

The Pennsylvania State University

The Graduate School

Department of Psychology

**GRAPH THEORETICAL NETWORK ANALYSIS TO EXAMINE RESTING  
STATE FUNCTIONAL CONNECTIVITY IN YOUNGER AND OLDER ADULTS  
AND ITS RELATIONSHIP WITH BEHAVIOR**

A Thesis in

Psychology

by

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## **Abstract**

Older adults experience many differences in their cognition compared to younger adults. One example is more difficulties with language production, which becomes more dysfluent with age. This study aimed to compare resting state functional connectivity in younger and older adults using graph theory in three networks — the language network, the task-positive network, and the task-negative network — to examine the extent to which the underlying structure of the resting state networks predicted task performance and task-based functional activation. Results indicated some group differences in the language and task-negative networks that were predictive of behavioral performance; however, these differences become null after correcting for multiple comparisons. Additionally, this study contains exploratory analyses demonstrating the current issues pertaining to thresholding and edge definition in the field of network science and the effect this has on results.

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# Chapter 1

## Introduction

### Cognitive Decline with Aging

Cognitive deficits are increasingly common as our brains undergo age-related changes. Older adults frequently experience declines across cognitive domains including memory, attention, executive function, and language (Buckner, 2004; Burke & Light, 1981; Burke & Shafto, 2008; Craik, 1994; Rogers, 2000). In regard to language, older adults frequently report increased language production difficulties, which are often described as highly frustrating and lead to withdrawal from social interactions (Burke & Shafto, 2004; Burke & Shafto, 2008; Hummert, Garstka, Ryan, & Bonnesen, 2004). Such difficulties result in dysfluent speech, which includes increased word retrieval failures (tip of the tongue states, or TOTs), increased use of filler words (e.g., *uh* and *um*), and slower speech rates (Burke & Shafto, 2004; Burke & Shafto, 2008).

Research to increase the understanding of behavioral declines in language production, and the associated neural declines, is vital to improve older adults' quality of life. In addition to a greater risk for withdrawing from social interactions, older adults who experience language production difficulties may have a decreased desire to communicate with others (Hummert et al., 2004). Additionally, when interlocutors perceive speech production difficulties in older adults, they often communicate with older adults using "elderspeak," which involves the interlocutor making accommodations for older adults such as using oversimplified speech, increased repetition, as well as use of the collective "we" (Hummert et al., 2004; Kemper, 1994; Ryan, Kennaley, Pratt, & Shumovich, 2000).

### Cognitive Theories of Aging

As individuals age, they experience a decline in numerous cognitive abilities related to processing, or fluid intelligence; however, this coincides with increases in semantic knowledge, or crystallized intelligence (Salthouse, 2010). Numerous



hypotheses exist that attempt to explain this pattern in cognitive aging across domains, including language production declines. The Inhibition Deficit Hypothesis explains age differences in cognitive performance as resulting from deficient inhibitory processes (Hasher & Zacks, 1988; Lustig, Hasher, & Zacks, 2007). As such, older adults have more difficulties inhibiting goal-irrelevant information that becomes activated and serves as a competitor to the goal-relevant information. In language, this applies to competing semantic concepts or phonological features. Older adults do not have the same inhibitory capabilities compared to younger adults to suppress irrelevant semantic knowledge or irrelevant phonological knowledge, potentially resulting in increased tip of the tongue states and speech errors. This theory relates to the idea that individuals' semantic knowledge increases with age; therefore, older adults should have more semantic knowledge to inhibit, leading to more speech production difficulties. However, recent research by Shafto, James, Abrams, and Tyler (2017) found that age-related increases in knowledge do not interfere with word retrieval and do not result in more tip of the tongue experiences, as the Inhibition Deficit Hypothesis posits. Critics of this hypothesis also point out the lack of a specific model that confuses theoretical inhibition and inhibition at the behavioral level, as well as the lack of direct behavioral evidence of this inhibition failure (Burke, 1997). Additionally, this theory does not explain why there are age deficits in language production but not in language comprehension.

The Transmission Deficit Hypothesis is another theory of cognitive aging; however, this hypothesis more fully explains why deficits are observed in certain language domains (i.e., production) but not others (i.e., comprehension; Burke, MacKay, Worthley, & Wade, 1991; Burke & Shafto, 2004). This hypothesis suggests that the word retrieval difficulties experienced by older adults are due to weakening connections in the phonological system. This theory further explains that as people age, semantic connections are maintained and strengthened with the acquisition of new knowledge. When older adults try to produce a word, the semantic and lexical representations for a specific word are activated. However, due to weakening connections within the phonological system, there is not enough activation to transmit excitation to all relevant

phonological components of a word. This weakening occurs as a function of age, as well as a result of infrequent or a lack of recent activation of certain phonological representations. This lack of recent or infrequent activation also explains why TOTs are more common for proper nouns and for low frequency words. Therefore, this account more fully explains the observations of language and aging; it accounts for the increases in semantic knowledge, as well as how this relates to declines in language production that coincide with maintained language comprehension abilities in older adults.

### **Neural Theories of Aging**

Behavioral differences observed as a function of age often coincide with neural changes to white and gray matter structure, as well as differential patterns of brain activation. For example, as individuals age, structural connections (white matter) between regions decline. This decline in white matter integrity is associated with worse performance on processing speed tasks, executive functioning, and memory (Gunning-Dixon & Raz, 2000).

Two models of neural aging will be explained to understand the relationship between functional connectivity and behavior. The hemispheric asymmetry reduction in older adults (HAROLD) model discusses differences in functional activation in younger and older adults while performing a cognitive task (Cabeza, 2002). According to the HAROLD model, while performing cognitive tasks pertaining to memory, perception, and inhibitory control, activity in prefrontal regions is less lateralized in older adults compared to younger adults. This model posits that this decreased lateralization may serve as a compensatory mechanism, resulting in maintained cognitive performance on par with younger adults.

Another model of neural aging is the compensation-related utilization of neural circuits hypothesis, or CRUNCH (Reuter-Lorenz & Cappell, 2008). This model examines the role that task plays in neural overactivation. In younger adults, as task demand increases, so does functional activation of brain regions. In older adults, this overactivation is considered compensatory neural recruitment at lower levels of task

demand and helps maintain performance. However, as task demands increase, older adults reach a resource ceiling and experience underactivation of brain regions needed to perform the task, resulting in a drastic decline in task performance. This underactivation is possibly caused by the task becoming too difficult (Cabeza & Dennis, 2012). When this occurs, participants disengage with the task or attempt a new strategy that they are unable to maintain, resulting in declines in activation. Additionally, with increased task demand comes increased working memory load. Additional items that surpass one's working memory limit are not processed and interfere with the maintenance of current information, contributing to declines in functional activation.

Keeping in mind these neural theories of cognitive aging is important when considering the resting state functional connectivity (RSFC) of younger and older adults in language networks, as well as other networks related to task performance and how this RSFC predicts task performance. Additionally, while these theories refer to task-based activation patterns, it is important to determine if similar patterns of neural activation are observed in RSFC as well.

### **Resting State Functional Connectivity**

Resting state functional connectivity (RSFC) examines how signals from brain regions are correlated (i.e., working together) across time while participants are not performing an explicit task (Biswal, Yetkin, Haughton, & Hyde, 1995). Numerous studies have shown that brain regions in neural networks that function together during task demonstrate synchronous correlations while participants are at rest (Rosazza & Minati, 2011). Such neural networks include the default mode network (DMN), the executive control network (ECN), the dorsal attention network (DAN), the task-positive network, and the salience network (Deco, Jirsa, & McIntosh, 2010; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001; Zhang et al., 2014). Additionally, the DMN, ECN, and DAN have all exhibited age-related alterations in their resting state functional connectivity that are associated with cognitive deficits in older adults (Andrews-Hanna et al., 2007; Zhang et al., 2014). However, very few studies have examined a language-

specific network to examine functional correlations during rest. If the language network is strongly correlated during rest, then examining differences in functional connectivity across younger and older adults will further our understanding as to why older adults are experiencing a marked decline in speech production.

Resting state functional connectivity has value in being used to predict behavioral task performance, as well as being used clinically to predict symptom severity in disease states (Mennes et al., 2010). For example, a study by Tian, Ren, and Zang (2012) found that resting state functional connectivity in the bilateral inferior frontal cortex (IFC), bilateral middle occipital cortex (MOC), left inferior temporal cortex (ITC), and specific regions of the DMN (i.e., bilateral precuneus, bilateral medial prefrontal cortex, and left inferior parietal lobule) reliably predicted stop signal reaction time during a stop signal task. Another study found that resting state activity predicted performance on an n-back working memory task (Zou et al., 2013). With increased task difficulty, there was increased resting state activity in the bilateral inferior parietal lobules (IPL), middle frontal gyrus, precentral gyrus, and precuneus. The predictive nature of resting state functional connectivity for task performance depended on working memory load.

While numerous studies have been done looking at the DMN, as well as other networks, few studies have examined the resting state language network's effect on cognitive performance. One study examining the language network measured the extent to which RSFC in the language network predicted performance on the F-A-S verbal fluency test in younger adults aged 18 to 30 (Miró-Padilla, Bueichekú, Ventura-Campos, Palomar-García, & Ávila, 2017). In this study, the researchers used seed regions from meta-analyses and conducted a pairwise resting-state functional connectivity analysis. After correlating F-A-S verbal fluency scores with RSFC of language regions, they found that higher functional connectivity between the thalamus and cerebellum and lower functional connectivities between the left inferior frontal gyrus (IFG) and right insula and between the supplementary motor area (SMA) and right insula were associated with improved performance on the verbal fluency measure (Miró-Padilla et al., 2017).

In the clinical domain, resting state functional connectivity has reliably predicted symptoms in a variety of diseases and disorders, including Alzheimer's disease (Wang et al., 2007). In Alzheimer's disease (AD), research using resting state functional connectivity demonstrated that compared with healthy control participants, patients with AD had decreased positive correlations between prefrontal and parietal brain regions and increased positive correlations within the prefrontal lobe, parietal lobe, and occipital lobe (Wang et al., 2007). Overall, this study suggested that a frontal-parietal disconnection and increased within-lobe connectivities during resting state functional connectivity could serve as biomarkers for Alzheimer's disease.

The above examples demonstrate the value of resting state functional connectivity in established networks being used to predict cognitive task performance, as well as being used to predict symptom severity in Alzheimer's disease. Considering the predictive value of resting state functional connectivity and its potential usefulness in predicting task performance in other cognitive domains, such as language, further investigation of the language network during resting state may predict age-related language declines (Miró-Padilla et al., 2017).

## **Network Science Overview**

Network analysis applies graph theoretical methods to explore properties of a variety of networks (Rubinov & Sporns, 2010). Many graph theory network measures are useful in cognitive neuroscience to examine the relationships brain regions have within a network (e.g., DMN, task-positive, language), as well as examining the relationships of global, whole-brain networks. Graph theory principles allow researchers to apply the mathematical study of networks to define brain networks. Brain networks can be defined using structural or functional data. In the present study, the three networks of interest — the language network, task-positive network, and task-negative network — will be defined using functional connectivity data. This method will allow us to further understand the manner in which the regions, or nodes, in different brain networks interact and function together. This will lead to better understanding of which

nodes are more essential in a network and which nodes cluster within a network. For further description of network definition in this study, please see the methods section.

For the current study, four graph theoretical measures will be employed. The first measure is *degree*. Degree is a nodal measure that describes the number of connections, or edges, that a specific node has with other nodes in the network (Rubinov & Sporns, 2010). For example, if the left inferior frontal gyrus (IFG) in the language network is connected to six other nodes within the language network, then the left IFG has a degree of six. *Betweenness centrality* measures the most influential nodes (brain regions) within a network and is defined as the fraction of all shortest paths in the network that pass through a given node. *Clustering coefficient* is a local measure that equals the fraction of triangles around an individual node. Clustering coefficient measures the amount of a node's neighbors that are also neighbors with each other. Lastly, *global efficiency* measures how easily it is for pairs of nodes to communicate with each other within a network. The global efficiency of a network is defined as the average inverse shortest path length.

## **The Present Study**

In the current study, I aim to examine the resting state functional connectivity differences between younger and older adults in three networks: the language network, the task-positive network, and the task-negative network. While a prior study has examined RSFC in the language network in relation to cognitive performance, that study examined undergraduate students (Miró-Padilla et al., 2017). In the current study, we aim to examine both younger adults and older adults to study the differences in how younger and older adults' RSFC of the language network, as well as the two other networks mentioned, predict task performance. I predict that there will be significant differences in these networks between younger and older adults, with older adults' networks showing less RSFC, being less efficient, and being less integrated. These network differences will be measured using graph theoretical network approaches. Additionally, based on neural theories of aging that discuss increased right hemisphere

functional activation in older adults, I hypothesize that the RSFC in the three networks will exhibit increased right hemisphere activation. The language network will demonstrate the greatest degree of right hemisphere overactivation consistent with HAROLD and CRUNCH. This is due to the language network being highly left lateralized in right-handed individuals; therefore, decreased asymmetry in the language network RSFC will be indicative of compensation and be associated with improved task performance. Alternatively, it is possible that this increased right hemisphere activity will correspond with worse task performance on the language task, demonstrating dedifferentiated networks that work less efficiently. While these neural theories of aging refer to task-based functional activation, given that RSFC literature has shown that RSFC is predictive of activation during task, it is likely that if the language network is recruiting right hemisphere homologous regions during task, they are also functioning synchronously with the left hemisphere language regions during rest.

Consistent with prior literature demonstrating the predictive value of RSFC on behavior and clinical symptoms, I predict that RSFC in younger and older adults will predict accuracy and reaction time performance on a language-based task and will also predict the functional activation of language regions during the task. More specifically, while group differences are expected in all three networks, I hypothesize that the resting state network differences in the language network will predict behavioral performance and task-based functional activation of the language regions. Additionally, since the language paradigm used in this study is a task, it will likely recruit regions in the task-positive network. As such, the RSFC of the task-positive network likely contributes to task completion and may also predict behavioral performance and task-based functional activation. This is consistent with literature that suggests that many issues older adults face with language production are related to the nature of the task and not declines in the language network (Davis, Zhuang, Wright, & Tyler, 2014; Shafto & Tyler, 2014). However, the RSFC in the task-negative network should not significantly predict the functional activation that occurred during the two task conditions of interest (outlined in the methods section below) due to the task-negative network disengaging during task. However, due to literature suggesting that older adults have a decreased ability to

disengage the task-negative network during task, the results for older adults will likely be more variable (Andrews-Hanna et al., 2007).



## Chapter 2

### Methods

#### Participants

Twenty younger adults between the ages of 18 and 32 (females = 10, mean age = 23.7 years) and twenty older adults between the ages of 60 and 79 (females = 15, mean age = 67) participated in the picture-word interference study. All participants were healthy, right-handed, native English monolingual speakers who had no reported history of neurological or psychological disorders. All participants had normal or corrected-to-normal vision, which was measured using the Freiburg Visual Acuity and Contrast Test (Bach, 1996). Ishihara Plates were used to assess participants' color vision (Clark, 1924). Additionally, all participants scored at least a 27 on the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). One older adult was excluded from the resting state analyses because the number of TRs censored due to motion prevented a reliable correlation from being determined. This is due to there being less than five minutes of data acquisition time (Van Dijk et al., 2010). Another older adult was excluded from the analyses due to an incidental finding during the data quality assurance procedure. See table 1 for demographic information of the 38 participants included in the resting state analyses. All participants provided written informed consent and all experimental procedures were approved by the Institutional Review Board of The Pennsylvania State University.

**Table 1. Participant Demographics**

	<b>Younger Adults</b>	<b>Older Adults</b>
<b>N</b>	20	18
Age (years)	M = 23.7 (4.32)	M = 67.06 (6.40)
Sex (M/F)	10/10	4/14
Education (years)	M = 16.6 (2.72)	M = 16.78 (2.24)

Values in parentheses denote standard deviations.

## Neuropsychological Battery

Before completing the MRI session, participants completed a neuropsychological battery to measure aspects of cognition including speed, inhibition, working memory, and language abilities. All participants' neuropsychological battery tests were completed prior to my arrival at Penn State. Participants completed assessments to determine their handedness and language history. Paper and pencil materials were used to assess verbal fluency (FAS and animal names), forward and backward digit span, the MMSE, the WAIS vocabulary test, author recognition test, magazine recognition test, and comparative reading habits. The program E-Prime was used to assess non-verbal working memory. Part 1 of the verbal memory test was immediate recall of 16 words. Part 2 of the verbal memory test was a 20 minute delayed recall of the 16 words presented in part 1 and recognition of whether presented words on a computer screen are new or were in part 1. The speed of processing task, digit symbol task, and the Stroop task were also conducted in E-Prime on a computer. See table 2 for neuropsychological testing information.

**Table 2. Neuropsychological Testing Information**

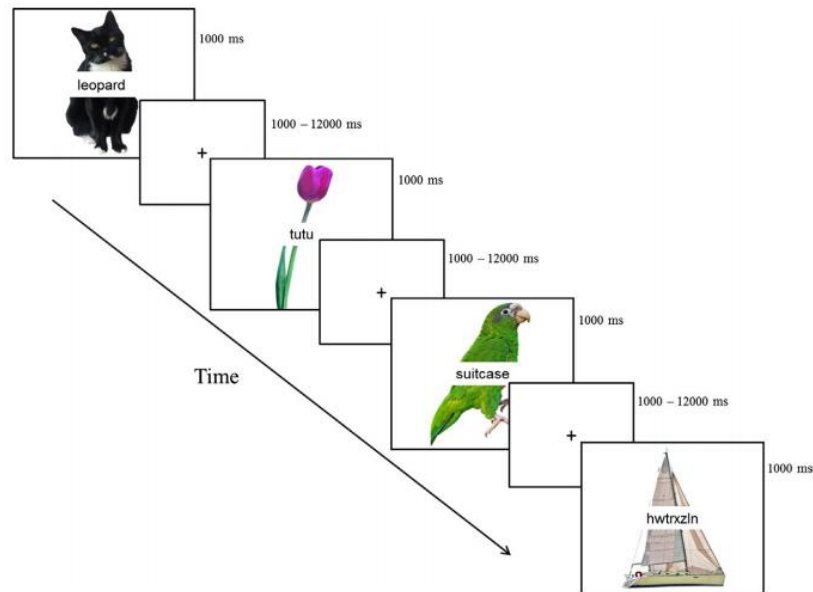
Neuropsychological Test	Younger	Older
	Mean (SD)	Mean (SD)
MMSE	29.25 (0.91)	28.67 (1.08)
Vocabulary	53.25 (8.13)	56.39 (5.63)
Immediate Recall	12 (1.86)	11.22 (1.70)
Delayed Recall*	11.2 (2.26)	9.05 (2.58)
Verbal Fluency	66.2 (15.50)	69.18 (15.45)
Simple Speed	264.8 (36.17)	279.13 (33.31)
Complex Speed*	282.96 (28.40)	343.47 (81.50)
Digit Span Forward	7.15 (1.09)	7.11 (1.37)
Digit Span Backward	5.3 (1.30)	4.72 (1.23)
Digit Symbol*	1291.29 (260.66)	1841.21 (344.94)
Stroop Effect*	12.35 (30.67)	87.67 (63.35)
Nonverbal Working Memory*	0.76 (0.07)	0.66 (0.11)
Author Recognition*	14.60 (8.76)	35.11 (15.42)
Magazine Recognition*	12.70 (6.63)	23.94 (7.31)

\*Scores for which there is a significant age difference,  $p < .05$

## **Picture Word Interference Task**

Stimuli for the picture-word interference (PWI) task consisted of 240 colored images, 60 unique items per condition, and were presented with a written distractor word embedded within the picture. Pictures were taken from two normed databases (Brodeur, Guérard, & Bouras, 2014; Moreno-Martínez & Montoro, 2012). All images depicted common, concrete objects from a variety of categories. Frequencies for all stimuli were obtained from the English Lexicon Project (Balota et al., 2007). The average frequency of the target picture name was 7.48 (SD = 1.91) and ranged from 2.30 to 12.44.

Distractor words were concrete nouns from the following categories: categorical, phonological, unrelated, and non-word. Words were used only once. Four distractors, one for each condition, were created for each of the 240 target pictures. Participants were presented with a target image only once but every target appeared with every distractor condition across participants. Categorically-related distractors were semantically, but not associatively, related to the target image. Phonologically-related distractors shared at least two initial phonemes with the target image. Unrelated distractors were neither categorically nor phonologically related to the target image. Non-word distractors consisted of random consonant strings that did not have the same word onset as the target image. Experimental stimuli were created prior to my arrival at Penn State. For full details of this manipulation and subsequent results, please see Rizio et al. (2017). See figure one for an example of each task condition. For the current study, only the categorical and phonological task conditions will be analyzed.



**Figure 1. The Picture Word Interference Task.** Conditions include: categorical, phonological, unrelated, and nonword. Correct responses to each target picture: “cat,” “tulip,” “parrot,” and “sailboat,” respectively (Figure adapted from Rizio, Moyer, & Diaz, 2017).

### Resting State fMRI Procedure

The resting state run was completed before completion of the PWI task. This ensured that participants had no knowledge of the task. Because the PWI task is a language production task and the language network is of interest in this study, participants’ knowledge of and thoughts about the task could affect the functional correlations between language regions and influence subsequent resting state functional connectivity analyses. Participants were instructed to relax in the scanner with their eyes open and to look at a fixation cross that appeared on the screen. The resting state run was 6 minutes in length.

### Acquisition of fMRI Data

Imaging data were collected at The Pennsylvania State University, University Park campus using a 3T Siemens Prisma Fit MRI scanner with a 20-channel head coil. T1 weighted anatomical images were collected using a magnetization-prepared rapid acquisition gradient echo (MP RAGE) sequence with an anterior to posterior phase

encoding direction and a 7ms echo spacing. The following spatial parameters were set: FOV = 256 mm<sup>2</sup>, matrix = 256, and a voxel size of 1 mm<sup>3</sup>. The following timing parameters were set: TR = 2300ms, TE = 2.28ms, TI = 900ms. The flip angle was 8°. Fat suppression was not used. One hundred sixty contiguous slices, 1 mm thick, were acquired in ascending order.

Before the first functional run, an advanced shim was applied to increase homogeneity of the magnetic field to help prevent signal dropout and image distortion. Both the resting state and task-based functional images were collected using an echo-planar imaging (EPI) sequence with an anterior to posterior phase encoding direction and a 0.49ms echo spacing. The following spatial parameters were set: FOV = 240 mm<sup>2</sup>, matrix = 80, with a voxel size of 3 mm<sup>3</sup>. Forty-one contiguous slices were acquired in interleaved order. The following timing parameters were set: TR = 2500ms, TE = 25.0ms. The flip angle was 90° and fat saturation was used. For the resting state run, 142 volumes per run were collected. During the PWI portion of the scan, 126 volumes per run were collected. Two additional volumes were acquired and deleted at the start of each run (both resting state and the PWI task) to reach steady state equilibrium. All fMRI imaging data were collected by other researchers within the Language and Aging Lab prior to my arrival at Penn State.

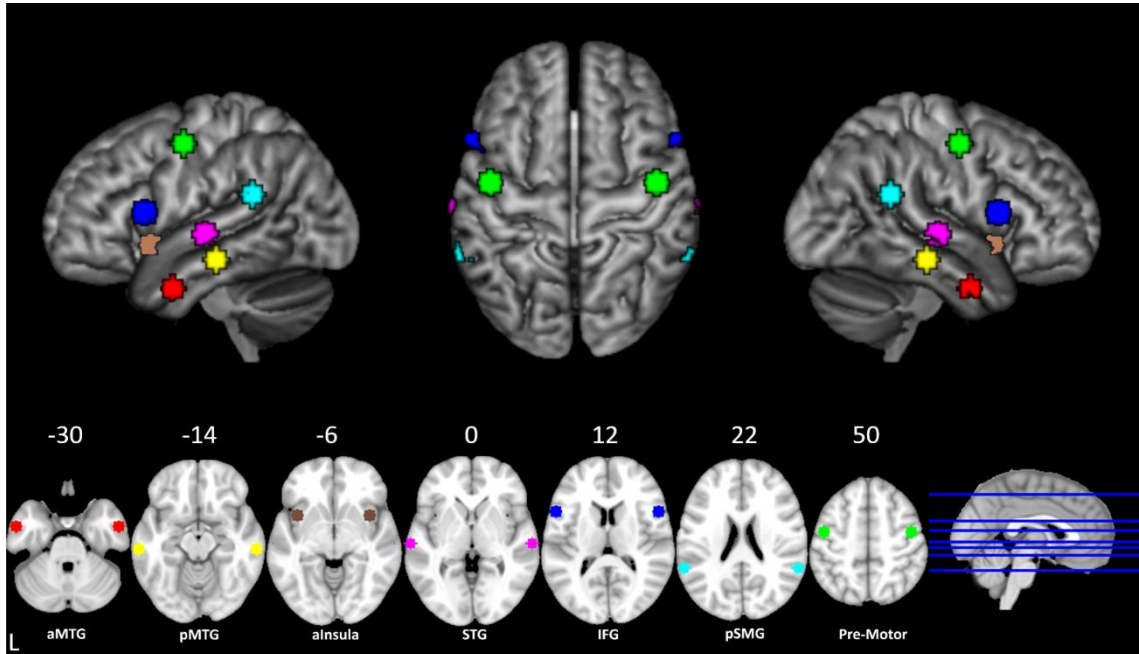
### **Resting State fMRI Preprocessing Procedure**

Functional and anatomical images were visually inspected for artifacts and signal drop-out. Processing and analyses were done using AFNI version 16.0.00 (Cox, 1996). Volumes were first censored, removing time points when more than 10% of the voxels were outliers. Extreme signal changes, indicative of outliers, were also removed. Slice-timing was done to realign all slices to the same time point, correcting for maturation of the BOLD signal over time. Motion correction was conducted to correct for head motion, as well as identify time points with excessive motion. The anatomical images were normalized to standard MNI space. During registration, functional images were aligned to anatomical images and both were normalized to standard space, allowing for group

comparisons by standardizing each participant's brain. Spatial smoothing was conducted using a smoothing kernel of 4 mm to increase the signal to noise ratio, as well as to reduce the impact of single voxels which may be spurious. Band-pass filtering was done with the low frequency threshold set to 0.01 Hz and the high frequency threshold set to 0.1 Hz. Any frequencies outside of this range were eliminated as noise that was not a part of the neural signal. Segmentation was conducted to segment the anatomical images into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) and the white matter was regressed out. Regression analyses were run with 6 motion parameters in place to censor images above the motion threshold of 0.5 mm.

### **Language Network Regions of Interest**

The resting state language network was chosen using the Hickok and Poeppel (2007) dual-stream model of speech processing as a framework. Coordinates for the regions were chosen based on meta-analyses on language production and were confirmed using the Harvard-Oxford Cortical Structural Atlas in FSL (Adank, 2012; Brown et al., 2009; Desikan et al., 2006; Eickhoff, Heim, Zilles, & Amunts, 2009; Skipper, Devlin, & Lametti, 2017). Seven left hemisphere language regions were chosen, as well as their right hemisphere homologues, and were defined by drawing 6 mm spheres using the `fslmaths` command (Smith et al., 2004; Woolrich et al., 2009). The right hemisphere homologues were defined as the mirror image of the left hemisphere regions because the language network is highly left lateralized in right-handed individuals and there is no reliable way to elicit right hemisphere homologues without testing left-handed individuals. The regions include the inferior frontal gyrus (IFG), anterior insula, premotor area (PM), posterior supramarginal gyrus (pSMG), anterior and posterior middle temporal gyrus (aMTG and pMTG, respectively), and superior temporal gyrus (STG). Coordinates used for the regions are provided in table 3.



**Figure 2. The Language Network.** The top image shows the network on the rendered brain, the bottom image shows the location of the bilateral ROIs. Colors in the multislice image correspond to colors in the rendered brain.

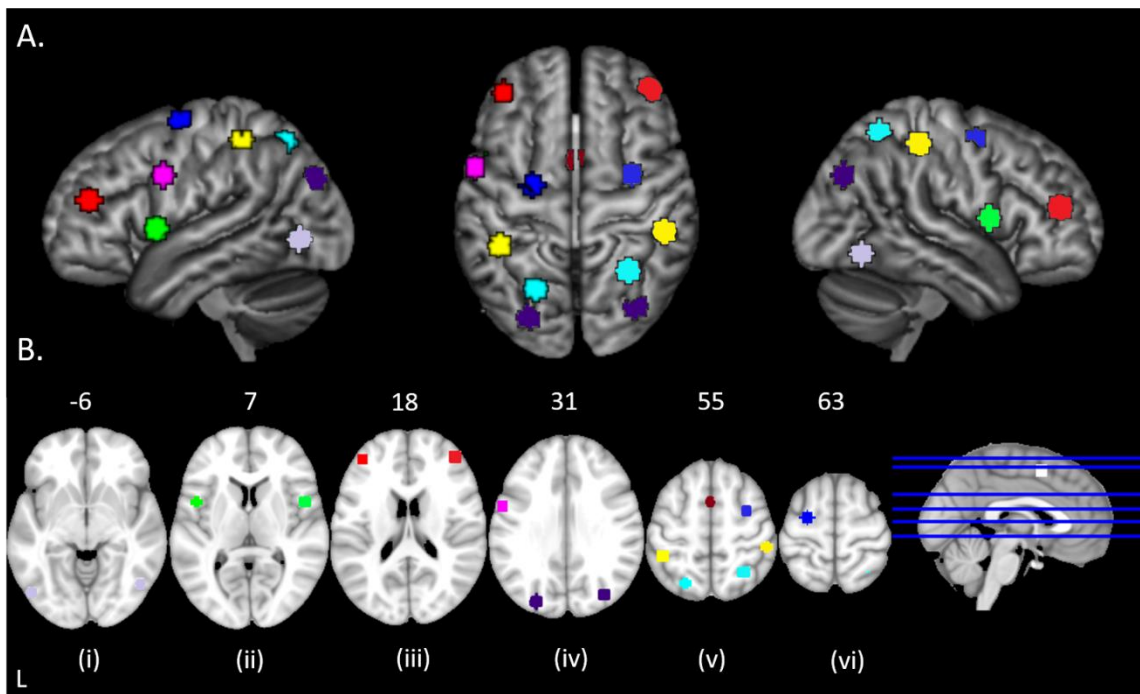
**Table 3. Language Network ROI Coordinates**

Region	X	Y	Z
Inferior Frontal Gyrus (IFG)	$\pm 54$	14	12
Anterior Insula	$\pm 38$	10	-6
Premotor Area (PM)	$\pm 46$	-8	50
Posterior Supramarginal Gyrus (pSMG)	$\pm 60$	-46	22
Anterior Middle Temporal Gyrus (aMTG)	$\pm 54$	-2	-30
Posterior Middle Temporal Gyrus (pMTG)	$\pm 62$	-26	-14
Superior Temporal Gyrus (STG)	$\pm 64$	-20	0

**Note.** Coordinates for the ROIs are in MNI space.

### Task-Positive Network Regions of Interest

The task-positive network was constructed using the coordinates for the task-positive network in Fox et al. (2005). These coordinates were provided in talairach space and were converted to MNI space using the Lancaster transform (icbm2tal) in the GingerALE software package (Eickhoff, Laird, et al., 2009; Lancaster et al., 2007; Talairach & Tournoux, 1988). The regions in the task-positive network include: the intraparietal sulcus (IPS), inferior parietal lobule (IPL), orbital gyrus, frontal eye field (FEF), inferior precentral sulcus, supplementary motor area/pre-supplementary motor area (SMA/pre-SMA), dorsal lateral prefrontal cortex (DLPFC), middle temporal region (MT<sup>+</sup>), and insula/frontal operculum. The regions were constructed in the same manner as stated above for the language network regions. The coordinates for the task-positive network can be found in table 4.



**Figure 3. The Task-Positive Network.** (A) Task-positive network ROIs on a rendered brain. (B) Slices illustrating all ROIs in the network. (i) bilateral middle temporal region (ii) bilateral insula/frontal operculum (iii) bilateral DLPFC (iv) dark purple is the bilateral orbital gyri (ventral intraparietal sulcus), light purple is the left inferior precentral sulcus (v) maroon is the SMA, yellow is the bilateral IPL, cyan is the bilateral IPS, blue is the right FEF (vi) blue is the left FEF. Colors in (B) correspond to colors in (A).



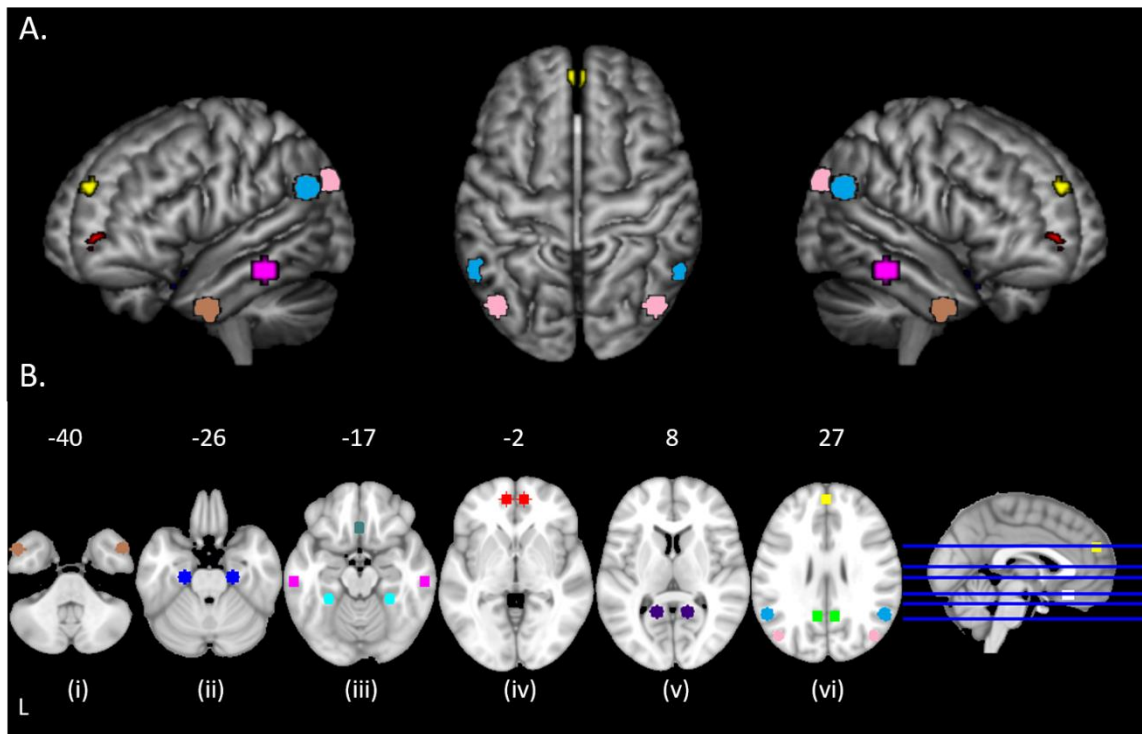
**Table 4. Task-Positive Network ROI Coordinates**

<b>Region</b>	<b>X</b>	<b>Y</b>	<b>Z</b>
Intraparietal Sulcus (IPS)	-22.86	-64.83	52.93
	28.45	-55.55	58.25
Inferior Parietal Lobule (IPL)	-43.22	-41.43	54.55
	50	-34	52
Orbital Gyrus	-26.17	-81.36	32.05
	34	-76	34
Frontal Eye Field (FEF)	-24.02	-6.45	64.78
	31.47	-1.43	55.91
Inferior Precentral Sulcus	-56.34	3.82	35.29
Supplementary/Pre-Supplementary Motor Area (SMA/pre-SMA)	-0.64	6.58	52.26
Dorsolateral Prefrontal Cortex (DLPFC)	-41.61	44.38	21.68
	41.7	46.65	16.08
Middle Temporal Region (MT <sup>+</sup> )	-48.9	-72.35	-0.78
	48	-66	-10
Insula/Frontal Operculum	-46.96	6.85	4.82
	49.26	6.89	10.4

**Note.** Coordinates for the ROIs are in MNI space. All coordinates were taken from Fox et al. (2005) and were converted from talairach space. The coordinates for the right IPL, right orbital gyrus, and right middle temporal region were altered due to the ROIs largely being off the template brain after drawing the sphere. The coordinates were altered to prevent under sampling.

## Task-Negative Network Regions of Interest

The coordinates for the task-negative, or default mode, network were taken from Andrews-Hanna, Reidler, Sepulcre, Poulin, and Buckner (2010). This network only includes left-hemisphere regions; therefore, right hemisphere regions were constructed using the mirror image of the provided coordinates. The regions in the task-negative network include: the anterior medial prefrontal cortex (aMPFC), posterior cingulate cortex (PCC), dorsal medial prefrontal cortex (dMPFC), temporal parietal junction (TPJ), lateral temporal cortex (LTC), temporal pole (TempP), ventral medial prefrontal cortex (vMPFC), posterior inferior parietal lobule (pIPL), retrosplenial cortex (RSC), parahippocampal cortex (PHC), and the hippocampal formation (HF<sup>+</sup>). The regions were constructed in the same manner as stated above for the language network regions. The coordinates for the task-negative network can be found in table 5.



**Figure 4. The Task-Negative Network.** (A) Task-negative network ROIs on a rendered brain. (B) Slices illustrating all ROIs in the network. (i) bilateral temporal pole (ii) bilateral HF (iii) light purple is the bilateral LTC, cyan is the bilateral PHC, teal is the vMPFC (iv) bilateral aMPFC (v) bilateral retrosplenial cortex (vi) pink is the bilateral pIPL, light blue is the bilateral TPJ, green is the bilateral PCC, yellow is the dMPFC. Colors in (B) correspond to colors in (A).

**Table 5. Task-Negative Network ROI Coordinates**

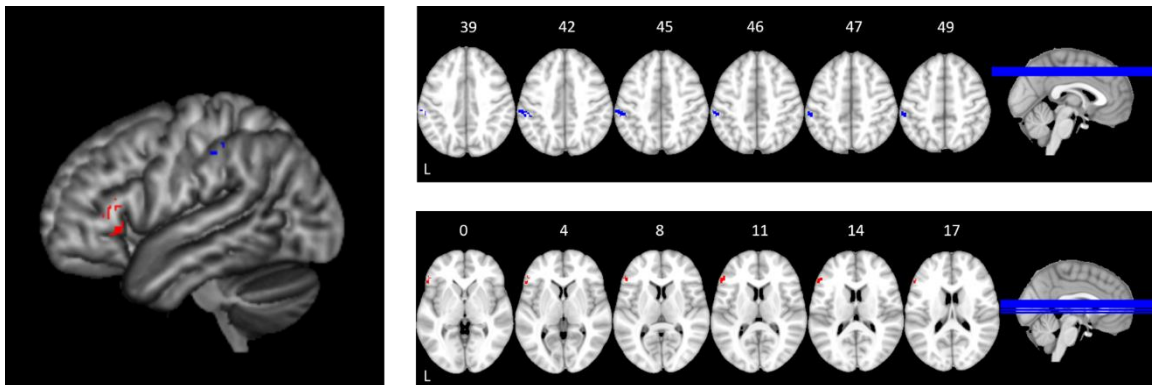
<b>Region</b>	<b>X</b>	<b>Y</b>	<b>Z</b>
anterior Medial Prefrontal Cortex (aMPFC)	±8	52	-2
Posterior Cingulate Cortex (PCC)	±8	-56	26
dorsal Medial Prefrontal Cortex(dMPFC)	0	52	26
Temporal Parietal Junction (TPJ)	±54	-54	28
Lateral Temporal Cortex (LTC)	±60	-24	-18
Temporal Pole (TempP)	±48	6	-40
ventral Medial Prefrontal Cortex (vMPFC)	0	26	-18
Posterior Inferior Parietal Lobule (pIPL)	±44	-74	32
Retrosplenial Cortex (RSC)	±14	-52	8
Parahippocampal Cortex (PHC)	±28	-40	-12
Hippocampal Formation (HF <sup>+</sup> )	±22	-20	-26

**Note.** Coordinates for the ROIs are in MNI space. All coordinates were taken from Andrews-Hanna et al. (2010) except the aMPFC and TempP, which were altered. The aMPFC was altered due to ROI overlap after drawing the 6 mm spheres to prevent an issue of non-independence. The TempP was altered due to the ROI largely being off the template brain after drawing the sphere. The coordinate was altered to prevent under sampling.

### **Functional Regions of Interest**

Two functional activation ROIs were created based on results from Rizio, Moyer, and Diaz (2017). The phonological ROI was defined based on significant functional activation that overlapped in younger and older adults in the left supramarginal gyrus (SMG) during the phonological task condition. The left SMG mask was created using the Harvard-Oxford Cortical Structural Atlas in FSL and was thresholded at 50% and was binarized using the `fslmaths` command (Desikan et al., 2006). The anterior division of the

SMG was used in mask creation due to this region corresponding with significant functional activation in Rizio, Moyer, and Diaz (2017). The SMG was chosen for the phonological condition due to its role in phonological decision making (Hartwigsen et al., 2010; Twomey et al., 2015). The categorical ROI was defined based on significant functional activation that overlapped in younger and older adults in the left inferior frontal gyrus (IFG) during the categorical task condition. The left IFG mask was created using the Harvard-Oxford Cortical Structural Atlas in FSL and was thresholded at 50% and was binarized using the `fslmaths` command. The IFG pars triangularis division was used in mask creation due to this region's role in semantic selection and retrieval (Schnur, Lee, Coslett, Schwartz, & Thompson-Schill, 2005; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Zhao et al., 2011).

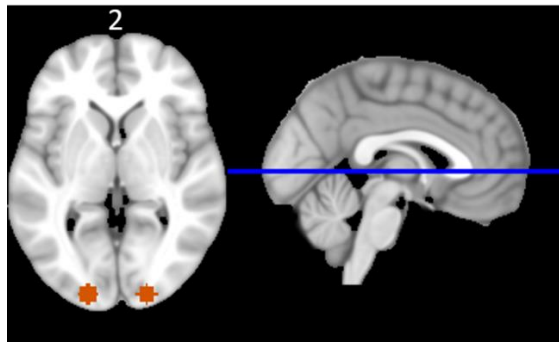


**Figure 5. Functional Regions of Interest.** The left SMG is in blue. The left IFG is in red. These ROIs were used to relate rsfMRI to significant functional activation common to younger and older adults during the phonological and categorical task conditions.

### Visual Control Regions

A control analysis was conducted using two regions in the visual cortex that correspond to visual region V2. MNI coordinates for the regions ( $\pm 19, -95, 2$ ) were taken from Andrews-Hanna et al. (2007). Two regions in the visual cortex were chosen as control regions because primary visual areas strongly activate in both younger and older adults in the presence of visual stimuli (Buckner, Snyder, Sanders, Raichle, & Morris, 2000). Additionally, interhemispheric connections between visual regions appear to

remain largely intact with normal aging (Myers, 1962). Therefore, functional connectivity between these two regions should not exhibit age differences, suggesting that any differences in the three networks of interest are due to age-related differences in those networks and not due to more global age differences.



**Figure 6. The Visual Control Regions.**

### **Network Analyses**

After creation of the regions of interest for the language, task-positive, and task-negative networks, resting state connectivity data was extracted for each ROI for each of the 142 volumes for all 38 participants. After extracting the functional connectivity data, bivariate correlations were run for all ROIs for each participant's three networks. This demonstrated how strongly each ROI was correlated with all other ROIs in the networks. High correlation values between two ROIs suggest that these regions are functioning together. After obtaining these correlation matrices, the diagonal of each matrix was changed from one to zero to exclude a region's correlation to itself from being included in network analyses. When calculating the graph theory network measures, connectivity matrices were thresholded where every correlation of  $r \geq 0.2$  was statistically significant (Dosenbach et al., 2007). Weights were maintained for all correlations greater than or equal to 0.2. Using the Brain Connectivity Toolbox (BCT) in MATLAB, weighted betweenness centrality, clustering coefficient (weighted and undirected), degree (undirected), and global efficiency (weighted) were calculated for the three networks for each participant.

## Chapter 3

### Results

#### PWI Task Behavior

Independent Samples *t*-tests were done to test for group differences in reaction time and accuracy performance in the categorical and phonological conditions of the PWI task. There were no significant group differences in reaction time performance in either condition. There was a significant group difference in categorical accuracy performance with younger adults having higher accuracy ( $M = .72$ ) than older adults ( $M = .65$ ),  $t(36) = 2.66$ ,  $p = .012$ , 95% CI [0.07, 0.03]. There was a significant group difference on phonological accuracy performance with younger adults having higher accuracy ( $M = .76$ ) than older adults ( $M = .69$ ),  $t(36) = 2.53$ ,  $p = .016$ , 95% CI [0.07, 0.03].

#### Language Network

An Independent Samples *t*-test was done to test for group differences in efficiency of the language network. Results indicated that there were no significant group differences in language network efficiency between younger ( $M = .31$ ) and older ( $M = .28$ ) adults,  $t(36) = 1.38$ ,  $p = .18$ , 95% CI [-0.02, 0.08]. Efficiency significantly predicted phonological reaction time, with increased efficiency corresponding to increased reaction time,  $b = 1453.40$ ,  $r = .43$ ,  $F(1, 36) = 8.10$ ,  $p = .007$ , 95% CI [418.13, 2488.67]. Efficiency also predicted categorical reaction time, with increased efficiency corresponding to increased reaction time,  $b = 1334.75$ ,  $r = .35$ ,  $F(1, 36) = 5.03$ ,  $p = .031$ , 95% CI [128.09, 2541.41]. Efficiency did not significantly predict accuracy for either condition.

A MANOVA was conducted to test for group differences in betweenness centrality between younger and older adults in the language network. The overall MANOVA was not significant,  $F(14, 23) = .84$ ,  $p = .62$  Pillai's Trace = .34, partial  $\eta^2 = .34$ , suggesting no significant differences in betweenness centrality of the language

network in younger and older adults. There were no significant group differences in betweenness centrality for any individual ROIs.

A MANOVA was conducted to test for group differences in clustering coefficient between younger and older adults. The overall MANOVA was not significant,  $F(14, 23) = 1.37, p = .24$ , Pillai's Trace = .46, partial  $\eta^2 = .46$ , suggesting no significant differences in clustering coefficient of the language network in younger and older adults. While the clustering coefficient for the overall network did not exhibit significant group differences, individual ROIs within the language network exhibited significant group differences in clustering coefficient. There was a significant group difference in the right pMTG clustering coefficient between younger and older adults, with younger adults having a higher clustering coefficient ( $M = .36$ ) than older adults ( $M = .28$ ),  $b = 0.08$ ,  $F(1, 36) = 4.81, p = .035$ . The right pMTG did not significantly predict accuracy or reaction time for either of the PWI task conditions. There was a significant group difference in the right STG clustering coefficient between younger and older adults, with younger adults having a higher clustering coefficient ( $M = .30$ ) than older adults ( $M = .23$ ),  $b = 0.07$ ,  $F(1, 36) = 4.47, p = .042$ . The right STG significantly predicted phonological reaction time,  $b = 809.78, r = .34, F(1, 36) = 4.58, p = .039$ , 95% CI [42.21, 1577.35]. As clustering coefficient of the right STG increased, so did phonological reaction time. The right STG did not significantly predict performance on either of the accuracy conditions or categorical reaction time.

A MANOVA was conducted to test for group differences in degree between younger and older adults. The overall MANOVA was not significant,  $F(14, 23) = .88, p = .59$ , Pillai's Trace = .35, partial  $\eta^2 = .35$ , suggesting no significant differences in degree of the language network in younger and older adults. While the degree for the overall network did not exhibit significant group differences, individual ROIs within the language network exhibited significant group differences in degree. There was a significant group difference in the left pMTG degree between younger and older adults, with younger adults having a higher degree ( $M = 7.50$ ) than older adults ( $M = 5.50$ ),  $b = 2.00, F(1, 36) = 7.05, p = .012$ . The left pMTG significantly predicted phonological

reaction time,  $b = 36.82$ ,  $r = .37$ ,  $F(1, 36) = 5.55$ ,  $p = .024$ , 95% CI [5.11, 68.53]. As left pMTG degree increased, so did phonological reaction time. There was a significant group difference in the left STG degree between younger and older adults, with younger adults having a higher degree ( $M = 8.85$ ) than older adults ( $M = 6.83$ ),  $b = 1.07$ ,  $F(1, 36) = 4.94$ ,  $p = .033$ . The left STG significantly predicted phonological reaction time,  $b = 31.43$ ,  $r = .37$ ,  $F(1, 36) = 5.59$ ,  $p = .024$ , 95% CI [4.46, 58.40]. As left STG degree increased, so did phonological reaction time. The left pMTG and left STG did not significantly predict performance on either of the accuracy conditions or categorical reaction time.

Linear regressions were run using efficiency, betweenness centrality, clustering coefficient, and degree of the language network to predict functional activation during the PWI task in the categorical and phonological ROIs. Efficiency, betweenness centrality, clustering coefficient, and degree did not predict functional activation in either the categorical or phonological ROI.

### **Task-Positive Network**

An Independent Samples *t*-test was done to test for group differences in efficiency of the task-positive network. Results indicated that there were no significant group differences in task-positive network efficiency between younger ( $M = .40$ ) and older adults ( $M = .40$ ),  $t(36) = -0.17$ ,  $p = .86$ , 95% CI [-0.06, 0.05]. Efficiency significantly predicted phonological reaction time, with increased efficiency corresponding to increased reaction time,  $b = 1057.06$ ,  $F(1, 36) = 4.78$ ,  $p = .035$ , 95% CI [76.44, 2037.68]. Efficiency did not significantly predict accuracy for either condition or categorical reaction time.

A MANOVA was conducted to test for group differences in betweenness centrality between younger and older adults. The overall MANOVA was not significant,  $F(16, 21) = .92$ ,  $p = .56$ , Pillai's Trace = .41, partial  $\eta^2 = .41$ , suggesting no significant differences in betweenness centrality of the task-positive network in younger and older



adults. There were no significant group differences in betweenness centrality for any individual ROIs.

A MANOVA was conducted to test for group differences in clustering coefficient between younger and older adults. The overall MANOVA was not significant,  $F(16, 21) = 1.27, p = .30$ , Pillai's Trace = .49, partial  $\eta^2 = .49$ , suggesting no significant differences in clustering coefficient of the task-positive network in younger and older adults. There were no significant group differences in clustering coefficient for any individual ROIs.

A MANOVA was conducted to test for group differences in degree between younger and older adults. The overall MANOVA was not significant,  $F(16, 21) = .24, p = .99$ , Pillai's Trace = .15, partial  $\eta^2 = .15$ , suggesting no significant differences in degree of the task-positive network in younger and older adults. There were no significant group differences in degree for any individual ROIs.

Linear regressions were run using efficiency, betweenness centrality, clustering coefficient, and degree of the task-positive network to predict functional activation during the PWI task in the categorical and phonological ROIs. Efficiency, betweenness centrality, clustering coefficient, and degree did not predict functional activation in either the categorical or phonological ROI.

### **Task-Negative Network**

An Independent Samples *t*-test was done to test for group differences in efficiency of the task-negative network. Results indicated that there were no significant group differences in task-negative network efficiency between younger and older adults,  $t(36) = 1.99, p = .054$ , 95% CI [-0.0008, 0.08]. Efficiency significantly predicted phonological reaction time, with increased efficiency corresponding to increased reaction time,  $b = 1320.40, F(1, 36) = 4.32, p = .045$ , 95% CI [32.20, 2608.59]. Efficiency did not significantly predict accuracy for either condition or categorical reaction time.

A MANOVA was conducted to test for group differences in betweenness centrality between younger and older adults. The overall MANOVA was not significant,

$F(20, 17) = 1.42, p = .23$ , Pillai's Trace = .63, partial  $\eta^2 = .63$ , suggesting no significant differences in betweenness centrality of the task-negative network in younger and older adults. There was a significant group difference in the left LTC, with older adults having higher betweenness centrality ( $M = 23.33$ ) compared to younger adults ( $M = 12.10$ ),  $b = -11.23, F(1, 36) = 5.46, p = .025$ . The left LTC did not significantly predict accuracy or reaction time in the categorical or phonological PWI conditions.

A MANOVA was conducted to test for group differences in clustering coefficient between younger and older adults. The overall MANOVA was not significant,  $F(20, 17) = .99, p = .51$ , Pillai's Trace = .54, partial  $\eta^2 = .54$ , suggesting no significant differences in clustering coefficient of the task-negative network in younger and older adults. While the clustering coefficient for the overall network did not exhibit significant group differences, individual ROIs within the task-negative network exhibited significant group differences in clustering coefficient. There was a significant group difference in the left PHC clustering coefficient between younger and older adults, with younger adults having a higher clustering coefficient ( $M = .35$ ) than older adults ( $M = .28$ ),  $b = 0.07, F(1, 36) = 5.77, p = .022$ . There was a significant group difference in the right temporal pole clustering coefficient between younger and older adults, with younger adults having a higher clustering coefficient ( $M = .33$ ) than older adults ( $M = .26$ ),  $b = 0.07, F(1, 36) = 4.88, p = .034$ . There was also a significant group difference in the bilateral vMPFC clustering coefficient between younger and older adults, with younger adults having a higher clustering coefficient ( $M = .36$ ) than older adults ( $M = .30$ ),  $b = 0.06, F(1, 36) = 4.41, p = .043$ . The left PHC, right temporal pole, and bilateral vMPFC did not significantly predict accuracy or reaction time in the categorical or phonological PWI conditions.

A MANOVA was conducted to test for group differences in degree between younger and older adults. The overall MANOVA was not significant,  $F(20, 17) = 1.65, p = .15$ , Pillai's Trace = .66, partial  $\eta^2 = .66$ , suggesting no significant differences in degree of the task-negative network in younger and older adults. While the degree for the overall network did not exhibit significant group differences, individual ROIs within the

task-negative network exhibited significant group differences in degree between younger and older adults (see table 6). In all ROIs where group differences existed, younger adults had higher degree, on average, than older adults did. Linear regressions were run to determine which ROIs exhibiting group differences predicted accuracy and reaction time on the phonological and categorical conditions of the PWI task. Left hippocampal formation degree significantly predicted phonological accuracy,  $b = 0.007$ ,  $r = .34$ ,  $F(1, 36) = 4.75$ ,  $p = .036$ . As left hippocampal formation degree increased, so did accuracy on the phonological condition. Left PHC degree significantly predicted phonological reaction time,  $b = 20.13$ ,  $r = .35$ ,  $F(1, 36) = 4.89$ ,  $p = .033$ . As left PHC degree increased, so did phonological reaction time. Right retrosplenial cortex degree significantly predicted categorical reaction time,  $b = 23.58$ ,  $r = .33$ ,  $F(1, 36) = 4.33$ ,  $p = .045$ ; and phonological reaction time,  $b = 23.65$ ,  $r = .37$ ,  $F(1, 36) = 5.70$ ,  $p = .022$ . As right retrosplenial cortex degree increased, so did categorical reaction time and phonological reaction time. Left aMPFC degree significantly predicted categorical reaction time,  $b = 30.80$ ,  $r = .38$ ,  $F(1, 36) = 5.94$ ,  $p = .020$ ; and phonological reaction time,  $b = 31.90$ ,  $r = .44$ ,  $F(1, 36) = 8.55$ ,  $p = .006$ . As left aMPFC degree increased, so did categorical reaction time and phonological reaction time.

Linear regressions were run using efficiency, betweenness centrality, clustering coefficient, and degree of the task-negative network to predict functional activation during the PWI task in the categorical and phonological ROIs. Efficiency, betweenness centrality, clustering coefficient, and degree did not predict functional activation in either the categorical or phonological ROI.

**Table 6. Task-Negative Network Age Differences**

ROI	$\beta$	F	M		p
			Younger	Older	
Left aMPFC*	2.35	4.82	12.85	10.50	.035
Right aMPFC	1.10	.70	12.10	11.00	.41
Left PCC	2.12	4.08	14.40	12.28	.051
Right PCC	0.76	0.63	14.20	13.44	.43
dMPFC*	3.42	5.64	12.75	9.33	.02
Left TPJ	2.26	3.36	12.15	9.89	.08
Right TPJ	0.62	0.22	11.95	11.33	.64
Left LTC	1.54	1.40	12.60	11.06	.24
Right LTC	-0.59	0.16	9.85	10.44	.69
Left TempP*	3.67	6.17	10.50	6.83	.02
Right TempP*	3.93	7.39	11.15	7.22	.01
vMPFC	1.83	1.64	12.50	10.67	.21
Left pIPL	1.08	.60	13.30	12.22	.44
Right pIPL	-0.86	0.31	10.20	11.06	.58
Left RSC	2.36	3.91	13.25	10.89	.056
Right RSC*	2.93	5.96	13.10	10.17	.02
Left PHC*	2.97	4.94	12.25	9.28	.03
Right PHC	2.45	2.94	10.95	8.50	.10
Left HF*	3.89	7.59	8.45	4.56	.009
Right HF	1.11	0.42	7.00	5.89	.52

\*Scores for which there is a significant age difference,  $p < .05$

### Correction for Multiple Comparisons

Due to the number of comparisons made using regressions, conducted across the three networks, a Bonferroni correction was employed to correct for the possible number of false inferences made. After Bonferroni correcting for the age differences and predictions calculated using linear regressions, all results across the language network, task-positive network, and task-negative network become null.

### **Visual Control Analysis**

An independent samples t-test on the two visual cortex regions corresponding to area V2 indicated there were no significant differences in resting state functional connectivity between these two regions in younger ( $M = .61$ ) and older ( $M = .59$ ) adults,  $t(36) = .24, p = .81, 95\% \text{ CI } [-.12, .15]$ . Furthermore, resting state functional connectivity in the visual control regions did not significantly predict phonological or categorical reaction time or accuracy performance during the PWI task. Visual cortex regions' resting state functional connectivity did not predict phonological or categorical task-based functional activation.

## Chapter 4

### Discussion

This study aimed to examine resting state functional connectivity in the language network, task-positive network, and task-negative network (i.e., DMN) in younger and older adults using graph theoretical measures to determine the extent to which RSFC predicted accuracy and reaction time on the PWI task, as well as functional activation during the task. We expected to observe group differences in RSFC and network measures in all three networks. Additionally, we hypothesized that group differences in accuracy performance in the PWI task would be explained primarily by language network differences and task-positive network differences but not by task-negative network differences. Note that all of the following results that are discussed become null after correcting for multiple comparisons.

Overall, we found that the language network remained intact with age. Results indicated that there were no group differences in global efficiency between younger and older adults but that global efficiency predicted reaction time for both conditions. Considering there were no group differences in reaction time for either condition and if I were to speculate, this suggests that the older adults' global efficiency was maintained, namely the pairs of nodes within the language network were able to easily communicate with each other, resulting in preserved reaction time performance that was on par with younger adults. This same pattern of results was observed in the task-positive network and task-negative network as well, suggesting that overall, older adults had preserved functional integration and ease of communication between brain regions in all three networks that was similar to the younger adults' networks.

Younger adults had higher clustering coefficient in the right aMTG, pMTG, and STG, as well as higher degree in the left pMTG and left STG. However, these group differences were not predictive of accuracy performance as expected. The higher clustering coefficient in the right STG, which was observed in younger adults, predicted increased phonological reaction time. This finding was unexpected because consistent

with the neural theories of aging and our hypotheses, we predicted that the older adults would experience increased right hemisphere RSFC that would benefit their performance and that younger adults would demonstrate typical left-hemisphere lateralization, with very little right hemisphere connectivity. However, in younger adults, having increased clustering coefficient in the right STG predicted worse performance. This supports the notion that the younger adults in this study had less functional segregation in their language network than what is typically observed. This means that the younger adults' brains were less able to process highly specialized language functions in their left hemisphere because the right STG neighbored other nodes in the network, resulting in worse reaction times.

The higher degree in the left pMTG and left STG predicted worse reaction times in the phonological condition. This highlights that higher degree does not necessarily equal better performance. A region having a higher degree means that it is connected to more regions within the network. However, it is possible that a region in a network should not have a high degree if it is typically a non-essential region for performing a particular function. Because higher degree in the left pMTG and left STG predicted worse performance, these regions likely should not be as connected within the network for optimal performance. Due to the younger adults having higher degree in these regions compared to the older adults, and since there were no group differences in reaction times for either condition, it is possible that the sample of younger adults did not have highly functionally segregated networks, resulting in worse behavioral performance. They also may be experiencing more cross-talk with other regions that are non-essential or are in other networks. This pattern of connectivity is often expected in older adults; however, it is important to examine if the younger adults are also experiencing more cross-talk, which could explain their poorer performance. Future analyses will examine this. The implications of network cross-talk are outlined below.

There were no significant group differences in the task-positive network. This finding was unexpected because while prior research suggests that the language network may remain intact with age, the differences in language production behavior in younger

and older adults is likely due to the demand of the task (Davis et al., 2014; Shafto & Tyler, 2014). Older adults were expected to perform worse due to increased task demands. Therefore, we expected to see more differences in the task-positive network during resting state compared to the task-negative network, and for this to predict age differences in accuracy on the PWI task. We expected to observe decreased global efficiency, lower clustering coefficient, suggesting less network integration, as well as lower degree or differences in betweenness centrality. However, there were no significant group differences in the graph theory network measures for RSFC between younger and older adults' task-positive networks.

The group differences observed in the DMN were not unexpected as numerous studies report declines in this network in older adults. However, we did not expect these differences to predict behavioral performance on the PWI task. Left hippocampal formation degree was higher in younger adults than in older adults, and as degree increased, so did phonological accuracy performance. This same result was also observed in the left dMPFC. Additionally, right retrosplenial cortex degree was higher in younger adults and significantly predicted categorical accuracy, with higher degree corresponding to increased accuracy. The graph theory measures did not significantly predict functional activation in the categorical and phonological conditions for all three networks.

We also hypothesized that older adults would exhibit increased functional activation in prefrontal regions, as well as increased right hemisphere activation as a function of task demand, consistent with the neural theories of aging, HAROLD and CRUNCH. However, this was not observed in any networks and in the language network, three right hemisphere nodes had higher clustering coefficient in younger adults, suggesting that these nodes in younger adults' were more integrated than in older adults.

However, when considering all of these results together across networks, it is important to note that after Bonferroni correcting, these results are null and are likely due to type I error.



## Limitations

When considering the current analysis methods employed for this study, several limitations must be discussed. The sample included only 38 participants and as a result, is likely underpowered. With an underpowered sample, the possibility of type 2 error increases, resulting in not detecting effects that exist. Therefore, it is possible that some effects relating to group differences in the three resting state networks exist and are relatively small and will need a larger sample to detect significant group differences. Since each ROI in the three networks were used as predictors, a larger sample needs to be collected to overcome the power issue in future studies.

We were also limited in our ability to fully test the dedifferentiation hypothesis, where overactivation in older adults is a result of less specialized and efficient (i.e., less integrated) networks leading to worse task performance (Li & Lindenberger, 1999). This is because the current analysis approach looked within the three networks but did not look across networks. It is also possible that older adults are engaging in a wider network to perform the language task; however, if those regions were not included in the pre-determined networks then this would not be detected.

Another limitation relates to missing data. During network definition, edges were defined as greater than or equal to a correlation value of 0.2. Therefore, all edges below this threshold were zeroed and were not included in subsequent graph theory analyses. As a result of this, each participant has a certain number of missing cell values in their correlation matrices in all three networks. Also considering that with fewer nodes, graph theory measures become less reliable, it is possible that these missing values contributed to the null results. Therefore, it is possible that with a different threshold value, the results of this study would change. To explore this possibility, the same analyses as described above in the methods section were conducted with a threshold of  $r = .1$ . To compare the average number of missing values per network across younger and older adults and across threshold values, please see Appendix A. To summarize, there were no significant differences in the number of missing cell values in younger and older adults for all networks except the task-negative network thresholded at  $r = .2$ . In this network,

older adults had significantly more missing values than younger adults. Looking between threshold values, there was a significant difference in the number of missing cell values depending on whether the network was thresholded at  $r = .1$  or  $r = .2$  for all three networks. In all three cases, there were more missing values for the network thresholded at  $r = .2$ . Although  $r = .1$  is not a standard threshold value in the field, this speaks to the larger issue currently present in network science — that there is a lack of agreement on appropriate threshold practices. Decisions made by researchers regarding threshold values and edge definition can influence the results. To view the results of this exploratory analysis, please see Appendix B. All results discussed below are from the exploratory analysis with the lowered threshold value.

With the lowered threshold value, the results for betweenness centrality in the language network were approaching significance and with a larger sample, could become significant. Concerning the language network, the three individual nodes that showed significant group differences included the left aMTG, the right aMTG, and the right STG. In all three nodes, older adults had higher betweenness centrality than younger adults. This suggests that in older adults, these nodes are more essential to the network structure and serve as hubs compared to the language networks of younger adults. Additionally, two of the nodes were in the right hemisphere suggesting overactivation in the right hemisphere in these nodes in older adults compared to younger adults that may have served as a compensatory mechanism. However, none of these nodes significantly predicted accuracy or reaction time performance.

While many of the results did not change after lowering the threshold, likely due to an underpowered sample, the overall MANOVA for betweenness centrality of the task-negative network was significant and significantly predicted reaction time for both conditions. For both conditions, the right hippocampal formation and right posterior cingulate cortex, when controlling for other nodes, drove this effect. Younger adults showed higher betweenness centrality in both regions, though these group differences were not significant, and as betweenness centrality increased, reaction times decreased. This suggests that differences exist in which nodes are most essential in the network for

younger and older adults and that changes to the underlying network structure observed during resting state are predictive of behavioral performance. Additionally, it is possible that these differences in younger and older adults' betweenness centrality in the default mode network during resting state relate to older adults' increased difficulty in disengaging the DMN during task and effect task performance.

We did not expect the degree of numerous regions in the DMN to predict accuracy and reaction time performance due to the DMN disengaging during task. After conducting the exploratory analysis with the lowered threshold, there is some evidence to suggest that the older adults were not successfully disengaging the default mode network during task (discussed above), suggesting possible neural dedifferentiation; however, there is also evidence that younger adults were also not disengaging the DMN during task. In addition to the differences found in betweenness centrality in the DMN after lowering the threshold, we found that younger adults had higher degree in the left PHC, which predicted worse phonological reaction time; higher degree in the right RSC, which predicted worse categorical and phonological reaction times; and higher degree in the left aMPFC, which predicted worse categorical and phonological reaction times. This suggests that the younger adults were not fully disengaging the default mode network. Relatedly, results in the language network showed increased right hemisphere RSFC in younger adults, possibly suggesting that the young adults did not have highly segregated networks and experienced cross-talk across networks, which is what is hypothesized to be occurring within the older adults. This similarity in network structure and possible cross-talk may explain why very few group differences were observed.

It is also possible that the younger adults were not as engaged in the task. While DMN activity is expected during resting state, we did not hypothesize RSFC in this network to predict behavior. However, the younger adults may not have been fully attending to the task; thus, allowing their minds to wander and keeping the DMN online during task performance. The fact that higher degree again predicted worse performance, this time in regions in the DMN, highlights the notion that higher degree does not always equate to better performance. It results in different underlying network structures,

increases the average shortest path length, makes the network less integrated and less efficient, and may not lead to optimal performance.

The analyses using RSFC to predict functional activation during task were also impacted by lowering the threshold value for edge definition. Results in the task-positive and task-negative networks indicated that after lowering the threshold, betweenness centrality in both of these networks significantly predicted functional activation in the phonological ROI (left SMG). This demonstrates the value of resting state functional connectivity being used to predict behavior.

### **Future Directions**

Due to there being RSFC differences in younger and older adults and significant accuracy differences, there are likely age differences that were not able to be detected employing these current methods. Additionally, as demonstrated with the exploratory analysis, more group differences were detected with a lower threshold for edge definition, suggesting that another analysis method may be more suited to detect the group differences. Using an ROI analysis method, where regions are defined a priori and are the same across participants, is likely not the best approach considering the increased variability in older adults' brains (MacDonald, Nyberg, & Bäckman, 2006; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003). Therefore, it is possible that age differences were not being captured in the ROIs we defined but were located elsewhere in the brain that were predictive of accuracy performance. While this method is useful for analyzing functional connectivity data when one has specific hypotheses about the brain regions involved, as was the case in this study, a seed-based approach or a whole-brain approach will likely lead to more robust and conclusive evidence regarding group differences in RSFC and their predictive value for task performance. Using one of these two methods will also allow us to increase the number of nodes in the networks, resulting in greater reliability of the graph theory measures, as the reliability of these measures tends to decline with fewer nodes. Additionally, not defining the networks a priori with a threshold for edge definition will result in fewer missing values and a more powered sample.

Future analyses will more fully test the dedifferentiation hypothesis. There is likely more cross-talk between networks in older adults compared to younger adults, whose networks are typically more modular. By collapsing across networks and looking at all regions simultaneously, we will be able to detect the extent to which older adults' networks were less specialized. Therefore, future analyses will collapse across the three networks, which will afford us a larger network with more nodes, allowing us to increase our ability to observe variation, which is limited in smaller networks.

### **Overall Conclusion**

This study used RSFC and network analyses to compare differences in the language network, task-positive network, and task-negative network between younger and older adults and examined if differences in network structure predicted behavioral performance on a picture-word interference task. Results, while null after correcting for multiple comparisons, indicated that both younger and older adults were recruiting regions in their language networks that should not have been recruited for optimal performance, possibly explaining the lack of group differences in reaction time performance in both the phonological and categorical condition. Unexpectedly, the degree of numerous regions in the task-negative network predicted behavioral performance on the PWI task, suggesting that both younger and older adults were likely not fully disengaging their task-negative network during task. Future analyses will better test the neural dedifferentiation account by collapsing across the three networks to determine the extent to which cross-talk during resting state is occurring between the networks and how this predicts behavioral performance.

## Appendix A

### Missing Value Comparisons

Analyses were run using a threshold value of  $r = .2$ . To examine the role that threshold value had in analysis, all analyses were also run with a threshold of  $r = .1$ . This allowed for comparisons of how many cells in the correlation matrices per participant for each network had a value of zero, resulting in missing values that were not used in subsequent statistical analyses. When counting the number of zeroes in each correlation matrix, the zeroes on the diagonal were not included. Independent Samples  $t$ -Tests were run to determine if there was a significant difference in the amount of missing data in younger and older adults. Paired Samples  $t$ -Tests were run to determine if there was a significant difference in the amount of missing data depending on whether the threshold was  $r = .1$  or  $r = .2$ . Results are summarized in the tables below.

**Table 7. Missing Values Between Groups**

<b>Network</b>	<b>Group</b>	<b>Mean</b>	<b>Percent</b>	<b>Std. Deviation</b>
Language Network ( $r = .1$ )	Younger	27.00	32.14	13.32
	Older	34.50	41.07	12.15
Language Network ( $r = .2$ )	Younger	40.35	48.04	14.67
	Older	40.67	56.75	13.36
Task-Positive Network ( $r = .1$ )	Younger	20.55	18.35	13.33
	Older	17.28	15.43	14.32
Task-Positive Network ( $r = .2$ )	Younger	35.10	31.34	16.68
	Older	29.89	26.69	18.74
Task-Negative Network ( $r = .1$ )	Younger	49.00	27.22	25.60
	Older	61.22	34.01	22.86
Task-Negative Network ( $r = .2$ )*	Younger	72.25	40.14	30.74
	Older	91.72	50.96	22.70

Note. \* $p < .05$ . For the language network there were 84 possible cells that could have missing values, for the task-positive network there were 112 possible cells, and for the task-negative network there were 180 possible cells.

**Table 8. Missing Values Between Thresholds**

<b>Network</b>	<b>Threshold</b>	<b>Mean</b>	<b>Std. Deviation</b>
Language***	$r = .1$	30.55	13.14
	$r = .2$	43.82	14.36
Task-Positive***	$r = .1$	19.00	13.72
	$r = .2$	32.63	17.64
Task-Negative***	$r = .1$	54.79	24.80
	$r = .2$	81.47	28.62

\*\*\* $p < .001$

## Appendix B

### Re-analysis with Lowered Threshold

After lowering the correlation threshold from  $r = .2$  to  $r = .1$  for edge definition, the data was statistically re-analyzed to compare results using the two different threshold values. While the threshold value  $r = .1$  is a low value when defining edges via correlation and is not a field convention, this was an exploratory analysis that aimed to examine the effect that threshold definition has on the subsequent results.

### Language Network

An Independent Samples *t*-test was done to test for group differences in efficiency of the language network after lowering the threshold from  $r = .2$  to  $r = .1$ . Results indicated that there were no significant group differences in language network efficiency between younger ( $M = .32$ ) and older adults ( $M = .29$ ),  $t(36) = 1.36$ ,  $p = .18$ , 95% CI [-0.02, 0.08]. Efficiency still significantly predicted phonological reaction time, with increased efficiency corresponding to increased reaction time,  $b = 1471.46$ ,  $r = .42$ ,  $F(1, 36) = 7.55$ ,  $p = .009$ , 95% CI [385.26, 2557.66]. Efficiency also predicted categorical reaction time, with increased efficiency corresponding to increased reaction time,  $b = 1304.44$ ,  $r = .33$ ,  $F(1, 36) = 4.35$ ,  $p = .044$ , 95% CI [35.84, 2573.04]. Efficiency did not significantly predict accuracy for either condition.

The MANOVA examining the betweenness centrality for the language network was still not significant but was approaching significance with the lowered threshold,  $F(14, 23) = 1.92$ ,  $p = .08$ , Pillai's Trace = .54, partial  $\eta^2 = .54$ . With the lowered threshold, there were three individual ROIs (nodes) that demonstrated significant group differences. In the left aMTG,  $b = -7.39$ ,  $F(1, 36) = 5.37$ ,  $p = .026$ , younger adults had significantly lower betweenness centrality ( $M = 2.50$ ) than older adults ( $M = 9.89$ ). In the right aMTG,  $b = -8.74$ ,  $F(1, 36) = 4.15$ ,  $p = .049$ , younger adults had significantly lower betweenness centrality ( $M = 6.70$ ) than older adults ( $M = 15.44$ ). Lastly, in the right STG,  $b = -12.47$ ,  $F(1, 36) = 6.46$ ,  $p = .015$ , younger adults had significantly lower betweenness centrality ( $M = 4.20$ ) than older adults ( $M = 16.67$ ). These nodes did not significantly predict accuracy or reaction time on either of the task conditions.

The results did not change for the clustering coefficient of the language network after lowering the threshold. The overall MANOVA was still not significant  $F(14, 23) = 1.15, p = .37$ , Pillai's Trace = .41, partial  $\eta^2 = .41$ . Additionally, there were still significant group differences in the right pMTG and right STG.

The MANOVA for degree of the language network was not significant  $F(14, 23) = 1.18, p = .35$ , Pillai's Trace = .42, partial  $\eta^2 = .42$ . Additionally, there were still significant group differences in the left pMTG and left STG after lowering the threshold.

Linear regressions were run using efficiency, betweenness centrality, clustering coefficient, and degree of the language network after lowering the threshold to predict functional activation during the PWI task in the categorical and phonological ROIs. Efficiency, betweenness centrality, clustering coefficient, and degree did not predict functional activation in either the categorical or phonological ROI.

### **Task-Positive Network**

With the lowered threshold value for edge definition, there was still no significant group difference in task-positive network efficiency after running an independent samples  $t$ -test,  $t(36) = -.21, p = .83$ , 95% CI [-.06, .05]. Efficiency still significantly predicted phonological reaction time, with increased efficiency corresponding to increased reaction time,  $b = 1066.88, r = .34, F(1, 36) = 4.73, p = .04$ , 95% CI [72.04, 2061.71]. Efficiency did not significantly predict categorical reaction time or accuracy for either condition.

The overall MANOVA for betweenness centrality was still not significant after lowering the threshold,  $F(16, 21) = 0.90, p = .58$ , Pillai's Trace = .41, partial  $\eta^2 = .41$ . However, with the lowered threshold there were significant group differences in the left DLPFC,  $b = 11.93, F(1, 36) = 5.00, p = .032$ . Younger adults had a higher betweenness centrality ( $M = 18.60$ ) than older adults did ( $M = 6.67$ ). The left DLPFC betweenness centrality did not predict accuracy or reaction time in either of the PWI conditions.



The overall MANOVA for clustering coefficient was still not significant after lowering the threshold,  $F(16, 21) = 0.78, p = .69$ , Pillai's Trace = .37, partial  $\eta^2 = .37$ . There were no group differences in clustering coefficient for any individual nodes.

The overall MANOVA for degree was not significant after lowering the threshold,  $F(16, 21) = 0.70, p = .76$ , Pillai's Trace = .35, partial  $\eta^2 = .35$ . There were no group differences in degree for any individual nodes.

Linear regressions were run using efficiency, betweenness centrality, clustering coefficient, and degree of the task-positive network after lowering the threshold to predict functional activation during the PWI task in the categorical and phonological ROIs. Betweenness centrality in the task-positive network significantly predicted maximum functional activation in the phonological ROI (left SMG),  $F(16, 21) = 2.72, p = .02$ . This effect was driven by the left frontal eye field, the right insula/frontal operculum, and the right middle temporal region when controlling for all other nodes. As the betweenness centrality for the left frontal eye field and right insula/frontal operculum increased, so did functional activation in the left SMG,  $b = 0.01, t(21) = 2.71, p = .01$ , 95% CI [.002, 0.018], and  $b = 0.007, t(21) = 4.25, p < .001$ , 95% CI [.004, 0.11], respectively. As betweenness centrality in the right middle temporal region increased, functional activation in the left SMG decreased,  $b = -0.008, t(21) = -2.29, p = .03$ , 95% CI [-.015, -.001]. Betweenness centrality did not significantly predict functional activation in the categorical ROI (left IFG). Efficiency, clustering coefficient, and degree did not predict functional activation in either the categorical or phonological ROI.

### **Task-Negative Network**

Using the lowered threshold of  $r = .1$  and analyzing the task-negative network, there was still no group difference in network efficiency,  $t(36) = 1.90, p = .07$ , 95% CI [-.003, .08]. Efficiency still significantly predicted phonological reaction time, with increased efficiency corresponding to increased reaction time,  $b = 1493.04, r = .36, F(1, 36) = 5.51, p = .03$ , 95% CI [202.56, 2783.50]. Efficiency did not significantly predict categorical reaction time or accuracy for either condition.

Examining betweenness centrality, the MANOVA conducted to test for group differences between younger and older adults was significant with the new threshold,  $F(20, 17) = 3.60, p = .005$ , Pillai's Trace = .81, partial  $\eta^2 = .81$ . This suggests that there are significant differences in which nodes are most essential to the DMN in younger and older adults. Additionally, examining how this predicts behavior, the betweenness centrality for all of the nodes in the DMN significantly predicted categorical reaction time,  $F(1, 17) = 2.60, p = .026$ . This effect was driven by the right hippocampal formation and the right PCC when controlling for all other nodes. As the betweenness centrality for each of these nodes increased, categorical reaction time decreased. In the right hippocampal formation,  $b = -8.49, t(17) = -3.51, p = .003, 95\% \text{ CI} [-13.59, -3.39]$ , younger adults had higher betweenness centrality ( $M = 19.6$ ) than older adults ( $M = 12.44$ ), though this was not a significant group difference. In the right PCC,  $b = -11.82, t(17) = -2.27, p = .037, 95\% \text{ CI} [-22.81, -0.83]$ , younger adults had higher betweenness centrality ( $M = 9.20$ ) than older adults ( $M = 6.11$ ); however, this difference was not significant. Betweenness centrality for all nodes in the DMN also predicted phonological reaction time,  $F(1, 17) = 2.60, p = .026$ . This effect was driven by the right hippocampal formation,  $b = -7.17, t(17) = -3.33, p = .004, 95\% \text{ CI} [-11.71, -2.63]$ , and the right PCC,  $b = -13.89, t(17) = -3.00, p = .008, 95\% \text{ CI} [-23.68, -4.11]$ , when controlling for the other nodes. As the betweenness centrality for each of these nodes increased, phonological reaction time decreased.

When examining the clustering coefficient of the overall network, the MANOVA was not significant,  $F(20, 17) = 1.87, p = .10$ , Pillai's Trace = .69, partial  $\eta^2 = .69$ . This suggests there were no significant differences in clustering coefficient of the DMN between younger and older adults.

When examining the degree of the DMN, the overall MANOVA was not significant with the lowered threshold,  $F(20, 17) = 1.60, p = .17$ , Pillai's Trace = .65, partial  $\eta^2 = .65$ , suggesting there were no significant group differences in the overall degree values of the network for younger and older adults.

Linear regressions were run using efficiency, betweenness centrality, clustering coefficient, and degree of the task-negative network after lowering the threshold to predict functional activation during the PWI task in the categorical and phonological ROIs. Betweenness centrality in the task-negative network significantly predicted maximum functional activation in the phonological ROI (left SMG),  $F(20, 17) = 3.28, p = .008$ . This effect was driven by the right posterior inferior parietal lobule (pIPL) and the left temporal pole, when controlling for all other nodes. As the betweenness centrality for the right pIPL and left temporal pole increased, so did functional activation in the left SMG,  $b = 0.015, t(17) = 4.25, p = .001, 95\% \text{ CI } [.008, 0.022]$ , and  $b = 0.012, t(17) = 4.77, p < .001, 95\% \text{ CI } [.007, 0.017]$ , respectively. Betweenness centrality did not significantly predict functional activation in the categorical ROI (left IFG). Efficiency, clustering coefficient, and degree did not predict functional activation in either the categorical or phonological ROI.

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