data. The study was conducted in accordance with the Helsinki declaration. 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.

Figure 1. Participant Screening Process



Telephone screening criteria included exclusion for major physical disabilities, 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, MRI contraindications, and inability to follow study protocol and task instructions due to cognitive impairment. TICS-M was administered over the phone. An additional evaluation was included in the screening visit, including examination by a neurologist, geriatric depression scale, and detailed medical history.

Our fully screened sample consists of 192 community-dwelling individuals aged 85-99. We removed data from 13 participants from the analysis due to missingness related to administrator error, low visual acuity, participant's color blindness, or

participant not completing the task. This left a remaining 179 participants in our sample. Only 138 participants were given the questionnaire related to computer use since this was adopted after data collection had begun; therefore analyses with the computer frequency variable are based on those 138 participants. Data from this group of healthy agers were collected using a standardized protocol across the four McKnight Institutes: University of Alabama at Birmingham, University of Florida, University of Miami, and University of Arizona. We recruited participants through mailings, flyers, physician referrals, and community-based recruitment.

Table 1. Participant Characteristics

Participant Characteristics Total Sample (N=179)	
Age (Years), +/- SD (Years)	88.34 +/- 3.06 (85-99)
Education (Years), Mean +/- SD (range)	18.13+/-2.69 (11-22)
Race and Education Adjusted MoCA, Mean +/- SD (range)	24.78 +/- 2.51 (17-30)
NIH TB Cognitive Total Composite demographically corrected* standard score, Mean +/- SD (range)	104.75+/- 12.18 (71-135)
NIH TB Cognitive Fluid Composite demographically corrected* standard score, Mean +/- SD (range)	97.52 +/- 12.7 (75-130)
NIH TB Cognitive Crystallized Composite demographically corrected* standard score, Mean +/- SD (range)	110.7 +/- 12.84 (71-170)
Sex, N(%)	
Female	96 (53.63%)
Male	83 (46.36%)
Race/Ethnicity, N(%)	
Non-Hispanic Caucasian	165 (92.21%)
African American	6 (3.35%)
Hispanic Caucasian	5 (2.79%)
Asian	3 (1.67%)
Marital Status, N(%)	
Widowed	87 (48.6%)
Married	70 (39.1%)
Divorced	13 (7.26%)
Domestic Partnership	6 (3.35%)
Never Married	3 (1.67%)
Sample Subset (N=138)	
Computer Use Frequency, Mean +/- SD (range)	2.8+/-1.75(0-5)
NIH TB Uncorrected Total Cognition Composite Score, Mean +/- SD (range)	95 +/- 8.53 (76-116)
NIH TB Uncorrected Fluid Cognition Composite Score, Mean +/- SD (range)	80+/-9.38 (61-102)
NIH TB Uncorrected Crystallized Cognition Composite Score, Mean +/- SD (range)	112+/-7.87 (93-129)

**Note that demographic corrections are not available for individuals over age 85, therefore corrections for all participants, including those over 85 years of age, were based on normative data for individuals age 85 years old.*

Cognitive measures

Testing was performed by staff trained and certified across the four sites to administer the test battery. Testing was administered across two visits on separate days. We performed quality control on behavioral data through the double data entry tool in Redcap, wherein we entered data twice, and discrepancies were identified and corrected (Harris et al., 2019, 2009). The data were then again visually inspected and assessed for potential outliers and errors.

NIH TB-CB measures

We used scores from the NIH TB-CB (Gershon et al., 2013; Weintraub et al., 2014), including the Dimensional Change Card Sort (DCCS) Test, the Flanker Inhibitory Control and Attention Test, the Picture Sequence Memory Test, the Pattern Comparison Processing Speed Test, the List Sorting Working Memory Test, the Oral Reading Recognition Test, and the Picture Vocabulary Test. The Dimensional Change Card Sort (DCCS) Test measures executive function by indicating a target characteristic and then instructing participants to quickly select the object that matches the indicated characteristic for that trial (either shape or color). The Flanker Inhibitory Control and Attention Test measures executive function by having participants quickly select the correct direction of an arrow among a set of arrows. The Pattern Comparison Processing Speed Test measures processing speed by having participants quickly decide whether or not two images match. The Picture Sequence Memory Test measures episodic memory

by asking participants to place cards in a particular order from memory. The List Sorting Working Memory Test measures working memory by presenting an increasing number of pictures and then instructing participants to order the pictures by size and semantic category from memory. The Oral Reading Recognition Test measures language by having participants read aloud words shown on the screen. The Picture Vocabulary Test measures language by presenting a word verbally and instructing participants to select one of four images that best describes the word. Table 2 includes NIH TB-CB measures and their associated domains. Only raw or calculated scores were used for the analysis. We also performed follow-up analysis with demographically corrected scores for the NIH TB-CB scores.

Table 2. NIH Toolbox Measures and Associated Cognitive Domains

Measure	Scoring Measure	Associated Domains
Dimensional Change Card Sort Test (DCCS)	Computed Scores	Executive Function (Cognitive Flexibility and Attention)
Flanker Inhibitory Control and Attention	Computed Scores	Executive Function (Cognitive Flexibility and Attention)
Picture Sequence Memory Test	Theta Scores	Episodic Memory
Pattern Comparison Processing Speed Test	Raw Scores	Attention and Processing Speed
List Sorting Working Memory Test	Raw Scores	Working Memory and Executive Functioning
Oral Reading Recognition Test	Theta Scores	Language (Reading and Crystalized Abilities)
Picture Vocabulary Test	Theta Scores	Language (Receptive Vocabulary)

Standard Neuropsychological measures

We used standard neuropsychological tests with strong psychometric properties within the same domains as those used in the NIH TB-CB. Memory functioning was assessed through the California Verbal Learning Test II (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 1987), a word list learning task, and the Benson Figure Test (Beekly et al., 2007), a visual memory task. Executive functioning was assessed through the Trail Making Test B (Gaudino, Geisler, & Squires, 1995), visual attention and switching task; WAIS-IV Matrix Reasoning (Benson, Hulac, & Kranzler, 2010) subtest, which involves recognizing and utilizing pattern recognition and integration; and the Stroop Color Word-Inhibition test (Colin M. MacLeod, 1992; C M MacLeod, 1991), an inhibition task. Language/Vocabulary was assessed through the WAIS-IV Similarities (Benson et al., 2010), which involves explaining abstract relationships between two words. Processing speed was assessed through the WAIS-IV Coding and Symbol Search (Benson et al., 2010) subtests which both involve speeded visual processing. Lastly, working memory was assessed through the WAIS-IV Letter-Number sequencing subtest (Benson et al., 2010), a task involving sequencing a set of letters and numbers, and Digit Span (Beekly et al., 2007), a number recall task including recall backward. Table 3 includes the standard neuropsychological measures and their associated domains. Only raw or calculated scores were used. We also performed follow-up analysis with demographically corrected scores for the NIH TB-CB scores.

Table 3. Standard Neuropsychological measures and Associated Cognitive Domains

Measures	Scoring Measure	Domains
Trail Making Test (TMT) Part B	Time (number of seconds per line drawn)	Executive Functioning (Switching)
Letter-Number Sequencing	Number of correct trials	Working Memory (mental manipulation)
Digit Span Backward	Number of correct trials	Working Memory (mental manipulation)
California Verbal Learning Test (CVLT)	Total number of correct responses at delayed recall	Episodic verbal learning and memory
Matrix Reasoning (WAIS-IV)	Total number of correct responses	Perceptual Reasoning (Executive Function)
Coding (WAIS-IV)	Total number correct within the specified time limit	Processing Speed
Symbol Search (WAIS-IV)	The difference in number of correct responses and number of incorrect responses	Processing Speed
Similarities (WAIS-IV)	Total number of correct responses	Verbal Reasoning and Comprehension
Stroop Color-Word Inhibition	Interference score	Executive Functioning (Inhibition)
Benson Figure Test	Total score based on accuracy and placement of figure components	Episodic Visual Memory

Confirmatory Factor Analysis

Based on the methods of previous work from Mungas and colleagues (2014), we performed a series of confirmatory factor analyses, which allowed us to assess the degree to which the original conceptual model of the NIH Toolbox Cognitive Battery aligns with the factor structure of the NIH Toolbox Cognitive Battery and standard neuropsychological measures of the same cognitive domains within the oldest-old. We

compared models matching this conceptual model, as well as alternative models, detailed in Table 4.

Table 4. Alternative models

1 Factor Model		
Model	Factors	Measures used in Each Factor
1a	Global	All
2 Factor Models		
Model	Factors	Measures used in Each Factor
2a	Crystallized	Oral Reading Recognition, Picture Vocabulary, Similarities
	Fluid	Picture Sequence Memory, List Sorting WM, LNS, Digit Span Backward, CVLT, Benson Figure, DCCS, Pattern Comparison Processing Speed, List Sorting WM, TMT Part B, Matrix Reasoning, Coding, Symbol Search, Stroop Color-Word Inhibition, Flanker
2b	Memory	Picture Sequence Memory, List Sorting WM, LNS, Digit Span Backward, CVLT, Benson Figure
	Non-memory	DCCS, Pattern Comparison Processing Speed, List Sorting WM, TMT Part B, Matrix Reasoning, Coding, Symbol Search, Stroop Color-Word Inhibition, Flanker
3 Factor Models		
Model	Factors	Measures used in Each Factor
3a	Language	Oral Reading Recognition, Picture Vocabulary
	EM/WM	Picture Sequence Memory, List Sorting WM, LNS, Digit Span Backward, CVLT, Benson Figure
	EF/Speed	DCCS, Pattern Comparison Processing Speed, List Sorting WM, TMT Part B, Matrix Reasoning, Coding, Symbol Search, Stroop Color-Word Inhibition, Flanker
3b	Language	Oral Reading Recognition, Picture Vocabulary
	EM	Picture Sequence Memory, CVLT, Benson Figure
	WM/EF/ Speed	DCCS, Pattern Comparison Processing Speed, List Sorting WM, TMT Part B, LNS, Digit Span Backward, Matrix Reasoning, Coding, Symbol Search, Stroop Color-Word Inhibition, Flanker
4 Factor Models		
Model	Factors	Measures used in Each Factor
4a	Language	Oral Reading Recognition, Picture Vocabulary
	EM	Picture Sequence Memory, Benson Figure
	WM	List Sorting WM, LNS, Digit Span Backward

	EF/Speed	DCCS, Pattern Comparison Processing Speed, List Sorting WM, TMT Part B, Matrix Reasoning, Coding, Symbol Search, Stroop Color-Word Inhibition, Flanker
4b	Vocabulary	Picture Vocabulary
	Reading	Oral Reading Recognition
	EM	Picture Sequence Memory, CVLT, Benson Figure
	WM/EF/ Speed	DCCS, Pattern Comparison Processing Speed, List Sorting WM, Trail Making Part B, LNS, Digit Span Backward, Matrix Reasoning, Symbol Search and Coding, Stroop Color-Word Inhibition, Flanker
4c	Vocabulary	Picture Vocabulary
	Reading	Oral Reading Recognition
	EM/WM	Picture Sequence Memory, List Sorting WM, LNS, Digit Span Backward, CVLT, Benson Figure
	EF/Speed	DCCS, Pattern Comparison Processing Speed, List Sorting WM, TMT Part B, Matrix Reasoning, Coding, Symbol Search, Stroop Color-Word Inhibition, Flanker
5 Factor Models		
Model	Factors	Measures used in Each Factor
5a	Language	Oral Reading Recognition, Picture Vocabulary
	EM	Picture Sequence Memory, CVLT, Benson Figure
	WM	List Sorting WM, LNS, Digit Span Backward
	EF	DCCS, List Sorting WM, TMT Part B, Matrix Reasoning, Stroop Color-Word Inhibition, Flanker
	Speed	Pattern Comparison Processing Speed, Coding, Symbol Search
5b	Vocabulary	Picture Vocabulary
	Reading	Oral Reading Recognition
	EM	Picture Sequence Memory, CVLT, Benson Figure
	WM	List Sorting WM, LNS, Digit Span Backward
	EF/Speed	DCCS, Pattern Comparison Processing Speed, List Sorting WM, TMT Part B, Matrix Reasoning, Coding, Symbol Search, Stroop Color-Word Inhibition, Flanker
6 Factor Model		
Model	Factors	Measures used in Each Factor
6a	Vocabulary	Picture Vocabulary
	Reading	Oral Reading Recognition
	EM	Picture Sequence Memory, CVLT, Benson Figure
	WM	List Sorting WM, Digit Span Backward
	EF	DCCS, List Sorting WM, TMT Part B, Matrix Reasoning, Stroop Color-Word Inhibition, Flanker
	Speed	Pattern Comparison Processing Speed, Coding, Symbol Search

Following Mungas et al. (2014), we included the following tests of model fit: overall Chi-square test of model fit as well as the Tucker Lewis Index (TLI) (Tucker & Lewis, 1973), Comparative Fit Index (CFI) (Bentler & Bonett, 1980; Bentler, 1990), the root mean square error of approximation (RMSEA) (Browne & Cudeck, 1992), and Standardized Root Mean Square Residual (SRMR) (Bentler, 1989). We evaluated modification indices to see if there could be any significant improvement in the model by changing model parameters. We compared models using the Akaike Information Criterion (AIC). This approach can further establish the reproducibility of previous findings (Mungas et al., 2014) while extending it to our oldest-old cohort. We used R and the lavaan package to perform confirmatory factor analysis (Rosseel, 2012).

Evaluation of Validity

Convergent validity was assessed by examining factor loadings of NIH TB- CB on their domain factor and evaluating the correlation between an average of the standard neuropsychological measures of a domain and the NIH TB- CB of the domain. Discriminant validity was assessed by examining modification indices cross-loadings of NIH TB-CB measures, identifying high inter-correlation of factors, and evaluating the correlation between an average of the standard neuropsychological measures of a domain and the NIH TB-CB of a different domain. These methods of assessing validity of cognitive measures have been applied previously (Andresen, 2000; Noelle E Carlozzi et al., 2017; Heaton et al., 2014; Tulsky et al., 2017; Weintraub, Bauer, et al., 2013).

Multiple Regression with NIH TB-CB Composite Scores

Composite scores are automatically generated through the NIH TB-CB. Prior work that generated normative data indicated that there is a decline of fluid composite scores with age and a plateau of crystallized composite scores after middle age (Casaletto et al., 2015). The composite scores from our sample fit with this trend (Table 1) with relatively similar crystallized scores as other older adults and lower fluid scores than younger adults age groups (Casaletto et al., 2015). Three multiple linear regressions predicted the three NIH TB- CB Uncorrected Composite Standard Scores- Total, Crystallized, and Fluid. Predictors included years of education, age, gender (1=Male, 2=Female), race (1=White, 2= Black/African American, 3=Asian), and computer use frequency (0=No computer experience/Not used a computer in last three months, 1= Less than one hour a week, 2= 1 hour but less than 5 hours a week, 3= 5 hours but less than 10 hours a week, 4= 10 hours but less than 15 hours a week, 5= At least 15 hours a week). Table 1 includes descriptive statistics for these variables.

Results

Model fit

Based on prior studies, we hypothesized that the 5-factor model of the NIH TB-CB and standard neuropsychological measures would have a better fit than alternative factor models. We found that the 5-factor (Language, Memory, Working Memory, Executive, and Speed) and 6-factor (Vocabulary, Reading, Memory, Working Memory, Executive, and Speed) models have similar fit indices that indicate good fit (Table 5). The 6-factor model had a slightly smaller AIC (5-factor AIC=16210.229 and 6-factor AIC=16208.346). We, therefore, chose the 6-factor model as the best fit. The model

aligns with the original six domains of the NIH TB-CB (working memory, executive function, episodic memory, processing speed, language, and reading) (Gershon et al., 2013).

The 5-factor model found in Mungas et al. (2014) (Vocabulary, Reading, Memory, Working Memory, Executive/Speed) was different from the 5-factor model our study found to be a good fit in the oldest-old sample. Mungas and colleagues (2014) found that the model that combined executive and speed into one factor, and separated vocabulary and reading into two separate factors, was a better fit than a 5-factor model that separated executive and speed factors and instead combined vocabulary and reading into a language factor (Table 5). We did not find an inter-correlation between executive and speed factors>.9 as was found in prior studies (Mungas et al., 2014; Tulsky et al., 2017).

Table 5. Model Fit Indices

Model	Overall χ^2 [df]	CFI	TLI	RMSEA (90% CI)	SRMR	AIC
1a	283.765 [119]	0.784	0.753	0.088 (0.075-0.101)	0.075	16699.98
2a	240.598 [118]	0.839	0.814	0.076 (0.062-0.09)	0.072	16658.794
2b	274.544 [118]	0.794	0.763	0.086 (0.073-0.099)	0.074	16692.739
3a	223.483 [116]	0.859	0.834	0.072 (0.058-0.086)	0.071	16645.678
3b	220.664 [116]	0.862	0.839	0.071 (0.057-0.085)	0.068	16642.86
4a	195.412 [113]	0.892	0.87	0.064 (0.048-0.079)	0.065	16623.608
4b	215.099 [114]	0.867	0.842	0.070 (0.056-0.085)	0.067	16641.294
4c	221.732 [114]	0.858	0.831	0.073 (0.058-0.087)	0.07	16647.928
5a	172.573 [109]	0.916	0.896	0.057(0.040-0.073)	0.06	16608.769
5b	187.030 [110]	0.899	0.875	0.063 (0.047-0.078)	0.064	16621.225
6a	162.623 [105]	0.924	0.902	0.055 (0.038-0.072)	0.058	16606.818

Overall chi-squared measures how well a model compares to observed data. Comparative Fit Index (CFI) examines the discrepancy between data and the hypothesized model. Tucker Lewis Index (TLI) analyzes the discrepancy between the x^2 of the hypothesized

model and the null model. The Root Mean Squared Error of Approximation (RMSEA) analyzes discrepancy between the hypothesized model (with optimal parameter estimates) and population covariance matrix. The Standardized Root Mean Square Residual (SRMR) is the root of the discrepancy between the sample covariance matrix and model covariance matrix. The Akaike Information Criterion (AIC) is a value used to evaluate how well a model fits the data. Lower is a better fit.

Convergent Validity

Standardized coefficients for the 6-factor model (Table 6) showed NIH TB-CB measures loaded strongly on their respective factors, supporting convergent validity. Picture Vocabulary loaded very highly (.82) on the Vocabulary factor; List-Sorting loaded highly (.634) on the Working Memory factor; both DCCS and Flanker loaded strongly (.62 and .585) on the Executive Functioning factor; Picture Sequencing loaded strongly (.533) on the Memory factor, and Pattern Comparison had a moderate loading (.442) on the Speed factor. When we analyzed the correlation between an average of the standard neuropsychological measures of a domain and the NIH TB- CB of the domain, we found Picture Sequence, List-Sorting, Pattern Comparison, and Picture Vocabulary all had adequate correlations for convergent validity; however, Flanker and DCCS measures had weak correlations with the executive functioning standard neuropsychological measures, and therefore convergent validity was not supported based on this metric (Andresen, 2000). Since we did not have a standard neuropsychological measure available to load with the NIH TB-CB Oral Reading Task, convergent validity for the Reading domain was not assessed.

Table 6. Standardized coefficients for the 6-factor model

Latent Factor	Observed Indicator	Loading
Vocabulary	TB Picture Vocabulary	0.82
	WAIS-IV Similarities	0.664
Reading	TB Oral Reading	1
Episodic Memory	TB Picture Sequence Memory	0.533
	CVLT	0.703
	Benson Figure	0.413
Working Memory	TB List Sorting	0.634
	Letter Number Sequence	0.503
	Digit Span Backwards	0.648
Executive Function	TB DCCS	-0.62
	TB Flanker Test	-0.585
	WAIS-IV Matrix Reasoning	-0.555
	Stroop Interference	-0.293
	Trails B	0.675
Speed	TB Pattern Comparison	0.442
	WAIS-IV Coding	0.72
	WAIS-IV Symbol Search	0.807

Discriminant Validity

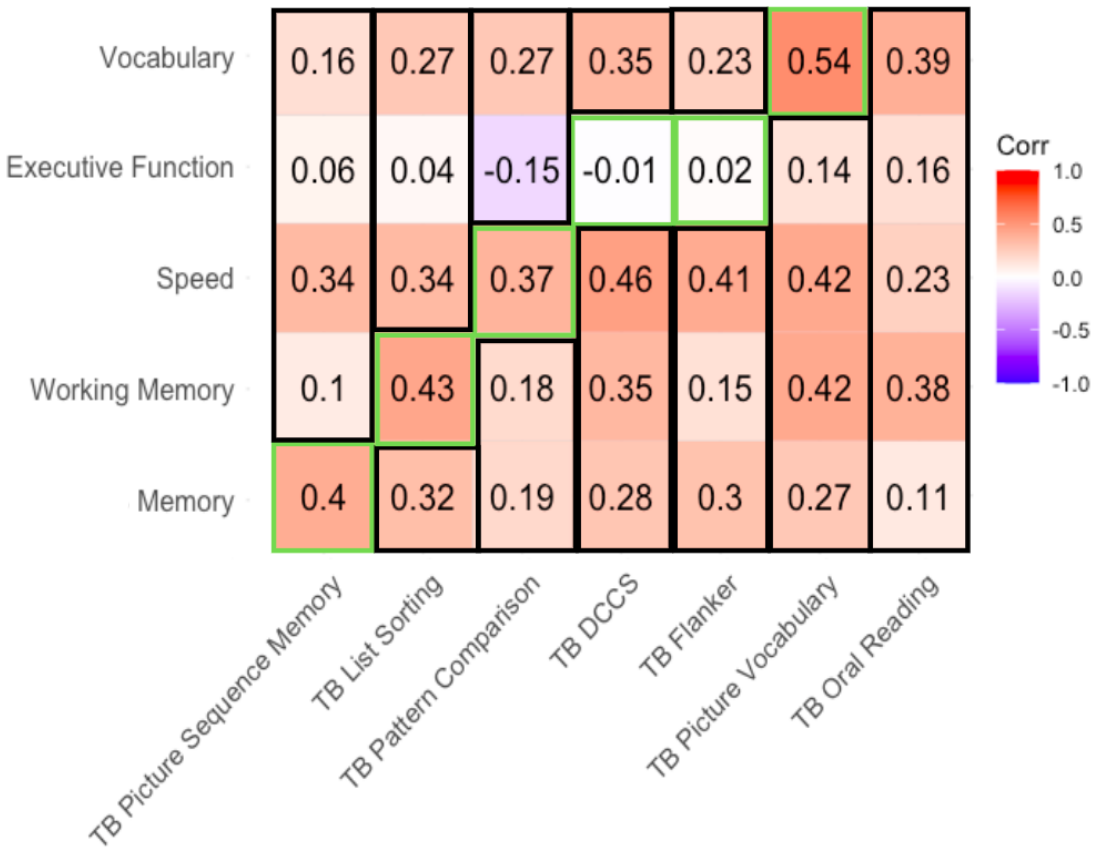
Only one weak modification index indicated a split loading of the NIH TB-CB Flanker measure on the Vocabulary factor. The lack of strong cross-loadings between factors indicated discriminant validity of our model. Additionally, the intercorrelations among the six factors (intercorrelation range of r=.157-.811; Table 7) were within acceptable limits as used in a prior NIH TB validity study (Tulsky et al., 2017). The consistently highest inter-correlations were between executive functioning and other domains (intercorrelations range of r=.428-.811; Table 7). While vocabulary and reading were correlated (r=.641), these two crystallized intelligence factors were also related to fluid intelligence factors; therefore, there was no clear crystallized/fluid separation.

Table 7. Inter-correlation of factors for the 6-factor model

	Episodic Memory	Working Memory	Speed	Executive Function	Vocabulary
Working Memory	0.487				
Speed	0.587	0.499			
Executive Function	-0.616	-0.77	-0.811		
Vocabulary	0.537	0.68	0.579	-0.715	
Reading	0.157	0.494	0.238	-0.428	0.641

The correlation between an average of the standard neuropsychological measures of a domain and the NIH TB-CB of a different domain indicated Picture Sequence, List-Sorting, Pattern Comparison, and Picture Vocabulary all had correlations to other domains that were smaller than the correlation to their domain (Figure 2). However, Flanker and DCCS measures had higher correlations to domains outside Executive Functioning; therefore, this metric indicates poor discriminant validity for these measures.

Figure 2. Correlations between NIH TB-CB Measures and standard neuropsychological Domain Average



TB= NIH TB-CB measures; green outline= within domain correlation, consistent with convergent validity; black outline= outside domain correlation, consistent with discriminant validity

Together, convergent and discriminant validity evidence indicates sufficient construct validity of the NIH TB-CB within an 85+ cohort, with relatively weaker construct validity for executive functioning measures in the NIH TB-CB.

Predictors of NIH TB-CB Composite Scores

Race (β=−3.5, p=.009), data collection site (β=1.98, p=.017), computer use frequency (β=1.19, p=.007), and years of education (β=.64, p=.021) were significant predictors of the NIH TB-CB Total composite score and the overall model's adjusted R^2 was .1541 (p<.001) There was a significant R^2-change of .164 (p<.001) between the first block of the covariate, site, and the second block with race, gender, age, years of education, and computer use frequency.

Only computer use frequency (β=1.12, p=.02) was a significant predictor of NIH TB-CB Fluid composite score, and the overall model's adjusted R^2 was .03 (p=.07). There was a significant R^2-change of .0717 (p=.042) between the first block of the covariate, site, and the second block with race, gender, age, years of education, and computer use frequency.

Race (β=−4.16, p=.001) and years of education (β=1.1, p<.001) were significant predictors of NIH TB -CB Crystallized composite score, and the overall model's adjusted R^2 was .21 (p<.001). There was a significant R^2-change of .17 (p<.001) between the first block of the covariate, site, and the second block with race, gender, age, years of education, and computer use frequency.

Follow-up Analysis with Demographically-Corrected Scores for the NIH TB-CB

We repeated the analysis with demographically-corrected scores for the NIH TB-CB and found no differences in the interpretation of the findings including no changes in determination of best fitting model, validity or predictors of NIH TB- CB Composite Scores (see Supplemental Table 1 and 2 for model fit indices and model standardized coefficients).

Discussion

In our cohort of cognitively unimpaired, older adults over 85 years of age, the NIH TB-CB tests and standard neuropsychological measures had convergent and discriminant validity, consistent with the six domains of cognition initially intended to be evaluated by the NIH TB-CB. These findings suggest the NIH TB-CB has construct validity in oldest-old adults, ages 85-99. The 5-factor model (model 5a), which combines reading and vocabulary into a language factor, also displayed a good model fit. There was relatively less evidence to support the combination of executive function and speed factors, as shown in the 5-factor model by Mungas and colleagues (2014). However, there were strong relationships between executive function and all other factors. We also found that computer use frequency strongly predicted the total and fluid NIH TB-CB composite scores, suggesting that either (1) greater experience with computers impacts performance on this tablet-based assessment or (2) having lower cognitive capacity (reflected in the NIH TB-CB scores) leads to less computer use.

Cognitive Dedifferentiation and the Executive Decline Hypothesis

Cognitive dedifferentiation describes the tendency for separable cognitive abilities (such as language and executive function) to become less separable with age; dedifferentiation may reflect underlying cognitive impairment (Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980; Batterham, Christensen, & Mackinnon, 2011; Hülür, Ram, Willis, Schaie, & Gerstorf, 2015; Wallert et al., 2021; Wilson, Segawa, Hizel, Boyle, & Bennett, 2012). Our findings of more widespread domain intercorrelations with executive functioning could reflect age-related cognitive dedifferentiation. We only included

healthy individuals in our sample, so this cognitive dedifferentiation may be a result of healthy aging.

A potential explanation for the strong relationship between executive function and other cognitive domains is that executive functions may play a greater role in supporting non-executive task performance in older people, as outlined in the executive decline hypothesis (Crawford, Bryan, Luszcz, Obonsawin, & Stewart, 2000; Ferrer-Caja, Crawford, & Bryan, 2002; Salthouse, Atkinson, & Berish, 2003). Prior factor analysis research has shown similar relationships between executive and non-executive tasks (Lamar, Zonderman, & Resnick, 2002). This reflects on a broader issue in classifying tests as measuring only a single domain. The NIH-TB was intentionally developed so that each cognitive domain would be linked to one or two tasks from the toolbox. The domains are not pure, however, and the tests used to assess each are likely to be affected by performance limitations in other domains.

We found that the best-fitting model was the 6 factor model, rather than the 5 factor model (model 5b) that Mungas et al (2014) found to best fit data for a younger sample. The difference in best-fit model could be due to increased associations of executive function with all other domains in the oldest-old. Both the hypothesis of greater cognitive dedifferentiation with age and the executive decline hypothesis would predict increased association of executive function with other domains, as was observed. Thus, our result is likely to represent a more holistic effect than simply reflecting a tight coupling between executive functioning and speed domains in this population.

Role of computer use frequency in cognitive performance

Younger age, higher education, non-Hispanic ethnicity, physical health, and mental health have been shown to be predictors of greater computer use (Werner, Carlson, Jordan-Marsh, & Clark, 2011). Additionally, perceptual speed moderates the relationship between age and technology ownership (Kamin & Lang, 2016). Previous work has indicated a relationship between cognitive performance and the level of computer experience (Fazeli, Ross, Vance, & Ball, 2013; Wu, Lewis, & Rigaud, 2019). Since computer use frequency was a significant predictor of total and fluid composite scores, technological familiarity may play a crucial role in performance on NIH TB-CB measures. Participants who were relatively less familiar with technology may have also experienced increased demand on executive functioning as they had to learn technological skills while also performing a cognitive task. Alternatively, since adept use of computers requires cognitive abilities such as executive functioning and processing speed, participants with lower cognitive abilities may tend to avoid engagement with computers in their daily lives due to the cognitive demands of computer use.

Additionally, there are key differences between paper-and-pencil tasks and tablet-based tasks that could impact performance, such as less ability to self-correct, less flexibility for the administrator to pace the task appropriately for the participant, and less engagement between the administrator and the participant (Aşkar et al., 2012). Attitudes towards computers could have resulted in a lower frequency of computer use and, therefore, a negative impact on their cognitive scores (Fazeli et al., 2013). Future work should investigate participants' disposition towards computers and their current computer use. This could impact the usability of the NIH TB-CB in older samples since older adults are less likely to have familiarity with technology than younger cohorts (Victorson

et al., 2013; Werner et al., 2011). Researchers may need to assess a participant's technology use to determine the appropriateness of using the NIH TB-CB. Alternatively, composite scores could account for current and past computer use in the calculation of standardized scores (Lee Meeuw Kjoe, Agelink van Rentergem, Vermeulen, & Schagen, 2021).

Limitations

This study has limitations. We did not have a standard neuropsychological measure similar to the Oral Reading test available in the dataset, so convergent validity for that factor could not be fully tested in our study. Our sample is also mostly white and highly educated, which limits the generalizability of this work. We also acknowledge that in our confirmatory factor analysis, we could not account for variability that may have occurred across data collection sites. However, substantial efforts were made to homogenize data collection across sites and we included site as a covariate in our regression models (Section "Predictors of NIH TB-CB Composite Scores"). Future work could further describe the oldest-old cohort through comparisons of this sample to other age cohorts who also completed the iPad version of the NIH TB-CB.

Conclusions

The NIH TB-CB was created to solve issues of inconsistency and difficulty of administration of neuropsychological testing in research, focusing on those ages 3 to 85. Our findings suggest that this test battery could be valuable for the assessment of cognitive health in individuals over 85. Having a common metric on an easy-to-use iPad

tablet could enable research studies to include larger and more representative samples of older adults, and researchers could easily compare these scores to other studies which have adopted the NIH TB-CB. The NIH TB-CB could also be helpful since it can provide precise timing metrics along with cognitive accuracy scores for use in aging studies. This work has confirmed the construct validity and the feasibility of the NIH TB-CB in an 85+ sample, which will provide a basis for the usability of the battery in future older adult research. However, there may be limitations in the NIH TB-CB's ability to validly assess individuals with low computer use and validly measure executive functioning, possibly due to age-related changes in executive functioning's relationship with other cognitive domains. This work provides a pathway towards broadening the age span of the NIH TB-CB to 99 years of age which will allow longitudinal and cohort studies to compare across almost the entire human lifespan (3-99).

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T32NS061788-12 07/2008 - 0.

Code is available at https://github.com/Visscher-Lab/validity_nihtb_mbar

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Supplemental Table 1. Model Fit Indices with demographically corrected NIH TB scores

Model	Overall χ^2 [df]	CFI	TLI	RMSEA (90% CI)	SRMR	AIC
1a	290.518 [119]	0.777	0.745	0.09 (0.077-0.103)	0.076	19686.013
2a	243.955 [118]	0.836	0.811	0.077 (0.064-0.091	0.073	19641.45
2b	281.336 [118]	0.787	0.755	0.088 (0.075-0.101)	0.075	19678.831
3a	225.225 [116]	0.858	0.833	0.073 (0.058-0.087)	0.072	19626.72
3b	222.291 [116]	0.862	0.838	0.072 (0.057-0.086)	0.069	19623.785
4a	193.334 [113]	0.895	0.874	0.063 (0.048-0.078)	0.065	19600.828
4b	216.551 [114]	0.866	0.841	0.071 (0.057-0.085)	0.068	19622.046
4c	222.776 [114]	0.858	0.831	0.073 (0.059-0.087)	0.072	19628.27
5a	170.821 [109]	0.92	0.9	0.056(0.039-0.072)	0.059	19586.316
5b	187.327 [110]	0.906	0.884	0.061 (0.045-0.076)	0.064	19595.821
6a	159.009 [105]	0.93	0.909	0.054 (0.036-0.07)	0.057	19582.503

Overall chi-squared measures how well a model compares to observed data. **Comparative Fit Index (CFI)** examines the discrepancy between data and the hypothesized model. **Tucker Lewis Index (TLI)** analyzes the discrepancy between the x^2 of the hypothesized model and the null model. **The Root Mean Squared Error of Approximation (RMSEA)** analyzes discrepancy between the hypothesized model (with optimal parameter estimates) and population covariance matrix. **The Standardized Root Mean Square Residual (SRMR)** is the root of the discrepancy between the sample covariance matrix and model covariance matrix. **The Akaike Information Criterion (AIC)** is a value used to evaluate how well a model fits the data. Lower is a better fit.

Supplemental Table 2. Standardized coefficients for the 6-factor model with demographically corrected NIH TB scores

Latent Factor	Observed Indicator	Loading
Vocabulary	TB Picture Vocabulary	0.817
	WAIS-IV Similarities	0.668
Reading	TB Oral Reading	1
Episodic Memory	TB Picture Sequence Memory	0.532
	CVLT	0.699
	Benson Figure	0.427
Working Memory	TB List Sorting	0.627
	Letter Number Sequence	0.510
	Digit Span Backwards	0.657
Executive Function	TB DCCS	-0.608
	TB Flanker Test	-0.556
	WAIS-IV Matrix Reasoning	-0.544
	Stroop Interference	-0.289
	Trails B	0.653
Speed	TB Pattern Comparison	0.433
	WAIS-IV Coding	0.727
	WAIS-IV Symbol Search	0.793

FRONTO-PARIETAL NETWORK SEGREGATION PREDICTS MAINTAINED PROCESSING SPEED IN THE COGNITIVELY HEALTHY OLDEST-OLD

by

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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 85+ 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

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 the oldest-old age (i.e., 85+ years) with documented excellent cognitive health. We then examined the relationship between cognitive behavior and 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 aged 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. The compensation hypothesis, which refers to the over-recruitment of brain regions within a network, while the dedifferentiation hypothesis, which refers to the loss of functional specialization and segregation in brain network activity and 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 higher levels of cognitive function in healthy agers is related to 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.

Results

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.

Exploratory Factor Analysis

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.

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).

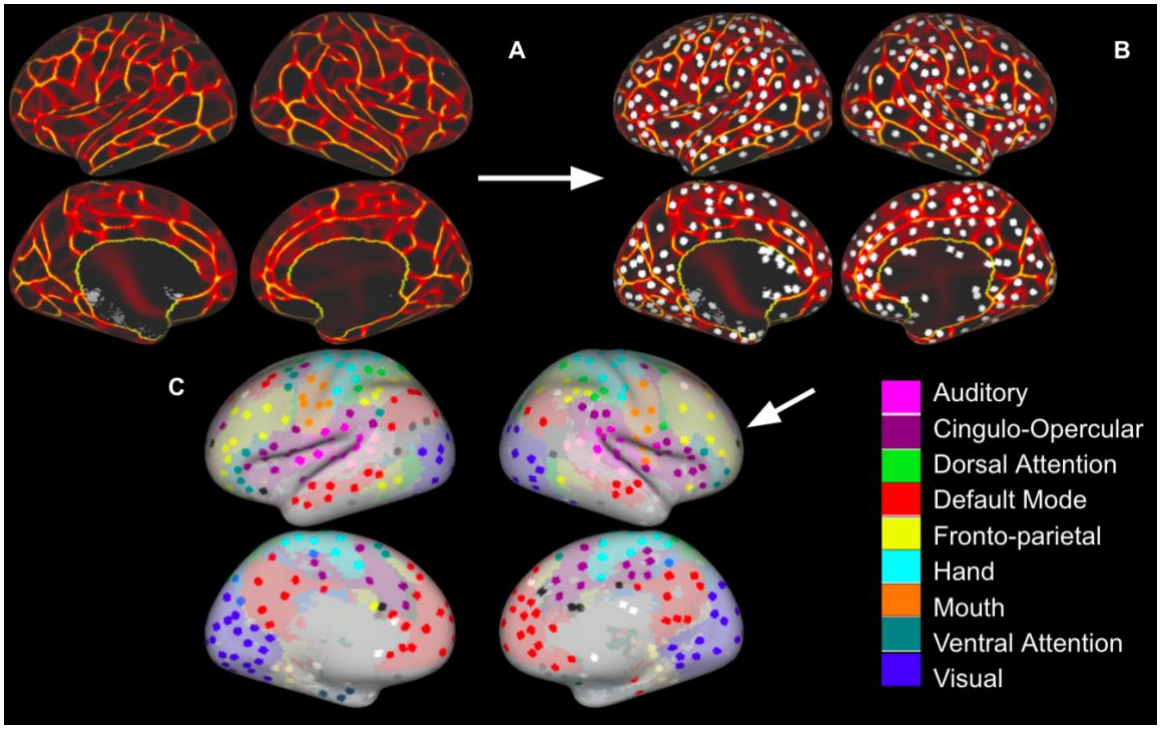

Figure 1. Regions of Interest Identification. *A: Functional connectivity boundary maps based on methods used by (Han et al., 2018); B: Local minima ROIs (3mm discs) based on methods used by (Chan et al., 2014); C: Local minima ROIs with the color of Network Membership of ROIs based on parcellation colors 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).

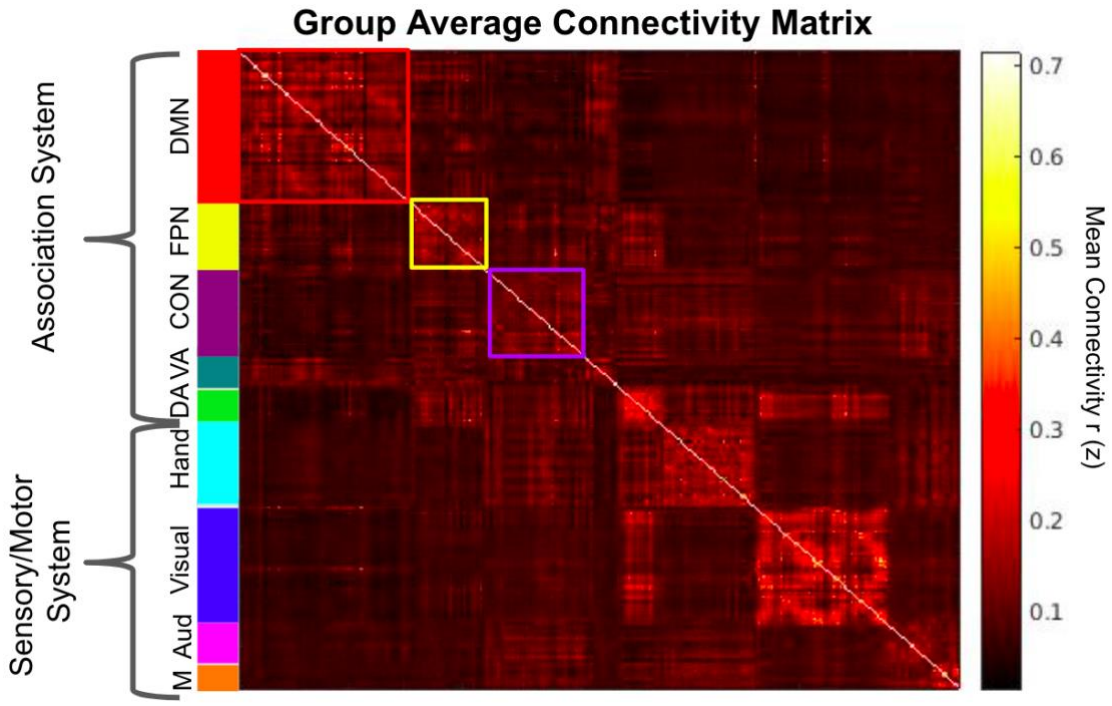

Figure 2. Group average Fisher's z- transformed correlation matrix of 321 nodes. The Association system consists of the Default mode (red), Fronto-parietal control (yellow), Ventral attention (teal), Cingulo-opercular control (purple), and Dorsal attention (green). The Sensory-Motor system consists of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

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).

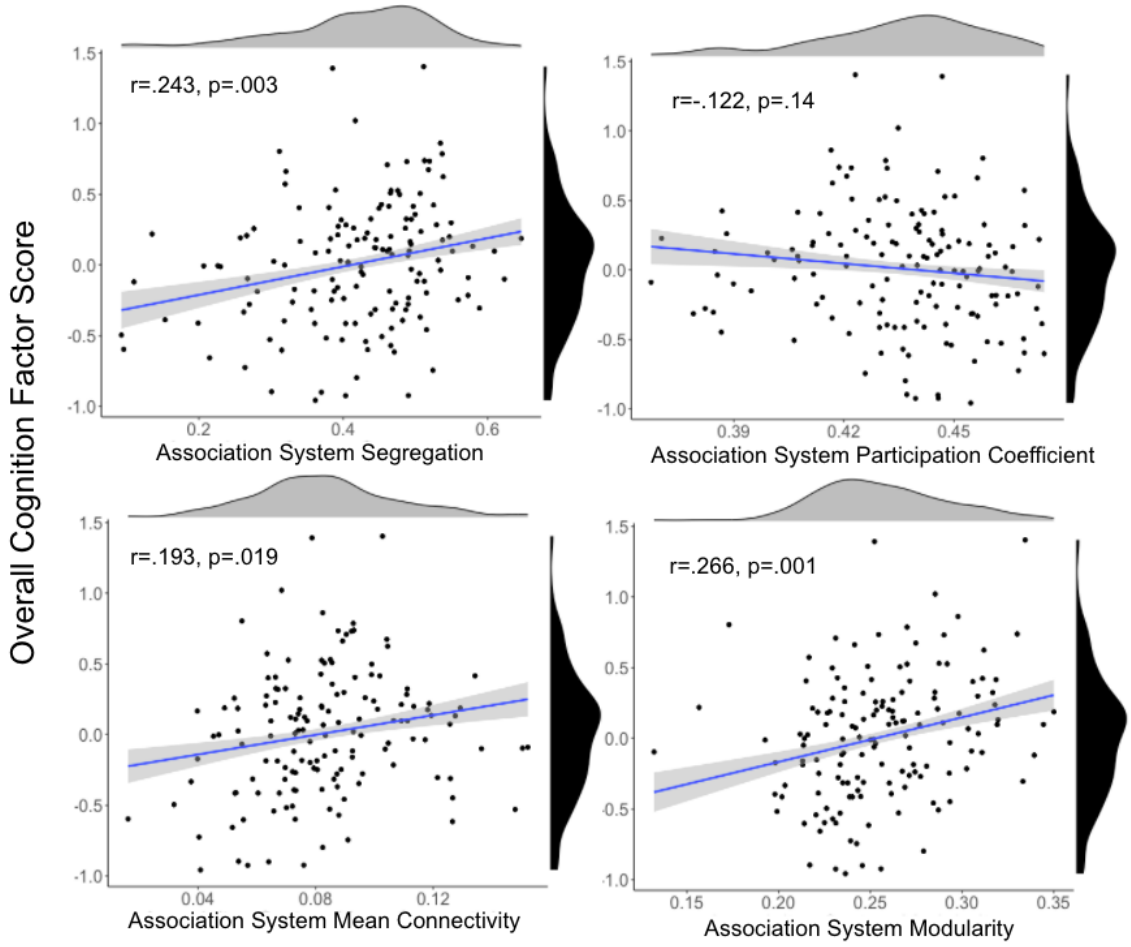

Figure 3. Scatter plots between Association System metrics and overall cognitive performance. Density plots for the variables are presented for each variable on the edge of the scatter plot. Overall cognition score is shown in black and association system metrics are shown in grey.

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.

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 remain 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 ($r=.159$, $p=.055$).

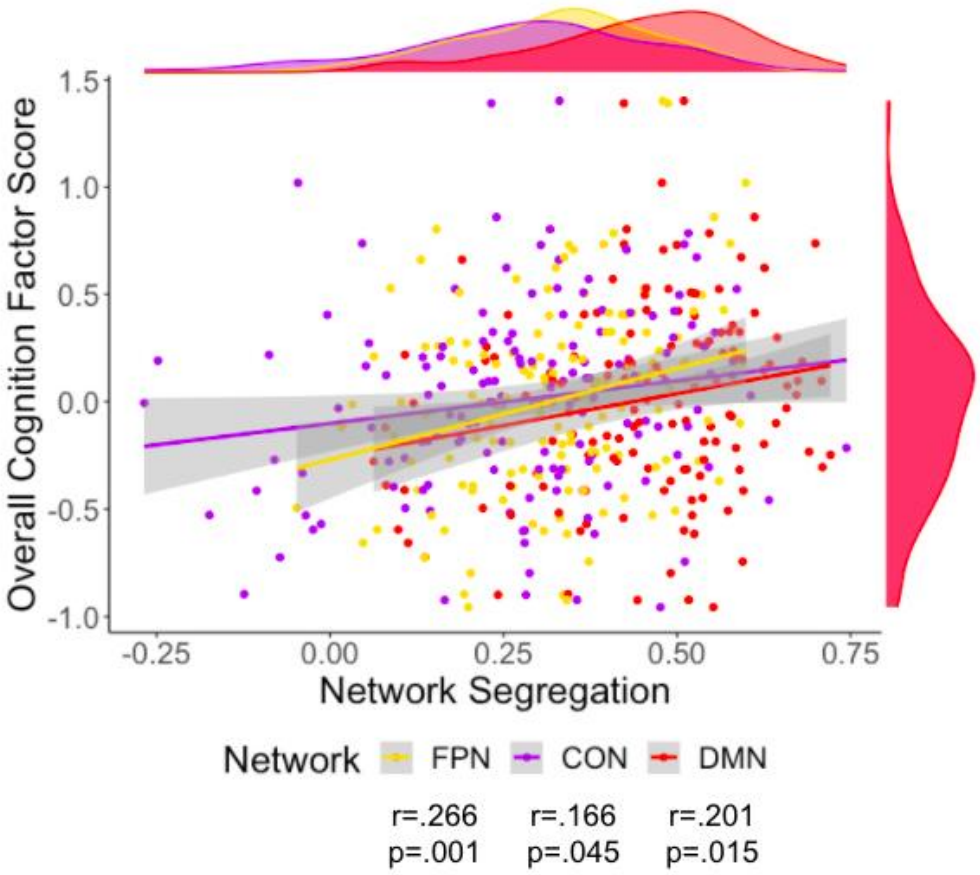

Figure 4. Scatter plot of Overall Cognition and FPN (yellow), CON (purple), and DMN (red) network segregation. Density plots for the variables are presented for each variable on the edge of the scatter plot. The colors on these plots match the network color in Figure 1. Only segregation for FPN and DMN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

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.

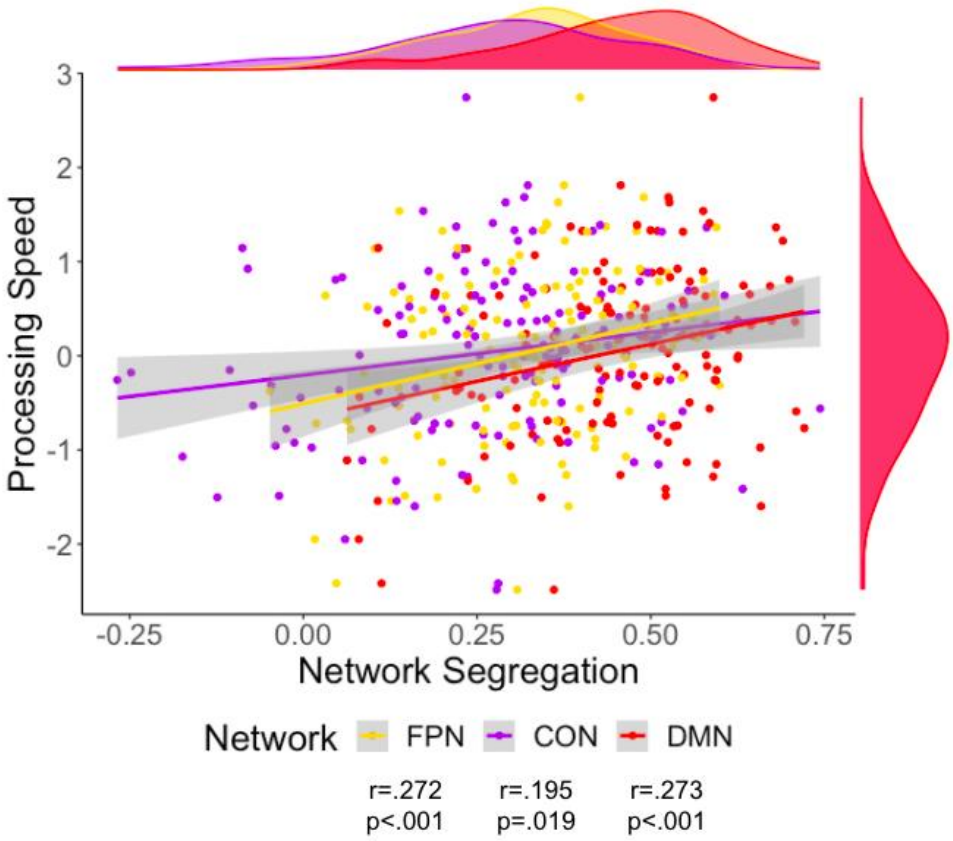

Figure 5. Scatter plot of Processing Speed and FPN (yellow), CON (purple), and DMN (red) network segregation. Density plots for the variables are presented for each variable on the edge of the scatter plot. The colors on these plots match the network color in Figure 1.

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 ($p=.132$).

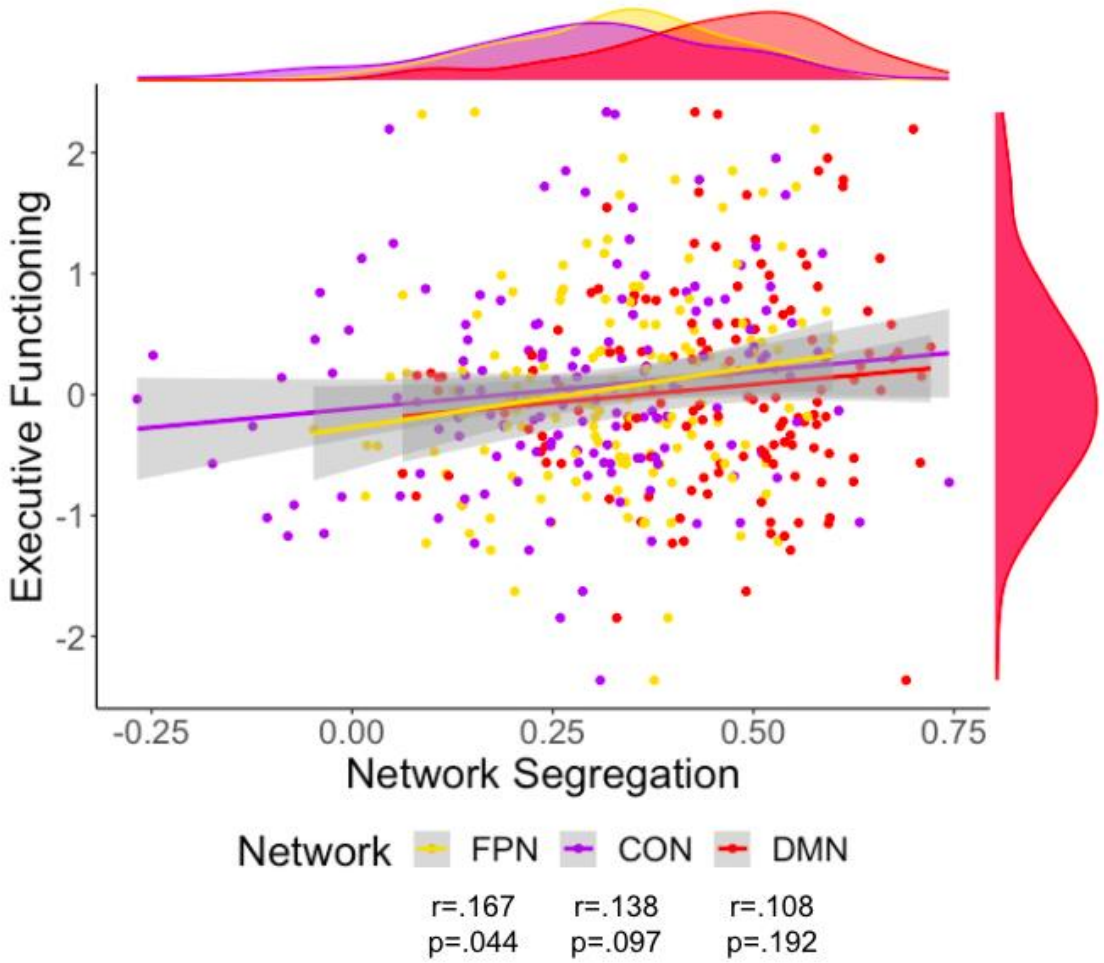

Figure 6. Scatter plot of Executive Functioning and FPN (yellow), CON (purple), and DMN (red) network segregation. Density plots for the variables are presented for each variable on the edge of the scatter plot. The colors on these plots match the network color in Figure 1. No relationships were significant 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).

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.

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.

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. We did this by examining dedifferentiation of the association system metrics of segregation, participation coefficient, modularity, and within-network connectivity and network segregation.

Dedifferentiation predicts preserved cognition in the cognitively healthy elderly

We found that association system segregation and modularity had positive, significant relationships with overall cognition. However, 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.

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.

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.

Materials and Methods

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%)

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.

Network Analysis

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.

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, white matter, 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.

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.

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).

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.

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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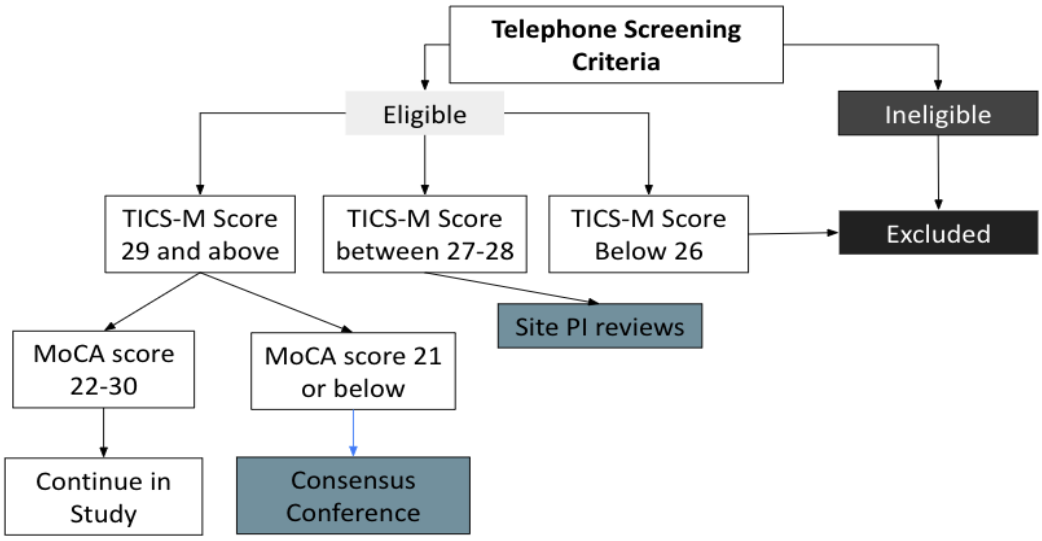
Data and code availability statement

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 Domains and Network Segregation**	**Memory**	**Working Memory**	**Language**
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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SUMMARY AND CONCLUSIONS

The population of people aged 85 and older is increasing steadily, meaning that the effort to improve healthy cognitive aging is increasingly urgent (Vincent & Velkoff, 2010). These studies help to describe healthy cognitive aging by 1) assessing the validity of extending the age range of the NIH TB-CB into the oldest-old age group, 2) creating a brain network parcellation from a sample of healthy oldest-old adults, and 3) relating performance in cognitive domains to segregation of the association system and association functional networks. Together, these studies extend the literature on dedifferentiation in the context of healthy aging.

Dedifferentiation

A common theme emerged in these studies about healthy aging. Dedifferentiation generally refers to the process of previously separable things becoming less distinct. In aging literature, this concept of dedifferentiation has been applied to both cognition and brain network dynamics. Through my dissertation studies, I have furthered our understanding of dedifferentiation in the context of successful aging.

Cognitive dedifferentiation describes how separable cognitive abilities become less separable from each other with age and this dedifferentiation may reflect underlying cognitive impairment (Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980; Batterham, Christensen, & Mackinnon, 2011; Hülür, Ram, Willis, Schaie, & Gerstorf, 2015; Wallert et al., 2021; Wilson, Segawa, Hizel, Boyle, & Bennett, 2012). While we generally found that our healthy agers had cognitive domain patterns similar to younger adults, the findings in the NIH TB-CB Validity study show more widespread domain intercorrelations with executive functioning. The observed dedifferentiation of executive

functioning is reflective of age-related cognitive dedifferentiation. Since our sample was only composed of healthy agers, this cognitive dedifferentiation may be a result of healthy aging.

Dedifferentiation is used in many ways to describe the dynamics of brain activity. Dedifferentiation refers to becoming more similar or less distinct, so this can be used to describe brain regions becoming less selective when they are functionally active, networks no longer only being called upon for only certain kinds of cognitive tasks, and the overall structure of network organization no longer showing distinct networks, but rather networks becoming less able to distinguish themselves from one another (Goh, 2011; Koen et al., 2020; Li, Lindenberger, & Sikström, 2001; Rakesh, Fernando, & Mansour L, 2020; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz, Stanczak, & Miller, 1999). Many properties of networks can be quantified and could reflect network dedifferentiation (Bullmore & Sporns, 2009; Damoiseaux, 2017; van den Heuvel & Hulshoff Pol, 2010). Network integration describes the strength of connections within a network; network participation coefficient describes how diverse the connections are for each node in the network (low participation coefficient means it prefers to connect to its own network, and high participation coefficient means it prefers to connect to other networks; modularity describes how easy it is to distinguish the parts (networks) from the whole (system); and segregation describes the balance of connection within the network to a connection outside the network (very high segregation means networks are not connected to one another and very low segregation means the networks are indistinguishable from one another) (Rubinov & Sporns, 2010; Wig, 2017). All of these metrics reflect some aspect of dedifferentiation in different ways. Measures like segregation go beyond the measurement of traditional network strength and provide

insight into how the system is organized and quantify the level of dedifferentiation in the system. Additionally, segregation can be studied at the system or network level. In older adults, functional networks have increased between-network connectivity, decreased within-network connectivity, and lower system segregation; therefore, older adults have more dedifferentiated networks (Chan et al., 2017; Damoiseaux, 2017; Iordan et al., 2017; Koen et al., 2020; Varangis et al., 2019). Studies of association system segregation have demonstrated that dedifferentiation increases with age at a rate that correlates with cognitive decline (Chan et al., 2014; Chong et al., 2019; Geerligs, Renken, Saliasi, Maurits, & Lorist, 2015; Han et al., 2018; Malagurski, Liem, Oschwald, Mérillat, & Jäncke, 2020; Ng et al., 2016). This work helped to shed light on how far into the aging process dedifferentiation can continue while cognitive functions are maintained. The findings of our study support the dedifferentiation hypothesis since I found that the association system cannot function as well and is not able to produce as high a level of cognitive performance when it is not well differentiated/well segregated.

We have also shown that FPN segregation is related to overall cognitive abilities and one of the key cognitive functions affected by aging — processing speed. 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 FPN. Therefore, sustainable healthy cognitive aging may be marked by maintaining segregated network organization.

I add to the literature on age-related dedifferentiation, showing that even in a very old and cognitively healthy sample, cognitive dedifferentiation may impact executive

functioning abilities and functional network dedifferentiation is related to cognitive abilities.

Validity of the NIH Toolbox Cognitive Battery

The NIH TB-CB was created to address problems of inconsistent batteries and difficulties in conducting neuropsychological testing in research among those ages 3 to 85. This test battery may be useful for assessing cognitive health in individuals aged over 85 as well. The use of the NIH TB-CB in aging research would enable researchers to include a larger and more representative sample of older adults in their research studies, and researchers can also easily compare their scores to those of other studies using the NIH TB-CB.

However, the NIH TB-CB has not been shown to validly measure executive functioning in the oldest-old. There could be age-related changes in the relationship between executive function and other cognitive domains. This finding may be due to a variety of influencing factors. An approach to explain these findings is cognitive dedifferentiation. Cognitive dedifferentiation describes how cognitive performance across a range of cognitive domains becomes more similar to each other with increasing age (Baltes et al., 1980; Batterham et al., 2011; Hülür et al., 2015; Wallert et al., 2021; Wilson et al., 2012). Another potential explanation for the strong relationship between executive function and other cognitive domains is the executive decline hypothesis. The executive decline hypothesis posits that executive functions play a greater role in supporting non-executive task performance in older people (Crawford, Bryan, Luszcz, Obonsawin, & Stewart, 2000; Ferrer-Caja, Crawford, & Bryan, 2002; Salthouse, Atkinson, & Berish, 2003). My findings fit within this hypothesis since the relationship

between executive functioning and other domains I observed could be reflecting how executive functions are supporting/executive functioning decline is undermining other cognitive functions in an aged sample. Additionally, each cognitive domain in the NIH-TB was created to correspond to one or two tasks in the toolbox. However, the cognitive domains are not pure and it is likely that performance limitations in any given domain, such as executive functioning, will affect the tests within all the domains. Taken together, these interpretations of the relationship between executive function and other cognitive functions give insight into how a cognitive battery such as the NIH TB-CB may over-represent executive functioning performance in more than just the specific executive function domain. It is likely that individuals with poor executive functioning, which is more likely to occur in aged individuals, will have artificially low scores in other domains. This is a major limitation to using the NIH TB-CB in aging research.

We also discovered that the measurement of cognition in older adults may be more sensitive to outside factors like familiarity with the technology used in the testing environment. A variety of factors have been shown to relate to the degree of an individual's computer use including age, education, ethnicity, physical health, and mental health (Werner, Carlson, Jordan-Marsh, & Clark, 2011), in addition to perceptual speed which moderates the relationship between age and technology ownership (Kamin & Lang, 2016). Studies have found that the level of computer experience is related to cognitive performance (Fazeli, Ross, Vance, & Ball, 2013; Wu, Lewis, & Rigaud, 2019). Technological familiarity may strongly influence performance on NIH TB-CB measures since computer use frequency was a significant predictor of fluid composite scores. Participants with less experience with technology may have also faced challenges of overloading their executive functioning capacity as they were required to learn new

technologies while also undertaking a cognitive task. On the other hand, due to the cognitive demands of using computers, participants with lower cognitive abilities may avoid engaging with computers on a regular basis due to their lack of executive function and processing speed. This could impact the usability of the NIH TB-CB in older samples and researchers may need to assess a participant's technology use to determine the appropriateness of using the NIH TB-CB. It would also be appropriate for the composite scores to account for current and past computer use in the calculation of standardized scores (Lee Meeuw Kjoe, Agelink van Rentergem, Vermeulen, & Schagen, 2021).

While there are some limitations to the appropriateness of the NIH TB-CB in an oldest-old sample, this work has confirmed the overall construct validity and the feasibility of the NIH TB-CB in an 85+ sample. I have provided a basis for the usability of the battery in future older adult research and recommendations for future development. The work provides a platform to expand the NIH TB-CB's age range to 99 years of age, enabling longitudinal and cohort studies that can compare almost the entire human lifespan (3-99 years).

Healthy Oldest-Old Network Parcellation

Dividing up the cortex has been heavily studied and done in a myriad of ways (Arslan et al., 2018; Fischl et al., 2002; Gordon et al., 2016; Han et al., 2018; Parisot et al., 2017; Wig, Laumann, Cohen, et al., 2014; Wig, Laumann, & Petersen, 2014). It is important to divide the cortex into sections because it allows us to study regions more specifically. The specificity of regions within a parcellation could be determined by many methods including, but not limited to functional connectivity, white matter pathways, task-based activation, and the combinations of many methods at once (Fischl & Sereno,

2018; Glasser et al., 2016; Salehi et al., 2020; Wang et al., 2015). We can use different degrees of specificity- for example, we could use the occipital lobe or we could be more specific with each of the areas of the visual cortex (V1, V2, V3, etc.). It is essential to accurately identify regions within a parcellation in order to use that parcellation to study features of the cortical regions (Bryce et al., 2021; Glasser et al., 2016; Gordon et al., 2017; Wig, Laumann, & Petersen, 2014; Zalesky et al., 2010). The brain organization of younger adults are generally a bit different from older adults and therefore parcellations based solely on younger adults could inaccurately align to an older adult's brain (Han et al., 2018). Therefore, understanding how a healthy aging cortex is subdivided is critical and especially relevant to my dissertation since brain network organization can change with age (Bagarinao et al., 2019). Studies in younger age groups have measured brain parcellation by creating boundaries between brain regions using changes in functional connectivity patterns, boundary-based mapping, and then identifying cortical nodes within these boundaries (Chan et al., 2014; Han et al., 2018). In my study, I applied the same methods to a sample of older individuals and even larger sample size than previously used for the analysis of the oldest-old part of the sample. The healthy elderly parcellation (85+) I created can be used for comparing healthy and disease-associated populations of this age group. I also used this age-appropriate parcellation to better describe the cortical mapping of networks in subsequent analyses in my dissertation. I am currently performing a follow-up analysis of the organization of the nodes in this parcellation and identifying networks without younger-adult-based network descriptors.

Processing Speed and Network Segregation

We sought to understand the brain basis of preserved cognition in functional network dynamics and specifically the underlying contribution of the association system and the FPN, DMN, and CON in supporting essential and valuable cognitive skills. Dedifferentiation is used to explain changes in how brain regions and networks become less distinguishable with age (Goh, 2011; Koen et al., 2020; Li et al., 2001; Rakesh et al., 2020; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz et al., 1999). Studies of the association system and association networks across the lifespan have shown that dedifferentiation is correlated with aging and a concurrent decline in cognitive functioning (Chan et al., 2014; Geerligs et al., 2015; Han et al., 2018). Our results are in line with other research on the segregation of the association system while demonstrating that segregation of the association system is an important aspect of cognitive functioning in the oldest-old brain (Chan et al., 2014; Chong et al., 2019)

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 and DMN was correlated with overall cognition and processing speed and FPN segregation was the greatest predictor of overall cognition and processing speed. Previous research supports the role of FPN and DMN in 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). The FPN regulates other brain networks in order to support cognitive functioning (Avelar-Pereira, Bäckman, Wåhlin, Nyberg, & Salami, 2017; Marstaller et al., 2015). In older adults, the FPN interacts less efficiently with the DMN compared to younger adults; the networks are synced during rest and across tasks, suggesting that aging renders the FPN less flexible in engaging and

disengaging networks (Avelar-Pereira et al., 2017; Grady, Sarraf, Saverino, & Campbell, 2016; Spreng & Schacter, 2012). Therefore, 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 the FPN functions as a control system, disruptions in its connectivity may be responsible for age-related decline in processing speed, which is the first and most noticeable change in cognition due to age (Ng et al., 2016; Oschmann & Gawryluk, 2020; Rieck, Baracchini, & Grady, 2021).

Since processing speed is one of the earliest and most impactful losses of cognition in aging (Deary et al., 2009; Salthouse, 1996; Vance, 2009; Wadley et al., 2021; Wahl, Schmitt, Danner, & Coppin, 2010), it is important to understand what makes intact processing speed possible in an aging population. I have shown that network segregation, and more specifically the FPN segregation is related to overall cognitive abilities and processing speed. The segregated nature of association networks facilitates the FPN's role as a central player in manipulating other networks efficiently.

This work supports previous research by demonstrating that processing speed can be maintained in old age despite dedifferentiation occurring in aging populations. This may be due to the maintained segregation of the FPN and DMN. In sum, healthy cognitive aging can be characterized by preserving a segregated network organization.

Conclusions

These studies provide resources for future work in aging in general and work in healthy aging. I have shown the strengths and weaknesses of the NIH TB-CB as a cognitive battery to be used in aging research. I have created a brain parcellation that can

be used to appropriately identify network nodes in oldest-old adults, and I have shown that segregation of networks is not only possible in the oldest-old brain, but maybe fundamental to intact cognition in oldest-old adulthood. Additionally, this work provides a pathway toward broadening the age span of the NIH TB-CB to 99 years of age, almost the entire human lifespan (3-99).

We hope this work will not only be impactful for healthy aging, but also for the development of future biomarkers and interventions in cognitive aging. In these studies, I identified relationships between the brain network dynamics and cognition, which could help inform cognitive interventions that target optimizing brain functioning and infrastructure and cognition in older adult populations. Additionally, because I have identified network segregation's relationship to processing speed, my work helps inform research that has indicated segregation as a predictor for future cognitive status and a biomarker for cognitive resilience in Alzheimer's Disease since processing speed declines are indicating factors of future Alzheimer's Disease and MCI (Chan et al., 2021; Ewers et al., 2021). Also, my work could help focus intervention studies that have shown network dynamics can be changed through cognitive training and exercise; meaning network segregation could be a modifiable risk factor for cognitive impairment (Iordan et al., 2017; Voss et al., 2010). Future intervention research could target network dynamics in the older adult population as a way to preserve cognitive functioning in aging. Overall, this work provides novel insight into the healthy oldest-old brain and intact cognition in the aging process.

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