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Task Residual Functional Connectivity in Language and Attention Networks

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TASK RESIDUAL FUNCTIONAL CONNECTIVITY IN LANGUAGE AND ATTENTION NETWORKS

by

STELLA TRAN

Under the Direction of Bruce Crosson, PhD

ABSTRACT

The present study compared network specificity between task-residual and resting state data types. Task-residual data capitalizes on the remaining variance after the mean task-related signal is removed from the time series. This study also examined how inter- and intrahemispheric connectivity (bilateral homologous regions and regions contained within the same hemisphere, respectively) within the language and attention networks change as a result of age. Task-residual functional connectivity evidenced stronger laterality of the language and attention connections and thus greater network specificity than resting state functional connectivity of the same connections. Using task-residual data may be optimal for characterizing the synchronized fluctuations between regions of discrete networks. Furthermore, alterations in intrahemispheric functional connectivity can be observed as early as middle age within the domain-general attention domain.

INDEX WORDS: Functional connectivity, Task residual, Resting state, Aging, Language, Attention

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STELLA TRAN

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DEDICATION

This work is dedicated to my parents and family.

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1   INTRODUCTION

1.1   Purpose of the Study

Functional magnetic resonance imaging (fMRI) techniques enable researchers to examine task-induced activity, as well as endogenous functional relationships between remote brain regions. In the absence of a specific task, low frequency blood oxygen level dependent (BOLD) fluctuations are presumed to represent "spontaneous" neural activity (Fox et al., 2006b). The temporal correlations of BOLD fluctuations between brain regions provide an estimate of functional connectivity (Biswal, 1995). Functional connectivity is thus characterized by the synchronized fluctuations that are interdependent within functionally related neural systems, or intrinsic functionally connected networks (ICNs) (Biswal et al., 2010). Various ICNs have emerged from functional connectivity MRI (fcMRI) studies and typically comprise regions that coactivate during engagement of a specific cognitive domain, including somatosensory, visual, auditory, attention, and language networks (reviewed in Lee et al., 2012). The degree to which constituent regions within an ICN show synchronized activity may serve as a measure of network integrity in healthy, typically developing individuals, as well as individuals with various neurocognitive pathology (Buckner et al., 2009; Pravàta et al., 2011; Jones et al., 2011).

Altered functional connectivity between components of ICNs in healthy older adults have offered insight into the different patterns of performance and task-related brain activation in older, as compared to younger adults (Antonenko et al., 2013; Geerlings et al., 2014; Chen et al., 2009). Several authors have reported that reduced functional connectivity in older adults is associated with reduced structural connectivity, changes in task-related signal, and poor performance (Chou et al., 2013). One study reported that individual differences in functional connectivity between subregions of orbitofrontal cortex accounted for 87% of the variance in

perceptual-motor speed (as measured by reaction time) in older adults: older adults with stronger functional connectivity had faster reaction times that those with weaker functional connectivity (Chen et al., 2009). These findings suggest that functional connectivity analyses are behaviorally relevant and well suited to capture age-related changes in neural mechanisms.

The goal of the current study is to determine how functional connectivity within language and attention networks are affected by age. Various methods exist to examine functional connectivity, including resting-state, task-related, and task-residual fMRI. Each of these methods can provide an index of the functional architecture and interdependence of brain regions. However, as explained in the following section, task-residuals may offer more specific information about a network than resting state data because they highlight time-variant effects of the task and de-emphasize irrelevant exogenous neural activity. For this reason, the current study will apply the task-residual method to analyze fcMRI data from a study of younger adults and middle aged adults. Prior to a discussion of the relevance of functional connectivity to aging, it is necessary to first review the unique advantages of task-residuals over resting state data analysis.

1.2   Resting State Versus Task Related Analysis

The dominant method in functional connectivity studies examines data collected while subjects are at "rest," or not engaging in an explicit cognitive task (Greicius et al., 2009). Resting state fcMRI studies aim to capture phasic fluctuations in tonic brain activity, or more specifically, intrinsic functional connectivity networks (ICNs) that are not contaminated by the effects of specific cognitive engagement of a task. Importantly, ICNs appear to be stable across data sets, participants, and scanners (Sadaghiani et al., 2010; Biswal et al., 2010). However, there is evidence that task engagement prior to a resting state scan can induce variation in correlations between networks, suggesting that functional connectivity results using resting state data may

not be consistent because antecedent mental states and cognitive tasks can introduce systematic changes in measures of connectivity (Stevens, 2010; Grigg & Grady, 2010; Waites et al., 2005). In addition, it is difficult to control cognitive and mental states of participants during resting scans, which may influence results in unpredictable ways (Stark & Squire, 2001; Binder et al., 1999; Arfanakis et al., 2000).

Alternatively, task-residual connectivity analysis offers potential solutions to the complications of resting state functional connectivity. In task-residual connectivity analysis, the effects of an active block or event-related task are regressed out of fMRI time series and the resultative residual time series is used in a covariance matrix (Fair et al., 2007; Andrews-Hanna et al., 2007; Zhang & Ray Li, 2010; Fornito et al., 2012). In BOLD activation studies, residuals are typically considered error variance when calculating the mean task-evoked signal. However, such residuals have been shown to account for behavioral differences (Al-Aidroos et al., 2012). Additionally, areas that are functionally related still show covariation of metabolic activity in the residual data (Davies-Thompson & Andrews, 2012). It has been demonstrated that BOLD fluctuations during a task contain task-related signal in addition to underlying endogenous neural activity, whereby both signals contribute to variability between trials (Fox et al., 2006b). Fox et al. (2006b) proposed that task evoked activity is linearly superimposed on spontaneous neural fluctuations observed during typical resting state scans. Based on this assumption, removing tasked evoked activity from the BOLD signal should theoretically preserve spontaneous neural fluctuations with some degree of equivalency to resting state.

Although some authors have interpreted the remaining endogenous neural activity in task-residual data and resting-state data as analogous (Uddin et al., 2008; Zhang & Li, 2010), there is evidence to suggest that these two approaches are not interchangeable (Rogers & Gore,

2008; Fair et al., 2007; Norman-Haignere et al., 2011). For example, although the mean effects of the task are regressed out, block-by-block variability (or trial-by-trial variability for event-related designs) relevant to the task remain in the error signal. Rogers and Gore (2008) concluded that task-residuals show neural fluctuations associated with the task context, and therefore do not yield identical results as the resting state method. Fair et al. (2007) proposed that correlations that were significant for task-residual data but not resting state could be attributed to time-variant effects of the task contained in the residuals. Chou et al. (2013) found that the linear association between reaction time and task-residual functional connectivity varied as a function of task demand, suggesting that functional connectivity in the residuals was altered by task condition. If task-residuals reflected only spontaneous neural fluctuations independent of the task effects, one would expect the relationship between reaction time and functional connectivity to be consistent across manipulations of the same task. However, the variation in functional connectivity due to manipulation of a task property suggests underlying task effects are present in the residuals. Similarly, another study in which participants were cued to press a button found that trial-by-trial variability in functional connectivity accounted for the force of button presses (Fox et al., 2007). Both studies provide evidence that residual data may be task-specific and not solely comprised of task-unrelated spontaneous fluctuations. The block-by-block variability may encompass the coordinated activity of brain regions involved in a given task that are not consistently represented in the hemodynamic response (HDR) function, such as variation in task difficulty between individual items or blocks. As items differ subtly in the neural demands they elicit, interregional components of the functional network that cooperate to support those demands may show covarying fluctuations. As a result, the specificity of variation may not be captured in the task signal but instead may accumulate in the residuals.

Several authors have capitalized on this unique quality of residual data to draw conclusions about network connectivity as a function of task condition (Davies-Thompson & Andrews, 2012; Al-Aidroos et al., 2012; Norman-Haignere et al., 2011). Al-Aidroos et al. (2012) reported that connectivity between occipital areas and ventral temporal areas varied in strength depending on whether the area was relevant to the stimuli: attending to faces strengthened the connectivity between occipital areas and the fusiform face area (FFA) but not between occipital areas and the parahippocampal place area (PPA), whereas attending to scenes strengthened the connectivity between occipital areas and the PPA but not between the occipital areas and the FFA. This pattern was observed even in cases where the task elicited robust responses from task-irrelevant areas (e.g., PPA during face attention). These findings suggest that task-residuals are sensitive to the functional interactions between regions as opposed to regions that are evoked in response to a stimulus but do not interact.

It has also been shown that when systems are entrained in a task, other systems remit in their signal (Lowe et al., 2000; Hampson et al., 2004). This suggests that spontaneous neural fluctuations found in task-residual data may be relatively reduced compared to resting state data. Thus, residuals may offer more specific information about connections within a network than resting state data because residuals highlight time-invariant effects of the task and de-emphasize irrelevant exogenous neural activity. Although resting state analyses may be the preferred method for functional interactions that are unrelated to a specific cognitive state, task-residual analyses may be more sensitive to functional interactions of specific network connections than resting state data. For these reasons, functional connectivity analyses with task-residual data may be well suited to distinguish brain areas that coactivate and are highly related versus brain areas that coactivate but are less related.

In research on aging, identification of specific task-related network connections can be used to address ongoing debates about the functional significance of changes in connectivity among older adults. It is well established that older adults show increased bilateral activation during tasks that elicit unilateral (either left- or right-dominant) activation in younger adults (Cabeza, 2002). What remains unclear is whether bilateral activation is compensatory or competing. The present study uses task-residual-based analyses to explore this question. In particular, it aims to interrogate whether functional changes in aging are due to a reduction in network integrity or compensatory mechanisms within language and attention connections.

1.3   Language and Attention Networks

The areas relevant to the language networks has been relatively well defined in the literature (Binder et al., 2009; Goldberg 1985, Picard & Strick, 2001). Conversely, attentional systems are relatively less well defined and will be discussed at greater length. The language network will refer to functional connectivity between areas related to semantic processing, as this cognitive domain is most relevant to the category-member generation task in which the participants engaged. Specifically, the language network will comprise the inferior frontal gyrus and posterior perisylvian area (Zlatar et al., 2013).

The proposed study also aims to examine the executive control attention network. Attention can be used to describe multiple, related cognitive processes, many of which involve conscious awareness, including processing information from external and internal stimuli, and across cognitive domains (Fuster, 2000; Vanhaudenhuyse et al., 2010; Posner & Peterson, 1989). The default mode (or task-negative) network is one attention system of increasing interest in the neuroimaging community. The default mode network (DMN) is a term used to describe areas that show negative BOLD signal during engagement in explicit tasks (Greicius et al., 2003).

Conversely, many of the same areas show positive BOLD signal during resting state scans. It is believed that the deactivation of these areas during goal-oriented activity and their pronounced activity during wakeful rest reflects internally guided thought processes, such as autobiographical memory, future projection, and self-referential cognition. This has also been identified as the task-negative network, and observed to be anticorrelated to the task-positive network, which is expressed as positive BOLD signal during goal-oriented states (Fox et al., 2005; Vanhaudenhuyse et al., 2010).

Many of the constituent regions of the task-positive and task-negative networks are shared with regions of what has been described as anterior intention and posterior attention regions, respectively. Intention is characterized by the selection of an action among many potential actions and engagement of regions that are required to initiate the selected action (Crosson et al., 2008). In contrast, attentional processes engage sensory cortices to focus on a stimulus among many competing stimuli. It has been suggested that frontal regions are involved in the intention process, which can serve to engage motor and cognitive systems in anterior regions and as well as to ready attention systems in posterior sensory areas (Nadeau & Crosson, 1997). The regions selected are brought into a heightened state of entrainment while other irrelevant regions maintain their tonic, relatively disengaged state. Nadeau and Crosson (1997) described this mechanism as intentionally guided attention, qualifying the directional flow of influence from anterior regions associated with intention to posterior regions associated with attention for the following reason. The internal selection of an action dictates the external stimuli to which an individual must attend to effectively perform the action. The mechanism of intention involves a top-down process that functions to engage goal-directed systems in preparation for the

execution of an action or response as well as to prime sensory cortices (Corbetta & Shulman, 2002).

Broadly speaking, brain systems of intention and attention can be compartmentalized into anterior regions responsible for response and response preparation and posterior regions responsible for sensation and perception, respectively. In general, the nature of the anterior intention system and the posterior attention system is such that when one system is engaged, the other becomes disengaged (Posner & Petersen, 1989). A similar interacting system has been described based on resting state functional connectivity (Fox et al., 2005, 2006). Fox et al. (2006) described a network of frontal dorsal regions associated with top-down processes and task engagement that include the pre-supplementary and supplementary motor areas. The researchers also described a network of relatively posterior and ventral regions that were modulated by changes in sensory stimuli that include the temporal-parietal junction. The opposing relationship between goal-oriented task-positive and attentional task-negative systems is reflected by negative correlation (Fox et al., 2006), suggesting that the intention-attention network can be examined by the interface between regions in both systems. The attention system examined in the proposed study will comprise an anterior intention region and a posterior attention region. The specific regions of interest within language and attention networks will be discussed in a subsequent section. However, it is necessary at this point to discuss how language and attention are affected by age.

1.4 Age Related Changes in Task Evoked Activity

Prefrontal and medial temporal areas are especially vulnerable to alterations in the course of aging (Park & Reuter-Lorenz, 2009; Achard & Bullmore, 2007). Older and younger adults show differential neuronal activity during various cognitive tasks: older adults exhibit increased

bilateral prefrontal activity during cognitive tasks relative to younger adults (Cabeza, 2002; Reuter-Lorenz et al., 2000). Hemispheric Asymmetry Reduction in the Old (HAROLD), is a construct used to explain increased recruitment of cortical areas in bilateral prefrontal regions (Cabeza, 2002). For example, prefrontal areas that normally show increased activity in young adults show an enhanced response in older adults (Cabeza et al., 2004). In other tasks, prefrontal areas that normally show negative task-induced activity (i.e., decreased metabolic activity compared to baseline) in young adults show positive task-induced activity (i.e., increased metabolic activity compared to baseline) in older adults.

Differences in task-induced activity among younger and older adults are particularly evident during language and unimanual motor tasks, because the tasks tend to preferentially activate one hemisphere. When engaged in a right hand button press task, younger adults exhibit positive activity in the left primary sensorimotor cortex (contralateral to the active hand) and task-negative activity the right primary sensorimotor cortex (ipsilateral to the active hand) (McGregor et al., 2009). During the same task, older adults exhibit positive activity in the left primary sensorimotor cortex consistent with younger adults, but exhibit positive activity in the right primary sensorimotor cortex, the area that was negative in younger adults. Similar findings have been reported in language system. During a semantic fluency task, older adults showed more pronounced positive activity in the non-dominant right hemisphere compared to younger adults, including areas where younger adults displayed task-negative activity (Meinzer et al., 2012; Wierenga et al., 2008). These findings demonstrate prefrontal interhemispheric interactions in which areas of the contralateral hemisphere that are typically suppressed for young adults (i.e., show negative activity) show increased positive activity for older adults.

Profuse neural recruitment and reduced neural suppression may reflect a dedifferentiation of brain activity, where older adults show more diffuse neural representations than younger adults in response to a task. That is, the specialized and distinctive neural response observed in younger adults may be diminished in older adults, who instead show an overflow of activity beyond regions typically necessitated for the task (Park, 2004; Goh, 2011). A decrease in neural distinctiveness in posterior regions has also been observed (Park et al., 2004; Haan et al., 2002). Further research has also found that older adults show a shift in activity from posterior regions to anterior regions relative to younger adults (Davis et al., 2008). Together these findings suggest that aging is associated with alterations of long-range interactions between and within functional networks.

Age-related changes in functional activity have propagated a line of inquiry to elucidate the function of dedifferentiation in older adults (Sleimen-Malkoun, Temprado, & Long, 2014). This research has generated two primary hypotheses, namely, that the increased activation in aging is compensatory or deleterious. Studies in which recruitment of regions outside of typically activated regions of a network is beneficial to performance have led some authors to postulate that this activation pattern serves a compensatory role (Wingfield & Grossman, 2006; Goh et al., 2010; Burianová et al., 2013; Cabeza, 2002). Differentiation in neurodevelopmental literature states that neural structures adopt increasingly distinct cognitive functions during infancy and child development (Haan et al., 2002). During aging, this process is theorized to be reversed where neural structures become increasingly broad in their jurisdiction of cognitive functions (Park et al., 2004). There is evidence to suggest that the recruitment of additional regions (e.g., increased bilaterality) represents a reorganization of cognitive functioning to maintain equivalent performance to that of younger adults (Davis et al., 2012).

Alternatively, other researchers have suggested that the reduced distinctiveness of neural function reflects inefficient engagement of irrelevant brain regions (Logan et al., 2002; Meinzer et al., 2012; Cherry et al., 2010, Gazzaley et al, 2005). According to this view, the underlying structural and functional changes associated with aging reflect a disintegration of network coherence, resulting in inefficient processes or reduced signal-to-noise that are detrimental to performance (Sleimen-Malkoun, Temprado, & Long, 2014; Li, Lindenberger, & Sikstrom, 2001).

Confronted with a corpus of literature suggesting two opposing processes, it is important to consider alternative hypotheses. One possibility is that age-related changes in activation do not have direct behavioral relevance. That is, increased bilateral activation may be a result of other cognitions that do not contribute to or detract from performance on a task. Indeed, some authors have reported age-related functional changes that do not appear to have behavioral significance as evidenced by cognitive performance (Hedden et al., 2009; Zlatar et al., 2013). However, it has been suggested that functional network changes may need to reach a certain threshold before assessments and tasks can detect cognitive decline. It is also worth considering that the expression of both models may occur under different contexts (Cabeza et al., 2004). For instance, increased activation is compensatory in some cognitive domains or network regions but deleterious in others. To that end, research examining the mechanisms of age-related changes among various functional networks is informative.

In a study of the motor network, Riecker et al. (2006) found that older adults did not modulate additional ipsilateral activation in response to increasing motor task difficulty, providing conflicting evidence to the compensatory mechanism. The notion of compensatory function in aging was derived primarily from studies investigating prefrontal activity during

cognitive tasks. Yet some authors have reported an association between reduced performance during cognitive tasks and activation of nondominant hemisphere regions (Meinzer et al., 2012; Rajah & McIntosh, 2008). In an analysis of low-functioning older adults, Wierenga et al. (2008) found that activation of the right inferior frontal gyrus, a region that approximately mirrors Broca's area on the left hemisphere, was associated with worse word naming accuracy. The authors hypothesize that this mechanism may reflect a release from suppression of a task-irrelevant region. An increasing number of studies have investigated similar task-irrelevant cortical suppression, known as interhemispheric inhibition, as a potential physiologic mechanism underlying age-related changes in neural connectivity.

It has been established that aging is associated with wide-ranging alterations in communication between cortical regions that involve inhibitory processes (Goh et al., 2010; Fling & Seidler, 2012). Interhemispheric inhibition is said to prevent interference of irrelevant information from the nondominant hemisphere during tasks typically lateralized to the dominant hemisphere. The presence of interhemispheric inhibition is evidenced in fMRI as negative BOLD response in the motor cortex ipsilateral to the active hand and in transcranial magnetic stimulation (TMS) as extended duration of the ipsilateral silent period (iSP) in the ipsilateral motor cortex (Kastrup et al., 2008; Giovannelli et al., 2009). Young adults typically show negative BOLD responses and longer iSPs, whereas older adults typically show positive BOLD (or less negative BOLD) responses and shorter iSPs in the ipsilateral motor cortex (Gröschel et al., 2013; McGregor et al., 2011). Reduced interhemispheric inhibition during motor tasks in older adults has been implicated as a mechanism underlying inefficient functional communication between hemispheres (Fling & Seidler, 2012).

The loss of interhemispheric inhibition in aging is not restricted to motor areas: reduced interhemispheric inhibition has been linked to reduced negative BOLD in areas of language and attention networks as well (Zlatar et al., 2013). Furthermore, the loss of interhemispheric inhibition in aging has been associated with altered structural and functional connectivity (Langan et al., 2010). Trans-callosal connections that degrade with age may affect communicatory processes between bilateral brain regions. Thus, examining the relationship between cortical regions at a systems-level via functional and structural connectivity may help to elucidate the mechanisms of dedifferentiation in older adults.

1.5   Age Related Changes in Functional Connectivity

It has been proposed that with advancing age, brain systems become anatomically "disconnected" as a result of white matter degradation (O'Sullivan et al., 2001). The degree of structural integrity of white matter tracts is measured with diffusion tensor imaging and is represented by volume and directionality of water diffusion, as water preferentially diffuses along neural pathways as opposed to across them. White matter pathways are accepted as the anatomical foundation for the transfer of information. Older adults show disproportionate disruptions of white matter integrity in anterior regions of the brain (Salat, 2011; Head et al., 2009). In addition to the *structural* basis underlying the loss of connectivity, a preponderance of evidence exists to show that *functional* communication between brain regions is compromised as well (Goh, 2011; Andrews-Hanna et al. 2007; Chou et al., 2013).

Andrews-Hanna et al. (2007) examined the structural and functional connectivity of anterior-posterior regions of the default mode network (DMN), characterized by brain areas that become active during internally directed attention. In their sample of healthy older adults, white matter integrity was compromised between anterior and posterior regions of the DMN compared

to younger adults. This structural disruption was correlated with reduced functional connectivity in the same anterior-posterior regions. Furthermore, the reduced functional connectivity was associated with poorer performance on cognitive tasks. These findings are consistent with other research demonstrating reduced functional connectivity in older adults (Chou et al., 2013). The results also suggest that relatively long-range brain systems not only lose their anatomical connection but also their functional integration with age, and this degradation can have a negative impact on cognitive performance.

One important question is whether this reduction of structural and functional connectivity with age is consistent across brain systems. In a study investigating the motor network during a unimanual motor task, decreased interhemispheric structural connectivity was associated with increased interhemispheric functional connectivity between motor cortices and poor performance in older adults (Fling et al., 2012). Their finding suggests that between hemispheres, a negative relationship exists between structural connectivity and functional connectivity such that as structural connectivity is compromised in the corpus callosum, functional connectivity displays a release from inhibition. These and other results (Geerlings et al., 2014) demonstrate that strong functional connectivity is not universally beneficial to performance. Additionally, although many areas with reduced structural connectivity in aging have shown attenuated functional connectivity, reduced structural connectivity does not universally necessitate a parallel change in functional connectivity. Areas that are connected by multisynaptic pathways can also display functional connectivity. Thus, functional connectivity is not constrained by direct structural connections, but can also reflect pathways involving more complex circuitry (Fling et al., 2011) which may vary within and between networks.

Research in language networks further demonstrate how strong functional connectivity can have either a positive or negative association with performance depending on whether the constituent regions are relevant for the task. Antonenko et al. (2013) used the left pars opercularis, a component of Broca's area involved in syntactic processing, as a seed region to examine functional connectivity in older and younger adults. Older adults showed weaker functional connectivity between intrahemispheric frontotemporal regions. This finding is consistent with other research demonstrating reduced functional connectivity within a functional network in older adults (Onoda et al., 2012; Ferreira & Busatto, 2013). With regard to bilateral communication, older adults exhibited stronger functional connectivity between *inter-*hemispheric regions, including the right angular gyrus, right pars opercularis, and right pars triangularis, which had a negative association with performance. This increased interhemispheric connectivity was associated with low fractional anisotropy (FA) values in the forceps minor, suggesting a negative relationship between structural integrity and functional connectivity with regard to bilateral connectivity. These results corroborate other data that suggest interhemispheric anatomical connections may provide inhibitory functions that enable the specificity and laterality observed in younger adults (Fling et al., 2011; McGregor et al., 2011, 2013).

Thus, although functional connectivity changes with age, it does not change in the same direction between every node in a network. The decrease in functional connectivity between constituent nodes of a functional network (e.g., intrahemispheric) and increase in functional connectivity between areas of relatively discrete networks where inhibition is typically expressed (e.g., interhemispheric) points to a general inefficiency in information transmission in older adults or an introduction of non-task relevant noise into the system. It is possible that while

strong intrahemispheric functional connectivity may indicate successful mutual-information processing between task-relevant regions, strong interhemispheric functional connectivity may reflect disinhibition of task-irrelevant functional regions that interferes during engagement in a task (Wierenga et al., 2008).

1.6 Age Related Changes in Functional Connectivity

Up to this point, the discussion of functional changes with increasing age has focused on older adult findings. Studies have shown that cognitive changes persist throughout the lifespan and declines can be observed prior to the age of 60 (Salthouse, 2009). Relatively fewer studies have interrogated functional changes as they relate to middle aged adults, which would offer a more comprehensive characterization of the course of functional changes throughout adult life. In one exception, McGregor et al. (2013) showed that loss of interhemispheric inhibition, as measured by positive BOLD in ipsilateral motor regions, occurs in sedentary middle aged adults (aged 40-60) as well as sedentary older adults. A functional connectivity analysis in adults aged 16-85 identified increases in functional connectivity between paralimbic areas and deceases in functional connectivity between regions of the DMN (Hampson et al., 2012). To date, functional connectivity in language and attention domains in middle aged cohorts is still poorly characterized. Examining functional alterations in connectivity in middle aged adults may elucidate whether changes occur gradually or with sudden and rapid onset in older age.

In the proposed study, inter- and intra-hemispheric functional connectivity will be analyzed using task-residual data derived from a generative verbal fluency task. As a preliminary investigation of the task-residual method, the first aim of this study will compare functional connectivity results from resting state and task-residual data in young adults. The second and third aims will use task-residual data to then address the question of how functional connectivity

between quintessential nodes of the language and attention networks in middle aged adults are different from those of younger adults.

1.7 Current Study

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In the proposed study, inter- and intra-hemispheric functional connectivity will be analyzed using task-residual data derived from a generative verbal fluency task. As a preliminary investigation of the task-residual method, the first aim of this study will compare functional connectivity results from resting state and task-residual data in young adults. The second and third aims will use task-residual data to then address the question of how functional connectivity between nodes of language and attention networks in middle aged adults are different from those of younger adults.

1.7.1 Regions of Interest

Each network will be defined by *a priori* regions of interest (ROIs). To examine the frontal language connections, the bilateral regions of the inferior frontal gyrus (IFG), comprised

of the pars orbitalis, pars triangularis, and pars opercularis. Posterior language connections will be defined by the bilateral posterior perisylvian (PPS) regions, comprised of the angular gyrus, supramarginal gyrus, and posterior regions of the superior and middle temporal gyri. These areas have been shown to activate in response to semantic and phonemic tasks (Binder et al., 2009) and show positive correlations to each other in resting state studies (Tomasi & Volkow, 2012).

To examine the relationship between anterior intention mechanisms and posterior attentional mechanism in both hemispheres, functional connectivity between the pre-supplementary motor areas (preSMA) and the retrospenial portion of the posterior cingulate cortices and the precuneus (PC/Pc) will serve as the posterior attention ROIs. The preSMA was selected for its involvement in prefrontal, task-positive, executive attention mechanisms and the selection of one action in favor of multiple competing actions (Lau et al., 2004; Nachev et al., 2007). The retrosplenial region of the posterior cingulate and precuneus together comprise an area of the task-negative (typically suppressed during cognitively demanding tasks) attention network. The PC/Pc region is involved in different kinds of attention, e.g., self-referential attention (Cavanna & Trimble, 2005, Vanhaudenhuyse et al., 2011), attention for emotional connotation (Cato, et al. 2004), and attention for external visual stimuli (Nadeau et al., 1997). These two anterior and posterior regions are consistently found to be anticorrelated in functional connectivity literature, such that as dorsal anterior goal-directed regions (e.g., preSMA) are invoked (Fox et al., 2006a), the posterior attentional regions remit (Fox et al., 2005).

1.7.2   Specific Aims

The first aim of the present study was to determine how functional connectivity of language and attention systems differ between task-residual and resting state data. Residual data contain inherent neural fluctuations as well as block-by-block variability because residual

data are derived from experiments with task-related activity. The constituent regions of a functional network cooperate to support the cognitive functions within their domain. Subtle variations in item difficulty or item demand will produce variability between blocks that may not be captured in hemodynamic modeling that assumes time-invariance but will still be contained in the residuals of such models. Deconvolution is an example of a means to estimate the HDR, however, other regression-based approaches likewise assume time-invariance and cause variance to remain in the residuals, such as modeling the HDR with a Gamma variate function or a block function (which in AFNI is the convolution of an incomplete Gamma function with a boxcar function). Those variations will be task-specific and thus are believed to accentuate the connectivity between regions that are related in a given network in terms of laterality and strength of functional connectivity. We expect more laterality in the task-residual data set because the language task will elicit more lateralized covariation in residuals than in resting state data. **Hypothesis 1** states that task-residual data in young adults will show stronger lateralization in the language and attention systems than resting state data.

      The second aim was to determine whether <u>intrahemispheric</u> functional connectivity within language and attention systems changes with age. Based on studies that show decreases in functional connectivity between constituent areas of a functional network as a function of age (Antonenko et al., 2013; Andrews-Hanna et al., 2007), we expect to see similar decreases in functional connectivity in the task-residuals between related regions in our sample of middle aged adults relative to younger adults. **Hypothesis 2** states that middle aged adults will exhibit <u>weaker</u> functional connectivity relative to young adults between the left lateralized areas of the language (inferior frontal gyrus and posterior perisylvian region) and attention (pre-supplementary motor area and posterior cingulate/precuneus).

The third aim was to determine whether <u>interhemispheric</u> connectivity within language and attention systems changes as a function of age. With regard to the direction of interhemispheric functional connectivity alterations in aging, there are two possible outcomes based on studies endorsing the compensation hypothesis and others endorsing the interhemispheric inhibition hypothesis. Some investigators have found that increased functional connectivity in frontal regions is associated with better motor performance (Chen et al., 2009; Langan et al., 2010), which could reflect increased communication between left and right sensorimotor cortices. Functional connectivity between previously independent regions belonging to two different networks has been shown to be strengthened after repeated entrainment (Lewis et al., 2009). Similarly, within a network, repeated coactivation of two regions as necessitated by a task sculpts connectivity between those regions (Lewis et al., 2009). If activation of right homologous regions is compensatory, interhemispheric connectivity will be stronger in middle aged adults relative to younger adults as an effect of continuous entrainment of right homologue areas during network activation. Task-residuals may be sensitive to this transmission of information because variations in task demands will show bilateral regions that are interacting in synchrony. Thus, **Hypothesis 3** states that middle aged adults will show <u>stronger</u> interhemispheric functional connectivity relative to younger adults between anterior areas language (left and right inferior frontal gyri) and anterior areas of attention (left and right pre-supplementary motor area).

Alternatively, some research suggests that non-dominant hemisphere activation is a result of an inability of the dominant hemisphere to suppress the non-dominant hemisphere (Fling et al., 2012). It is possible that right homologous regions are responding to the same stimuli as the left regions but in an independent manner, in which the left hemisphere activity facilitates

performance and the right hemisphere activity is irrelevant to performance. If right hemisphere activity is an irrelevant response to the stimuli, modeling the activity that is time-locked to the task should remove right hemisphere activity and leave insignificant residual activity. Variations in task demand that would generate block-by-block variability in the dominant hemisphere would remain in the residual data and be uncorrelated with nondominant hemisphere activity. If younger adults with intact interhemispheric inhibition mechanisms are better able to regulate interhemispheric interactions, nondominant hemisphere activity will display strong correlation with dominant hemisphere residual activity. Conversely, if older adults with reduced interhemispheric inhibition mechanisms cannot regulate interhemispheric interactions, nondominant hemispheric activity will display weak correlation with dominant hemisphere residual activity. Thus, **Hypothesis 4** states that middle aged adults to show <u>weaker</u> interhemispheric functional connectivity relative to younger adults between bilateral anterior areas language bilaterally (i.e., left and right inferior frontal gyri) and anterior areas of intention (i.e., left and right pre-supplementary motor area).

2 METHOD

2.1 Participants

A subset of thirty-four participants were selected from participants recruited for a parent study, the Cognitive Connectome Project at the University of Arkansas for Medical Sciences (UAMS). Recruitment and study procedures were completed in accordance with UAMS Institutional Review Board approval. Inclusion criteria for this study were healthy men and women in young and middle-aged cohorts (age range: 18-30 years; 35-50 years), native English speakers with at least an eighth grade reading and writing proficiency. There were a total of 21 young adults ($M = 23.24$, $SD = 2.57$, 12 females) and 13 middle aged adults ($M = 43.38$, $SD =$

5.01, 10 females). Exclusion criteria were presence and history of DSM-IV psychiatric disorders, previous self-reported neurological disorders or loss of consciousness for longer than 10 minutes, substance abuse or dependence (with the exception of nicotine dependence), and contraindications to MRI environment including ferromagnetic implants and pregnancy. Although left-handed participants were included in the Cognitive Connectome Project, they were excluded from the present study.

2.2   Recruitment and Procedures

Participants were recruited via community advertisement and underwent initial screening via a brief telephone interview. Eligible participants were consented to participate at the Brain Imaging Research Center (BIRC) of the Psychiatric Research Institute at UAMS. Participants underwent two MRI sessions and a neuropsychological assessment across 1-4 sessions as part of the Cognitive Connectome Project protocol. Each MRI session was preceded by a urine analysis to screen for pregnancy and illicit drug use.

2.3   Verbal Fluency Task and Resting State Scans

During the MRI session, participants were asked to silently generate as many words as possible that began with a specific category or letter prompt. The task consisted of one run containing 15 second blocks of alternating letter and semantic category prompts separated by 15 seconds of rest. The letter or cue word was presented for the entire 15 seconds of word generation. A total of five letters (i.e., R, P, W, S, J) and five categories (i.e., plants & flowers, clothing, foods, states, jobs) were presented to each participant. During rest (non-task) blocks, participants were shown a screen-centered fixation cross and instructed to cease word generation until the next trial. For the resting state scan, participants were instructed to "try not to think of

anything specific" and to "just relax and rest." Participants were asked to keep their eyes open

and focused on the fixation cross in the center of the screen for the 7-minute acquisition.

The data used in study was part of a larger project in which various cognitive and motor

tasks were administered in the scanner. These include the Finger-Tapping Task, Judgement of

Line Orientation, Flashing Checkerboard, n-back (0- and 2-back conditions), Verbal Paired

Associates, Encoding International Affective Picture System (IAPS) stimuli and Recognition

stimuli, Rating IAPS pictures, Iowa Gambling Task, Tower of London Task, letter and category

fluency, and the Multi-Source Interference Task. However, only the letter and category fluency

task was used for the present study.

2.4   Data Acquisition

Imaging data were acquired using a Philips 3T Achieva X-series MRI scanner. Anatomic

images were acquired with a Magnetization Prepared Rapid Acquisition Gradient Echo

(MPRAGE) sequence with the following parameters: matrix = 256 x 256; 22 sagittal slices; TR =

shortest; TE = shortest; FA = 8°; resolution = 0.94 x 0.94 x 1 mm^3. Functional images for the

early participants (1-50) were acquired using an 8-channel head coil with an echo planar imaging

(EPI) sequence and the following parameters: TR = 2000 msec; TE = 30 msec; FA = 90°; FOV =

240 x 240 mm^2; matrix = 30 x 30, 37 oblique slices parallel to orbitofrontal cortex; "Philips

interleaved" for participants 1-28 and interleaved for participants 29-49; resolution = 3.0 x 3.0 x

4.0 mm^3. Functional images for the remaining participants (51-79) were acquired using a 32-

channel head coil with the following parameters: TR = 2000 msec; TE = 30 msec; FA = 90°;

FOV = 240 x 240 mm; matrix = 80 x 80, 37 oblique axial slices parallel to orbitofrontal cortex;

sequential ascending acquisition; slice thickness = 2.5 mm with a 0.5 mm gap, resolution = 3.0 x

3.0 x 3.0 mm^3. Three warm-up TRs (6s) at the beginning of each functional run were discarded.

2.5   Analysis

2.5.1   Data Preprocessing

Each EPI time series (originally in nifti format) was converted to a bxh file, which served

as the input to a subsequent quality control tool. Images also underwent gross alignment to the

MNI152 template such that all orientations matched the orientations of the standard template.

Each 4D time series was inspected visually via FSL and via quality control metrics provided by

the Functional Bioinformatics Research Network (fBIRN) fMRI Quality Assurance Tool.

FSLview was used to identify time points in which excessive rotational movement is visible. The

fBIRN fMRI QA Tool (fmriqa_generate.pl) produces an HTML summary report of various

metrics that describe the quality of fMRI data. fBIRN quality control metrics were inspected in

the following order:

- Images of mask, mean, and standard deviation (across time) were inspected to confirm

  reasonable anatomy (e.g., no ghost artifact) and note potential motion-related artifact

  characterized by relatively high intensities around edges the brain in standard deviation

  images.

- Per-slice variation is a metric that identifies outlier slices within the entire time series by

  a "jackknife" technique of calculating the influence or potential bias that each slice has

  on the overall average across slices and time points. Significant per-slice variation is

  indicative of "spikes" introduced by scanner hardware during acquisition.

- The frequency spectrum displays the mean power at each frequency across all voxels.

  This metric was used to confirm a reasonably similar range of frequencies for each run.

- Center of mass in each of the x, y, and z dimensions were inspected to identify time

  points with excessive translational displacement from the center of the brain.

- Inherent smoothness in each dimension was also reviewed. Significant variation in smoothness would be indicative of issues during image reconstruction.

- The Outlier Voxel Percentages is a metric that calculates the percentage of outlier voxels in each volume using AFNI's 3dToutcount command. The Outlier Voxel Percentages metric in combination with visual inspection of the time series and standard deviation maps across time enabled identification of the effects of motion related noise and motion-related sources of outliers.

Functional images were pre-preprocessed using Analysis of Functional NeuroImages Software (AFNI) and fMRI Software Library (FSL). Skull stripping was performed on anatomic data using FSL's Brain Extraction Tool (BET) (Smith, 2002). Functional data underwent motion correction, slice timing correction to correct for varying acquisition orders, high pass filtering at .01 Hz, and smoothing with a 6mm Gaussian kernel using the FSL program Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC). The initial preprocessing step in MELODIC, motion correction, was applied with MCFLIRT (Jenkinson et al., 2002). MCFLIRT is a rigid-body motion correction tool that uses the middle volume as the initial reference image. Subsequently, slice timing correction was applied. This step required varying slice timing input files based on the three unique acquisitions: Philips interleaved, Philips default (i.e., interleaved), and sequential ascending. Phillips interleaved acquisition takes the square root of the total number of slices and rounds that number to the nearest integer, then acquires slices in intervals of that integer starting with 1. This is done to maximize the time between adjacent slices. Slice timing correction was thus not uniform for all participants because acquisitions varied. Within MELODIC, independent component analysis (ICA) was used to decompose each participant's functional time series into different spatial and

temporal components. ICA is a multivariate approach that enables imaging data analysis without a priori hypotheses regarding the time series. The components generated can represent task-related signal, task-related and task-irrelevant physiological events, and artifact. The optimal number of components was determined by MELODIC's automatic dimensionality estimation via principle component analysis (PCA).

FSL's FMRIB's ICA-based Xnoiseifier (FIX) was used to identify motion-related noise components (Salimi-Khorshidi et al., 2014; Griffianti et al., 2014). The "standard" fMRI dataset trained-weights file (Standard.RData) supplied with FIX was used to classify and remove noise components. A liberal threshold of signal vs. noise components of 20 was applied. FSL authors describe "sensible values" as ranging between 5-20. Lower thresholds are more likely to retain noise components. Thus, by selecting the high threshold of 20, noise components are more likely to be removed along with a greater risk of removing signal. All components labeled as noise were visually inspected via their IC spatial maps, IC time courses, and frequency spectra to confirm that no probable signal was removed. Probable signal was defined as components in which suprathreshold focal activity was present in regions of interest, and there was an absence of the following patterns of structured and unstructured noise: 1) heavily clustered activity at the frontal pole; 2) ring pattern around edges of brain; 3) "saw-tooth" pattern time course; 4) isolated, large spikes in time course; 5) diffusely distributed activity throughout brain; 6) clusters representing signal in CSF, white matter, and sinuses; 7) widespread activity isolated to 1-2 slices; 8) significant power in the frequency spectrum greater than 0.1 Hz. These criteria are roughly based on Kelly and colleagues' (2010) descriptions of common non-signal related patterns in MELODIC output.

The fBIRN Quality Assurance Tool was subsequently applied to the denoised task and rest data. The metrics described above in the first round of quality control inspection of raw data were compared to that of the preprocessed and denoised data. The outlier count metric was of particular interest at this stage to confirm that potentially problematic outlier voxels present in the raw data were reduced after denoising and that no significant outliers were introduced.

Single subject processing scripts for processing denoised data in AFNI were generated via afni_proc.py. The following processing blocks were used: align, volreg, tcat, mask, scale, regress. The first and last 2 TRs were removed from each functional run to remove images acquired prior to longitudinal magnetization reaching a steady state and to reduce effects of interpolation by slice timing correction. For task data, the block basis function was used to model the mean time series using BLOCK5 with a basis function amplitude of 1 and the duration of 15. Data were run through 3dREMLfit after 3dDeconvolve to correct for temporal correlations and to prepare for local white matter regression. Local white matter was regressed using ANATICOR to reduce bias in correlations contained within gray matter (Jo, et al., 2010). The resultant error time series, after extraction of effects of non-interest and task-related data, were then promoted for further analysis.

2.5.2   Region of Interest Selection

Regions of interest (ROIs) were defined by the Harvard-Oxford cortical brain atlas in MNI152 space. The anterior language region, inferior frontal gyrus (IFG), was defined by the pars triangularis, pars opercularis, frontal operculum to capture the medial extent of this functional region (i.e., to capture the banks of the anterior ascending ramus), and the superior portion of the frontal orbital cortex to encompass pars orbitalis. The right IFG was defined by capturing the right homologous regions. Bilateral posterior perisylvian regions were defined by

combining the angular gyrus, supermarginal gyrus – posterior division, superior temporal gyrus

(planum temporale and posterior division), and middle temporal gyrus – temporaloccipital part.

Executive attention regions consisted of the pre-supplementary motor area and the posterior

cingulate/precuneus. The pre-supplementary motor areas bilaterally comprised the

juxtapositional lobule cortex and medial portion of the superior frontal gyrus. The posterior

cingulate/precuneus regions bilaterally included the posterior division of the cingulate gyrus and

precuneus. Each ROI was backtransformed from standard space into each participant's native

EPI space using FSL's Non-linear Image Registration Tool (FNIRT).

2.5.3   Time Series Extraction

Within each ROI, the most active voxels in response to the language task were selected to

extract the error time series. This was performed to reduce the heterogeneity within large ROIs

and identify the voxels most relevant to the language network as assessed by the error time

course. This procedure comprised the following steps: The F-statistic, representing the ratio of

explained versus unexplained variability by the stimulus task regressors, was obtained for each

voxel within each ROI was extracted and sorted. A threshold was applied such that the top 2

percent of voxels were retained to generate a binarized relevant-voxel ROI mask for each region.

For the posterior perisylvian region, it was observed that the activity within this ROI reflected a

combination of spatially discrete task-positive and task-negative activity. There is evidence to

support that portions of this region are involved in the default mode network (or task-negative

network) as well as the language network (Wirth et al., 2011). For instance, the left angular gyrus

is associated with considerable overlap between the semantic network and the default mode

(task-negative) network (Jackson et al., 2016; Humphreys et al., 2015; Seghier, Fagan, & Price,

2010). Some researchers have suggested that the angular gyrus is responsible for domain general

functions rather than semantic processing exclusively (Humphreys et al., 2015). Thus, this ROI was further divided into two masks of task-positive and task-negative voxels in response to both letter and category stimuli. By segregating areas that are uniquely involved in DMN versus language processing for the present verbal fluency task, an increased specificity of relevant voxels was contained in each mask. The spatially distinct task-positive and task-negative masks then underwent the same thresholding as the other ROIs by retaining top 2 percent of voxels activated as quantified by the F-statistic.

The relevant-voxel ROI masks were then transformed from task to rest EPI space using FSL's FLIRT. For both task and rest analyses, the residual time series was extracted from the active-voxel ROI masks in each participant's native task and rest EPI space using AFNI's 3dmaskave. ROI pairs were correlated using AFNI's 1dCorrelate. Correlations were subsequently z-normalized using Fisher's r-to-z transformation. Tests of normality and homoscedasticity were conducted to verify the appropriateness of parametric test usage. In order to test whether the dependent variable was normally distributed, SPSS was used. Paired and independent sample t-tests and non-parametric tests were then calculated to determine if means were significantly different between data types and between age cohorts, respectively.

For the first aim, a laterality index was obtained at the subject level by subtracting the z-transformed correlation coefficient of right hemisphere ROI pairs from that of the left hemisphere ROI pairs. The difference served as a measurement of laterality for each subject. For ROI pairs in which a positive correlation was expected, higher values indicate stronger left hemisphere dominance and values closer to or less than zero indicate (weaker left hemisphere dominance) stronger right hemisphere dominance. Conversely, for ROI pairs in which a negative correlation was expected, more negative values indicated stronger left hemisphere dominance

and less negative values or positive values indicate (weaker left hemisphere dominance) stronger

right hemisphere dominance. Thus, one laterality index was calculated per subject for both

language and attention domains derived from resting state data and task-residual data.

For both language and attention, the laterality indices derived from language task-residual

data was compared against the corresponding laterality indices derived from resting state data

using one-tailed t-tests, for a total of two independent-groups t-tests. For instance, the average

laterality index of the language connections derived from language task-residual data was

compared against the average laterality index of the language connections derived from resting

state data.

3   RESULTS

3.1   Results for Aim 1: Comparison of Task Residual and Resting State Data

3.1.1   *Hypothesis 1a – Laterality of Language Connectivity (positive PPS)*

The following tests were performed on the 21 young adults of the study sample. The first

test of this aim also compared the task residuals vs. rest in the laterality of the IFG and PPS

intrahemispheric functional connectivity within nodes of the language network. However, the

PPS regions in this test was characterized by positive activity, thus we anticipated a positive

correlation between the language regions. Tests of normality were conducted to determine if the

laterality indices were normally distributed for both data types. Due to limited power of the

Kolmogorov-Smirnov test, the Shapiro-Wilk test is generally recommended for testing normality

(Ghasemi & Zahediasl, 2012). Results from the Shapiro-Wilk test showed that the laterality

indices derived from task data did not differ significantly from a normal distribution, $W(21) =$

$0.97, p = 0.82$. Similarly, the laterality indices derived from resting state data did not differ

significantly from a normal distribution, $W(21) = 0.92, p = 0.10$. A paired samples t-test was

conducted to compare the two data types (Table 1). Results showed that task data demonstrated **a trend** toward stronger laterality ($M = 0.21$, $SD = 0.39$) than resting state data ($M = 0.08$, SD $=$ 0.31), t (20) $=$ -1.72, one-tailed $p = 0.05$, $d = 0.37$.

In laterality indices (left minus right) the relative contribution of the hemispheres is lost. For example, a laterality of $+X$ might be obtained from a left-hemisphere z-score of $+X$ and a right-hemisphere z-score of *0*, from a left-hemisphere z-score of *0* and a right-hemisphere z-score of *-X*, or from a left-hemisphere z-score of $+1/2 X$ and a right-hemisphere z-score of *-1/2 X*, and so on. Hence, to better understand the contribution of the two hemispheres to the laterality comparison, means and standard deviations were calculated for connectivity z-scores within each hemisphere, and paired samples t-tests were conducted to examine the difference in functional connectivity between left and right hemisphere ROI pairs in both task and rest data. In task residual data, left hemisphere language regions were more correlated ($M = 0.65$, $SD = 0.34$) than right hemisphere language regions ($M = 0.44$, $SD = 0.36$), $t(20) = 2.51$, $p = 0.02$. In resting state

data, no significant difference was found in the functional connectivity between left ($M = 0.41$,

$SD = 0.29$) and right ($M = 0.33$, $SD = 0.28$) hemisphere language regions, $t(20) = 1.24$ $p = 0.23$.

One sample t-tests were also conducted to examine whether intra-hemispheric normalized

correlations were significantly different than zero. The correlations of each individual ROI pair is

important to note because the presence or absence of right hemisphere connectivity will also
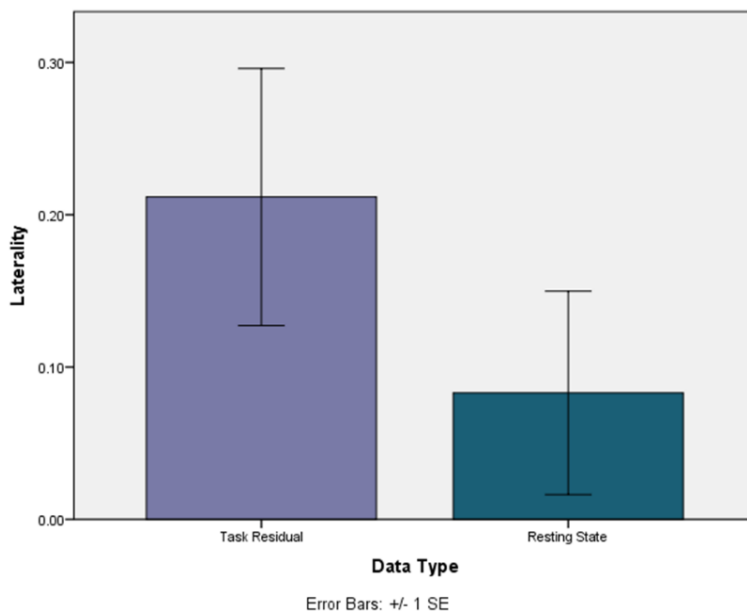
Figure 1. Laterality of Language Network

inform laterality indices. Results revealed that all intra-hemispheric correlations were significant:

left hemisphere task data ($M = 0.65$, $SD = 0.34$), $t(20) = 8.78$, $p = .000$; right hemisphere task

data ($M = 0.44$, $SD = 0.36$), $t(20) = 5.55$, $p = .000$; left hemisphere rest data ($M = 0.41$, $SD = 0.29$), $t(20) = 6.56$, $p = .000$; right hemisphere rest data ($M = 0.33$, $SD = 0.28$), $t(20) = 5.39$, $p = .000$. These results show that although functional connectivity exists between language regions

in both hemispheres in both task and rest data, there is stronger connectivity in the left

hemisphere in task data but not rest data.

Error Bars: +/- 1 SE
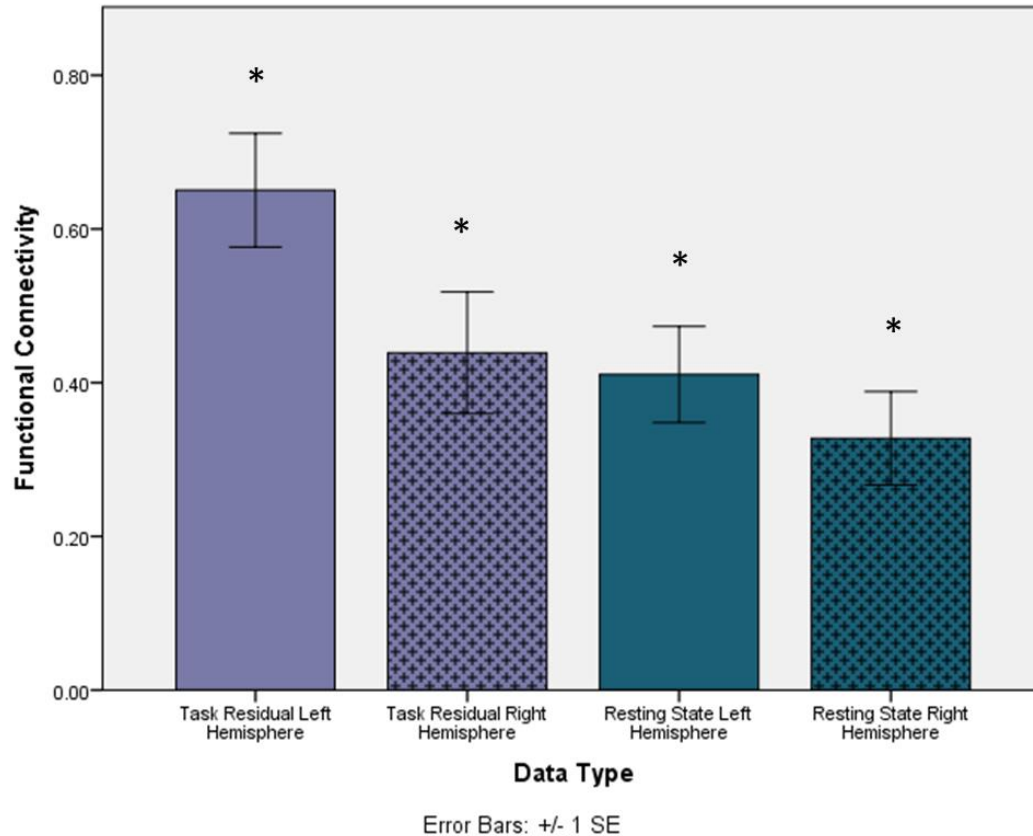
Figure 2. Functional Connectivity of Language Regions

3.1.2 *Hypothesis 1b – Laterality of the Intention/Attention Connectivity (positive PPS)*

The second test of this aim compared the task residuals vs. rest in the laterality of the preSMA and PCPc intrahemispheric functional connectivity of nodes within the intention/attention network. Results from the Shapiro-Wilk test showed that the laterality indices derived from task data did not differ significantly from a normal distribution, $W(21) = 0.96$, $p = 0.43$. Similarly, the laterality indices derived from resting state data did not differ significantly from a normal distribution, $W(21) = 0.97$, $p = 0.78$. A paired samples t-test **showed that task residual data demonstrated stronger laterality ($M = -0.09$, $SD = 0.31$) than resting state data ($M = 0.01$, $SD = 0.24$), t (20) = -1.85, one-tailed $p = 0.04$, $d = 0.36$ (Table 1).** The

intention/attention connections were more left lateralized in the task data than the resting state data.
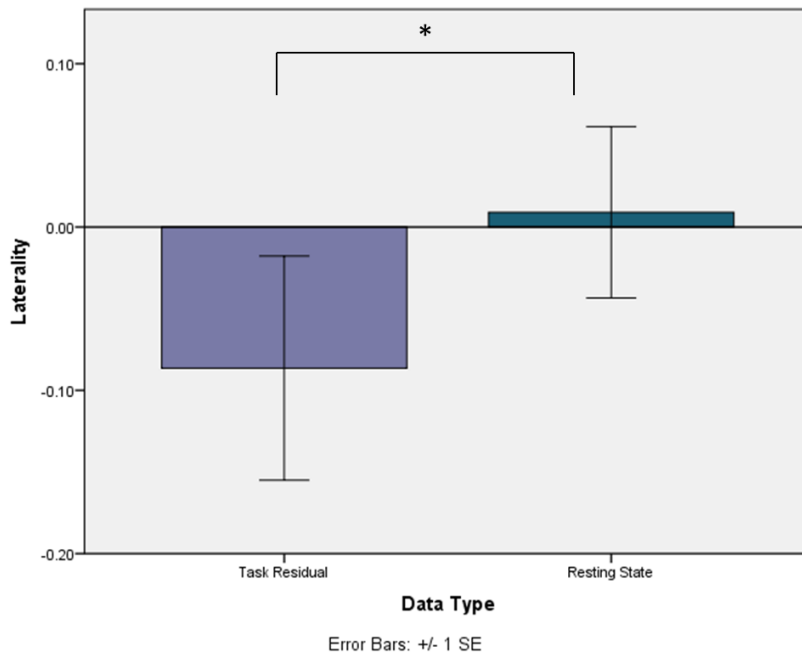
Figure 3. Laterality of Intention/Attention Network

To further investigate the nature of this finding, paired samples t-tests were conducted. In task data, no significant difference was found in the functional connectivity between left (M = -0.21, SD = 0.30) and right (M = -0.13, SD = 0.33) hemisphere language regions, $t(20)$ = -1.26 p = 0.22. Similarly, in resting state data, no significant difference was found in the functional connectivity between left (M = 0.08, SD = 0.18) and right (M = 0.07, SD = 0.23) hemisphere language regions, $t(20)$ = 0.17 p = 0.87. One sample t-tests were conducted to examine whether intra-hemispheric normalized correlations were significantly different than zero. Results revealed that in task residual data, left hemisphere correlations were significant (M = -0.21, SD = 0.30), $t(20)$ = -3.26, p = .004, but right hemisphere correlations were not (M = -0.13, SD = 0.33), $t(20)$ = -1.74, p = .097. In resting state data, there were no significant differences from zero in the left

hemisphere correlations ($M = 0.08$, $SD = 0.24$), $t(20) = 1.96$, $p = .064$, nor the right hemisphere

correlations ($M = 0.07$, $SD = 0.24$), $t(20) = 1. 33$, $p = .199$.
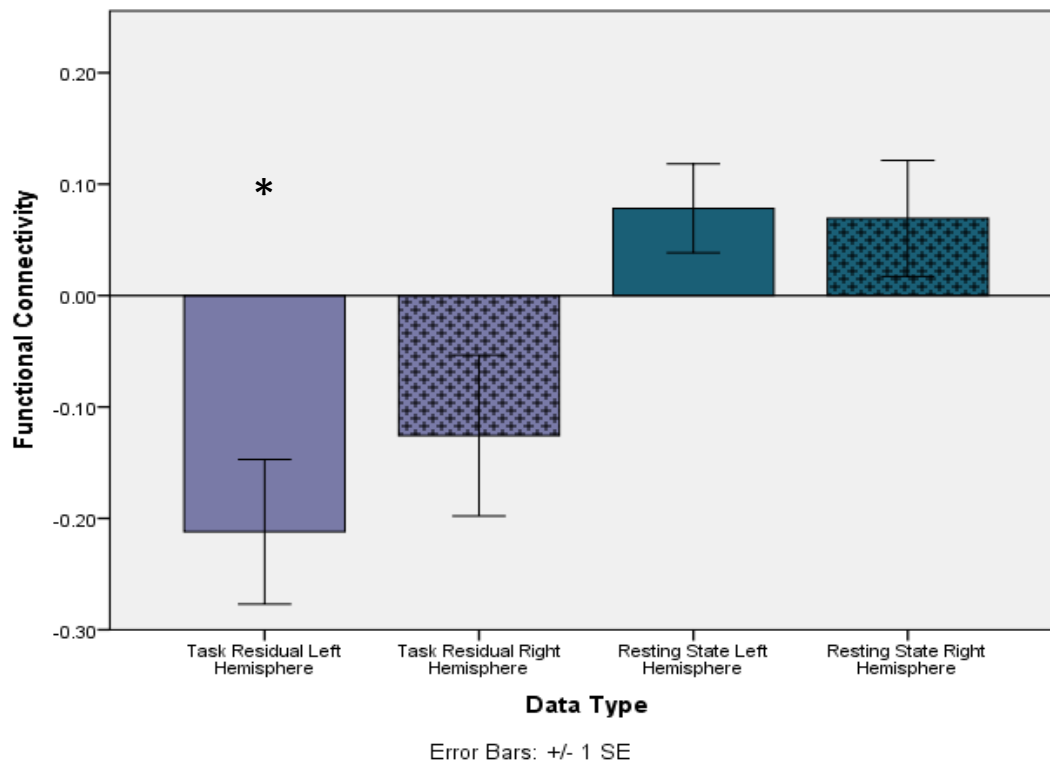
Figure 4. Functional Connectivity of Intention/Attention Regions

3.1.3   Hypothesis 1c – Laterality of the Language/Attention Connectivity (negative PPS)

The third test of this aim compared the task residuals vs. rest in the laterality of the IFG and PPS intrahemispheric functional connectivity of nodes within the language and attention networks. The PPS areas in this test were characterized by negative activity consistent with the DMN or task-negative network, thus we anticipated an anticorrelation between the anterior language regions and posterior regions associated with the DMN. Results from the Shapiro-Wilk test showed that the laterality indices derived from task data did not differ significantly from a normal distribution, $W(21) = 0.91$, $p = 0.06$. Similarly, the laterality indices derived from resting state data did not differ significantly from a normal distribution, $W(21) = 0.94$, $p = 0.23$. A paired samples t-test was conducted to compare the two data types (Table 1)**. Results showed that task data demonstrated stronger laterality ($M = -0.29$, $SD = 0.35$) than resting state data ($M = -0.07$, $SD = 0.29$), $t (20) = -3.31$, $p = 0.003$, $d = 0.68$.**
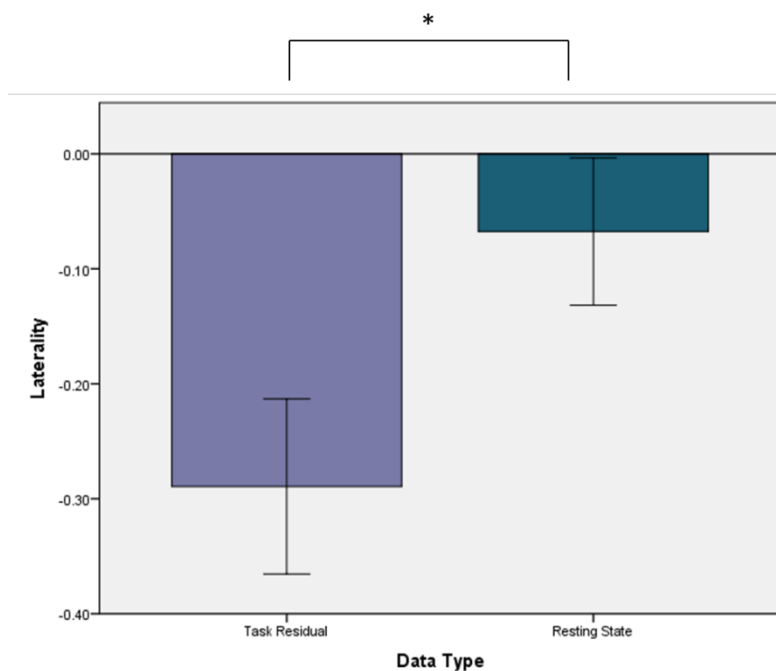
Figure 5. Laterality of Language/Attention Regions

Paired samples t-tests revealed that in task residual data, left hemisphere language regions were negative and more correlated (M = -0.26, SD = 0.33) than right hemisphere language regions (M = 0.03, SD = 0.33), $t(20)$ = -3.80, p = 0.001. In resting state data, no significant difference was found in the functional connectivity between left (M = 0.15, SD = 0.21) and right (M = 0.22, SD = 0.27) hemisphere language regions, $t(20)$ = -1.06, p = 0.30. One sample t-tests were conducted to examine whether intra-hemispheric normalized correlations were significantly different than zero. Results revealed that the correlation between left hemisphere task data was significant (M = -0.26, SD = 0.33), $t(20)$ = -3.70, p = .001, but the correlation between right hemisphere task data was not significant (M =0.03, SD = 0.33), $t(20)$ = 0.36, p = .72. In resting state data, both left and right intra-hemispheric correlations were significant: left (M = 0.15, SD = 0.21), $t(20)$ = 3.18, p = .005; right (M = 0.22, SD = 0.27), $t(20)$ = 3.74, p = .001.
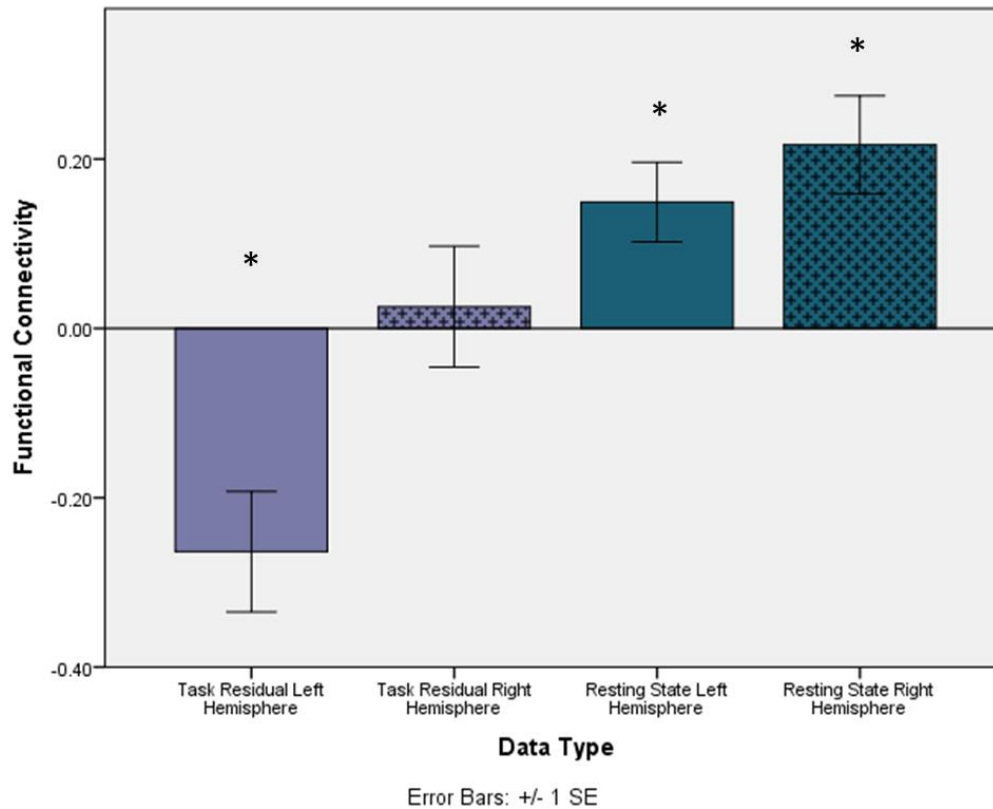
Figure 6. Functional Connectivity of Language/Attention Regions

Table 1. Task residual versus resting state laterality

Network	Task-residual		Resting state				
	M	SD	M	SD	t-test	p	d
Language Laterality (positive PPS)	0.21	0.39	0.08	0.31	-1.72	0.05	0.37
Attention Laterality	-0.09	0.31	0.01	0.24	-1.85	0.04*	0.36
Language/Attention Laterality (negative PPS)	-0.29	0.39	-0.07	0.29	-3.31	0.003**	0.68

*p<0.05. **p<0.01.

3.2   Results for Aim 2: Intrahemispheric Functional Connectivity Comparison Between Younger and Middle Aged Adults

3.2.1   Hypothesis 2a – Intrahemispheric Functional Connectivity Between Language Nodes (positive PPS)

The first test of this aim also compared younger and middle aged adults' left intrahemisheric functional connectivity between nodes of the language network. However, in this test, the posterior language region (LPPS) was characterized by positive values. Thus we anticipated a positive correlation between the anterior and posterior regions. Results from the Shapiro-Wilk test showed that z-transformed correlations between LIFG-LPPS in young adults deviated significantly from a normal distribution, $W(21) = 0.88$, $p = 0.02$. Similarly, the Q-Q plot, in which observed values and expected values are plotted on a graph, showed deviation from normality. Results from the Shapiro-Wilk test also showed that z-transformed correlations between LIFG-LPPS in middle aged adults also differed significantly from a normal distribution, $W(13) = 0.83$, $p = 0.02$. Levene's test for equality of variances was conducted to test the assumption of homogeneity of variance. Results from Levene's test showed that the variance between the two groups were not significantly different, $F(1,32) = 0.10$, $p = 0.76$. Due to the non-normal distribution of the young adult sample and the discrepancy between the group sizes, the Mann-Whitney U Test was conducted (Table 2). Results from the Mann-Whitney U Test revealed no differences in functional connectivity between young ($Mdn = 0.68$) and middle aged adults ($Mdn = 0.46$), $U = 103$, $p = 0.12$, $r = 0.31$. One sample Wilcoxon Signed Rank tests revealed that for both young and middle aged adults, intra-hemispheric normalized correlations were significant: young ($Mdn = 0.68$), $Z = 3.91$, $p = .000$; old ($Mdn = 0.46$), $Z = 3.18$, $p = .001$.
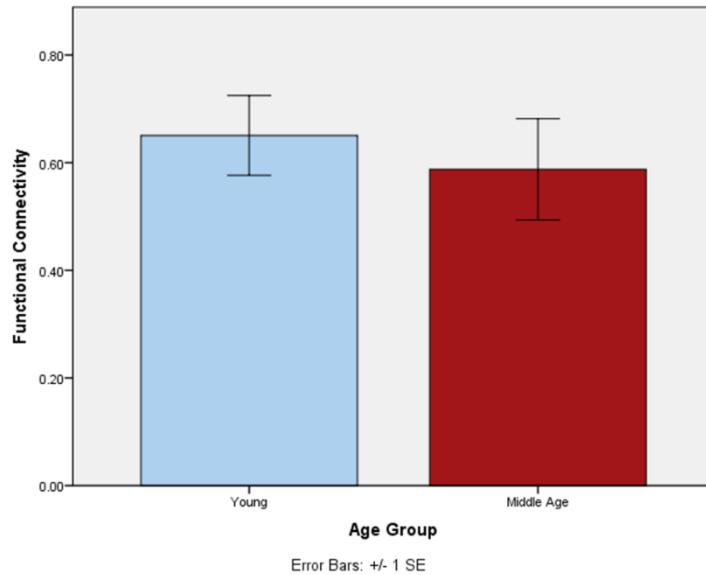
Figure 7. Intrahemispheric Functional Connectivity of Language Regions

3.2.2 Hypothesis 2b – Intrahemispheric Functional Connectivity Between Intention/Attention Nodes

The second test of this aim compared younger and middle aged adults' left intrahemisheric functional connectivity between nodes of the intention/attention network. In this test, the posterior language region (LPCPc) was characterized by negative values. Thus we anticipated an anticorrelation between the anterior and posterior regions. Results from the Shapiro-Wilk test showed that z-transformed correlations between LpreSMA-LPCPc in young adults did not differ significantly from a normal distribution, $W(21) = 0.93$, $p = 0.13$. Results from the Shapiro-Wilk test also showed that z-transformed correlations between LpreSMA-LPCPc in middle aged adults also did not differ significantly from a normal distribution, $W(13) = 0.94$, $p = 0.45$. Results from Levene's test showed that the variance between the two groups were not significantly different, $F(1,32) = 1.71$, $p = 0.20$. **Results from the independent samples t-test revealed that young adults (M = -0.21, SD = 0.30) had significantly stronger functional connectivity (characterized by more negative correlations) than middle aged**

adults (*M* = 0.03, *SD* = 0.35), *t*(32) = -2.13, one-tailed *p* = 0.02, *d* = .74 (Table 3). One sample

t-tests revealed that for young adults, intra-hemispheric correlations were significantly different

than zero (*M* = -0.21, *SD* = 0.30), *t*(20) = -3.26, *p* = .004. However, for middle aged adults, intra-

hemispheric correlations were not significant (*M* = 0.03, *SD* = 0.35), *t*(12) = 0.29, *p* = .78.

Figure 8. Intrahemispheric Functional Connectivity of Intention/Attention Regions

3.2.3   Hypothesis 2c – Intrahemispheric Functional Connectivity Between

Language/Attention Nodes (negative PPS)

The third test of this aim compared younger and middle aged adults' left intrahemisheric

functional connectivity between language and attention nodes. In this test, the posterior language

region (LPPS) was characterized by negative values. Thus we anticipated an anticorrelation

between the anterior and posterior regions. Tests of normality were conducted to determine if the

z-transformed correlations were normally distributed for both groups. Results from the Shapiro-Wilk test showed that *z*-transformed correlations between LIFG-LPPS in young adults deviated significantly from a normal distribution, $W(21) = 0.83$, $p = 0.002$. Similarly, the Q-Q plot, in which observed values and expected values are plotted on a graph, showed deviation from normality. Results from the Shapiro-Wilk test also showed that *z*-transformed correlations between LIFG-LPPS in middle aged adults did not differ significantly from a normal distribution, $W(13) = 0.98$, $p = 0.98$. Results from Levene's test showed that the variance between the two groups were not significantly different, $F(1,32) = 0.21$, $p = 0.65$. Due to the non-normal distribution of the young adult sample and the discrepancy between the group sizes, the Mann-Whitney U Test was conducted (Table 4). Results from the Mann-Whitney U Test revealed no significant differences in connectivity strength between young adults (*Mdn* = -0.34) and middle aged adults (*Mdn* = -0.25), $U = 114$, $p = 0.43$, $r = 0.01$. One sample Wilcoxon Signed Rank tests were conducted to examine whether intra-hemispheric correlations were significantly different than zero. For young adults, intra-hemispheric correlations were significantly different than zero (*Mdn* = -0.34), $Z = -2.94$, $p = .003$. Similarly, for middle aged

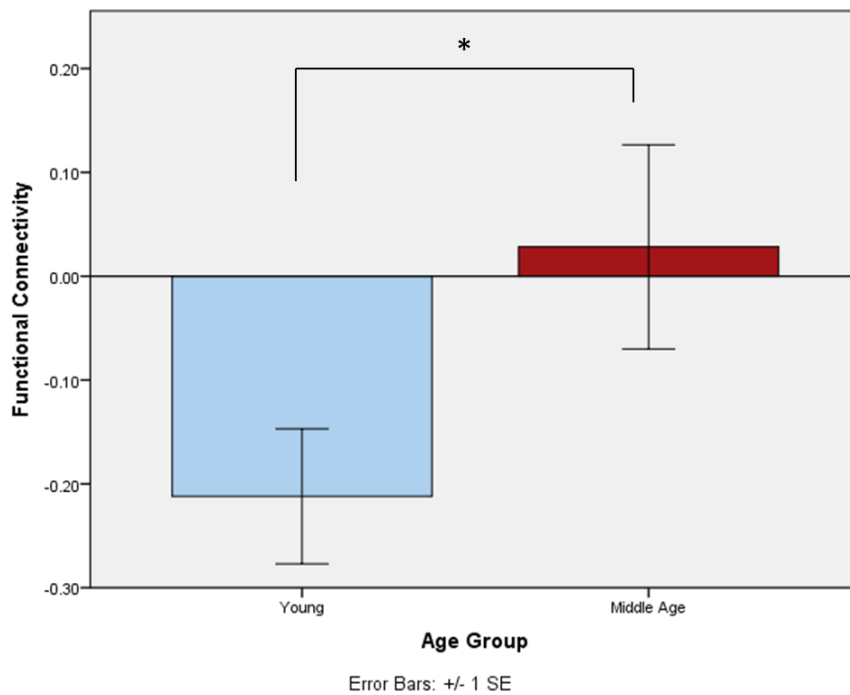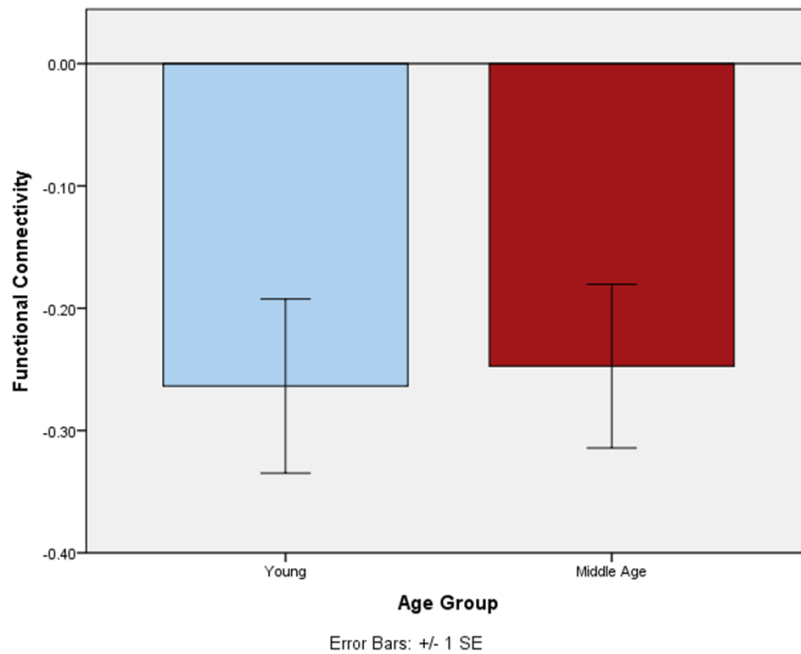adults, intra-hemispheric correlations were significant ($M = -0.25$, $SD = 0.24$), $t(12) = -3.96$, $p = .003$.

Figure 9. Intrahemispheric Functional Connectivity of Language/Attention Regions

Table 2. Aim 2 Age comparisons of intrahemispheric functional connectivity

Network	Young		Middle Age				
	Mean or Median	SD or IQR	Mean or Median	SD or IQR	t or U	p	d or r
Language Node FC	0.68	0.4	0.46	0.52 (SD)	103	0.12	0.31 (d)
Intention/Attention FC	(M) 0.21	(SD) 0.3	(M) 0.03	0.35	(t) -2.13	0.02*	0.74
Language/Attention FC	-0.34	0.36	-0.25	0.58	114	0.43	0.01

*$p<.05$, FC = Functional Connectivity

3.3 Results for Aim 3: Interhemispheric Functional Connectivity Comparison Between Younger and Middle Aged Adults

3.3.1 Hypothesis 3&4a – Interhemispheric Functional Connectivity Between Language Nodes

The first test of this aim compared young and middle aged adults' bilateral IFG functional connectivity between nodes of the language network. Results from the Shapiro-Wilk test showed that *z*-transformed correlations between LIFG-RIFG in young adults did not differ significantly from a normal distribution, $W(21) = 0.94$, $p = 0.17$. Results from the Shapiro-Wilk test also showed that *z*-transformed correlations between LIFG-RIFG in middle aged adults did not differ significantly from a normal distribution, $W(13) = 0.97$, $p = 0.87$. However, inspection of the Q-Q plots and histograms revealed deviance from normality in both groups. Results from Levene's test showed that the variance between the two groups were not significantly different, $F(1,32) = .01$, $p = 0.94$. Due to the non-normal distribution of both groups, the Mann-Whitney U Test was conducted (Table 5). Results from the Mann-Whitney U Test revealed no difference between functional connectivity in young (*Mdn* = 0.51) and middle aged adults (*Mdn* = 0.56), $U = 117$, $p = 0.49$, $r = 0.12$. One sample tests were conducted to examine whether inter-hemispheric correlations were significantly different than zero. Both young adults (*Mdn* = 0.51), $Z = 3.77$, $p = .000$ and middle aged adults (*Mdn* = 0.56), $Z = 3.18$, $p = .001$, showed inter-hemispheric correlations that were significantly different than zero.
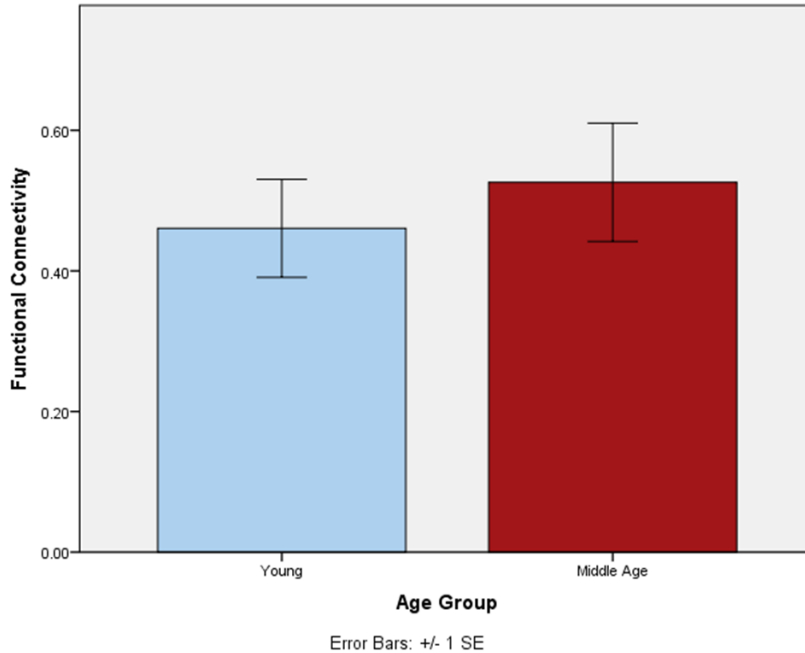
Figure 10. Interhemispheric Functional Connectivity of Language Regions

3.3.2   Hypothesis 3&4b – Interhemispheric Functional Connectivity Between Intention Nodes

The second test of this aim compared young and middle aged adults' bilateral preSMA functional connectivity of the attention network. Results from the Shapiro-Wilk test showed that z-transformed correlations between LpreSMA-RpreSMA in young adults did not differ significantly from a normal distribution, $W(21) = 0.98$, $p = 0.91$. Results from the Shapiro-Wilk test also showed that z-transformed correlations between LpreSMA-RpreSMA in middle aged adults did not differ significantly from a normal distribution, $W(13) = 0.90$, $p = 0.14$. However, inspection of the Q-Q plots and histograms revealed deviance from normality in the middle aged group. Results from Levene's test showed that the variance between the two groups were not significantly different, $F(1,32) = 0.07$, $p = 0.79$. Due to the non-normal distribution of one of the groups, the Mann-Whitney U Test was conducted (Table 6). Results from the Mann-Whitney U

Test revealed no difference between functional connectivity in young (*Mdn* = 0.66) and middle

aged adults (*Mdn* = 0.75), $U = 126$, $p = 0.71$, $r = 0.06$. One sample tests revealed that both young

adults (*M* = 0.65, *SD* = 0.63), $t(20) = 4.72$, $p = .000$ and middle aged adults (*Mdn* = 0.75), $Z =$

2.27, $p = .023$, showed inter-hemispheric correlations that were significantly different than zero.
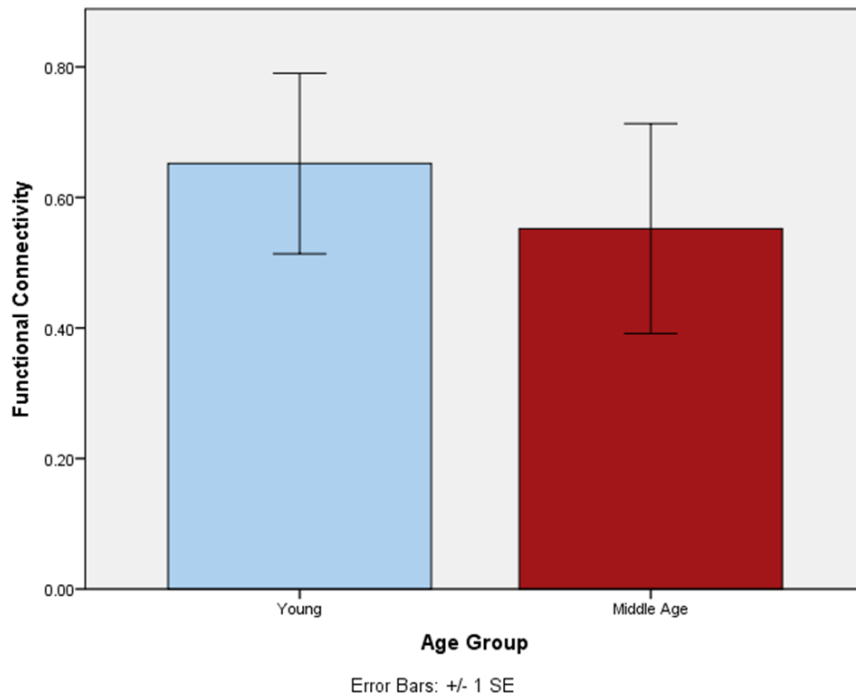
Figure 11. Interhemispheric Functional Connectivity of Intention Regions

Table 3. Aim 3 Age comparisons of interhemispheric functional connectivity

Network	Young		Middle Age				
	Median	IQR	Median	IQR	*U*	*p*	*r*
Language Node FC	0.51	0.34	0.56	0.5	117	0.49	0.12
Intention Node FC	0.66	1.06	0.75	1.15	126	0.71	0.06

FC= Functional Connectivity

4   DISCUSSION

In this study, we interrogated task-based and resting state approaches to characterize the

functional architecture of quintessential nodes in language and intention/attention. We observed

a significant difference in laterality between task-based residuals and resting state data. Task-residuals accentuated left lateralized communication between intrahemispheric nodes, extending a modest corpus of literature suggesting that functional connectivity is altered during task engagement and can be captured in task-residuals. We also examined the degree to which these network node connections were altered or fixed between young adulthood and midlife. The reduced functional connectivity between nodes of anticorrelated systems (i.e., intention and attention) at midlife demonstrates the importance of examining changes in cross-network interactions. Furthermore, that functional connectivity was reduced between regions of intention/attention but not language substantiates accounts that domain general and attention regions, including DMN connectivity, may be more susceptible to early age-related changes than other networks.

4.1   Task-Residual Versus Resting State Data

It was hypothesized that laterality of connectivity within language and executive attention networks derived from task residual data would be stronger (more left dominant) than resting state data. This hypothesis was supported by the present data for both language and attention, with the exception of the positive correlation of the posterior perisylvian region with Broca's area, which showed a trend towards significance in the hypothesized direction. Overall, the data suggest that task residual data highlights network specificity that is not present in the resting state data, yielding more strongly lateralized connectivity between language network regions.

Further testing of laterality of the positively correlated language connectivity demonstrated that left hemisphere regions were more strongly correlated than right in task residual data but not resting state data. A discrepancy in lateralized correlation could be due to a number of different reasons; a likely scenario would be that left hemisphere regions are

functionally connected while right hemisphere regions are not. It was revealed that right hemisphere functional connectivity indices were significant for both task residual and resting state data. However, despite the presence of right hemisphere connectivity, left hemisphere regions were still relatively more tightly coupled in their activity in task residual data. The fact that both left and right hemisphere functional connectivity were significant but equally strong in resting state data suggests that resting state data lacked the degree of network specificity that the task residual data afforded. The observed network specificity lends support to our conceptualization that preferentially increased activity in left hemisphere language regions during engagement in a language task remain in the residuals and show a correlation with one another above and beyond spontaneous and intrinsic fluctuations. Follow up tests of the intention/attention connections demonstrated that only correlations between left hemisphere task residual data were significantly different from zero. This is consistent with the finding that task residual data exhibited stronger left hemisphere laterality than resting state data. However, it is notable that resting state data did not yield significant connectivity between preSMA and PCPc regions.

The correlation between the anterior region dedicated to language functions and the posterior language region converging with DMN functions (characterized by negative activity in the posterior perisylvian region) was found to show stronger laterality in task residual data than resting state data. The possibility that this finding was driven by the task data having a larger discrepancy between left and right functional connectivity was the subject of further analyses. In these follow up comparisons between left and right regions, left hemisphere correlations were significantly stronger than right in task data but not resting state data, implicating an upregulation of left hemisphere activity and downregulation of irrelevant right hemisphere

activity. In resting state data, both left and right hemisphere correlations were significant, but in task residual data, only left hemisphere correlations were significant. Again, task residual data was more sensitive to lateralized effects of frontal language cortices on lateral portions of the DMN than resting state data. A possible explanation for this cross-network interaction is suppression of attentional mechanisms in the DMN so that subjects can focus on the demands of word generation in semantic and phonemic fluency.

It has been previously documented that task-based residual activity is sensitive to the functional interactions between regions and deemphasize activity of regions evoked in response to the same stimulus but do not interact (Al-Aidroos et al., 2012; Davis-Thompson & Andrews, 2012; Norman-Haignere et al., 2012). Previous accounts have largely focused on regions involved in face processing and visual attention. Our study extends this line of research by broadening the utility of task-residuals to explore nodes within language and executive attention networks. Although our study and the aforementioned experiments used slightly different analytical methods, markedly different tasks, and interrogate diverse networks, collectively, these investigations converge on the finding that task-based residuals can be used to feature the interdependence between regions of a network. Additionally, the functional interdependence reflects synchronized activity in the context of a task while accounting for stimulus-evoked responses.

4.2 Age-Related Changes

4.2.1 Intra- and Inter-Network Functional Connectivity

Our hypothesis that middle aged adults would exhibit differential interhemispheric functional connectivity when compared to young adults was not supported by the present data. This finding implies that the alterations in interhemispheric functional connectivity seen in older

adults are not observable at midlife. Thus, the question of dedifferentiation versus compensatory functions in aging cannot be determined by the present study. However, age-related differences were found between intrahemispheric attention regions. The data revealed that that middle aged adults exhibited weaker functional connectivity compared to young adults between left hemisphere regions of attention but not language. This finding suggests that at midlife, changes in functional connectivity between domain-general intentional and attentional systems is already evident, though changes in functional connectivity within domain-specific language systems do not reach significance. Our results corroborate other accounts that connections between DMN are more vulnerable to early age-related effects than other intrinsic networks (Hampson et al., 2013).

The present findings also support and extend established frameworks for understanding age-related change. Decreased functional connectivity between areas of the same network and increased functional connectivity between areas of discrete networks is a pattern of change described by an important distinction between intra-network and inter-network coupling (Antonenko et al., 2012, 2014; Ferreira et al., 2015; Chan et al, 2014). Antonenko and colleagues (2014) characterize intra-network coupling as the efficiency of communication between areas of the same network. In contrast, inter-network coupling is described as the successful differentiation from other networks. Under this framework, it can be restated that with increasing age, older adults undergo decreases in intra-network coupling and increases in inter-network coupling.

In the present study, we have referred to intra-network coupling as the equivalent of intra-hemispheric functional connectivity and inter-network coupling as inter-hemispheric functional connectivity. Although both decreased intra-network coupling and increased inter-

network coupling are observed in aging, our findings suggest that they do not occur simultaneously. We found changes in intrahemspheric but not interhemispheric functional connectivity at midlife; decreased intra-network coupling may occur relatively earlier in the course of aging compared to increased inter-network coupling. Reduced synchronized activity between constituent regions of a network (i.e., loss of intra-network coupling) may reflect and potentiate complex network reorganization that precedes dedifferentiation in functional connectivity (i.e., increased inter-network coupling).

Our findings extend the framework of intra- and inter-network coupling by additionally examining the interface of opposing systems. The network which we have broadly referred to as the attention network comprises regions that support intention and attention processes (Posner & Petersen, 1989). The opposing relationship between these two systems is characterized by an anticorrelation, in which one system activates while the other remits (Fox et al., 2006). This network dynamic is subtly different from the inter-network coupling described above. As we have discussed, loss of inter-network differentiation can reflect *increased* functional connectivity between regions of discrete networks. Contrastingly, when accounting for regions of discrete networks that consistently show an opposing interaction, disruption of this network dynamic results in *decreased* functional connectivity (Ferreira et al., 2015). In other words, the anticorrelation becomes weaker as networks lose their oppositional coherence. The age-related loss in functional connectivity between intention and attention systems found in the present study reinforces the concept of reduced inter-network segregation and functional distinctiveness in aging. This finding underlines the importance of integrating opposing network dynamics to the framework of understanding age-related changes.

4.2.2   Domain-General Versus Domain-Specific Networks

Furthermore, the age-related alterations do not affect all functional networks uniformly. Shifts in functional connectivity may selectively impact domain-general network regions during initial stages. Geerligs et al., (2015) found alterations in functional connectivity within networks supporting the DMN, cingulo-opercular, and fronto-parietal control networks, but not somatomotor and visual networks. Similarly, Chan et al. (2014) concluded that inter-network functional connectivity dramatically increased as a function of age in "association networks" (i.e., networks that integrate information across modalities), but less so in sensory networks. In their study, functional integrity of sensory networks (including visual, motor, and auditory systems) declined linearly with age. In contrast, the association networks (including cingulo-opercular control, dorsal attention, frontal-parietal control, salience, ventral attention, and default mode networks) exhibited a quadratic trend of decline; a gradual reduction in functional integrity was observed in earlier ages followed by marked declines after the fifth decade of life. These two studies suggest that alterations in the functional connectivity of networks do not occur uniformly across different brain systems, nor do they decline at the same rate.

In the context of the aforementioned studies, our findings further suggest that more complex functional networks (whose nodes participate in functions that traverse modalities, i.e., domain-general networks) may be more vulnerable to age related losses in functional integrity compared to highly specialized (domain-specific) networks. Although Chan and colleagues' study highlights how the functional independence of association networks decline more rapidly after the fifth decade, our results show that the precipice of these dramatic declines is still observable prior to the fifth decade of life, and that early declines are indeed network specific. Future studies will need to consider variable courses of age-related change for different

networks. Understanding how various functional systems and domains show differential deterioration will afford a more complete characterization of the neurocognitive aging process.

4.3 Convergence of Language and Default Mode Networks

The present thesis project deviated from the original proposal in that additional analyses were added in light of the observation that the posterior perisylvian region comprised discrete negative and positive activity. We thus interrogated the correlation between the anterior region dedicated to language functions and the posterior language region converging with DMN functions (characterized by negative activity in the posterior perisylvian region). Although this addendum was unanticipated, it was not unprecedented, as the posterior perisylvian region is not functionally homogenous. Functional dissociations have also been documented between the angular gyrus and posterior middle temporal gyrus, both of which are recruited for semantic retrieval (Davey et al., 2015). The posterior middle temporal gyrus appears more responsible for controlled, goal-directed semantic retrieval in the context of a task. It shows specific activation of weakly related semantic concepts in order to satisfy task demands rather than a general activation of strongly related semantic concepts. On the other hand, the mid-angular gyrus region is more responsible for automatic spreading activation of dominant semantic features. Davey et al. (2015) proposed that the mid-AG "could contribute to the reflexive (automatic) allocation of attention to activated concepts." In other words, the mid-AG engages in bottom-up semantic processing (as well as nonverbal processing) in the absence of executive demands or an explicit task, which are the conditions for acquiring resting state data. This latter finding is consistent with other studies linking the angular gyrus to the DMN: the AG demonstrates task-related deactivation (Seghier et al., 2010), shows activation during tasks involving episodic memory (Humphreys & Lambon Ralph, 2015), and has strong connections to regions implicated in the

DMN such as posterior cingulate, ventromedial prefrontal cortex, and hippocampus (Uddin et al., 2010). Thus, the degree to which regions of the PPS serve functions across domains and networks, its contribution may be considered domain-general.

4.4 Study Limitations

There were a number of limitations to this study. Firstly, the sample sizes for the two cohorts were of small and unequal numbers. A larger sample size for both groups would have increased statistical power to detect significant age-related differences. It is possible that the trend detected in aim 1 did not reach significance due to a lack of statistical power. However, that the observed trend was in the hypothesized direction offers an empirical warrant for further investigation.

Limitations due to lack of power also arise from the language task, as only one run was collected and participants engaged in alternating semantic and phonemic fluency. The single run yields a limited number of volumes from which to sample and model the time series to the block-convolved HRF. Additionally, although 10 stimuli were presented (five letters and five categories), the run was terminated during the last stimulus block. Consequently, the run ended before the fall of the hemodynamic response could be captured. This is less than ideal because it limits the number of hemodynamic transitions that increase power to model the HRF. The use of both semantic and phonemic stimuli in this task may also have reduced power because semantic and phonemic processes recruit slightly different regions (Humphreys & Lambon Ralph, 2014; Devlin et al., 2003). Thus, when averaging the response of active voxels in each ROI, the spatial distribution of activity reflected more heterogeneity than a single stimulus class would have, potentially reducing the coherence of correlations. Further, the lack of jittering induces multi-

colinearity in the design matrix, which prevents the use of model free methods of evaluating hemodynamic responses, such as deconvolution.

Another limitation was that data were collected with different acquisition parameters, as the two different size coils (8 and 32 channel) were used throughout the course of data collection. Consequently, participants varied in their voxel sizes (3x3x3mm versus 3x3x4mm) and acquisition type (sequential ascending, interleaved, versus Phillips interleaved). Accordingly, slice timing correction was handled differently and the smoothing kernel of 6mm FWHM affected data acquired with different geometries. The non-uniformity of preprocessing may introduce systematic noise.

Another notable matter pertains to the issue of circularity. Selection of relevant voxels from which to extract task-based and resting state time series were acquired from task data and used for analysis of both rest and task data. There appear to be two levels in which this procedure threatens to introduce bias. The first level is in the task-residual correlations. Kreigeskorte et al. (2009) argue that the selection of voxels cannot be based on the same data set in which analyses will be performed because it violates an assumption of random selection and that using the same data set to define ROIs will predetermine the results. In the present study, an *a priori* set of representative ROIs were used based on existing literature interrogating language and intention/attention domains and not dependent on the present data set. While it is true that the present study draws from the same data set to select relevant voxels within *a priori* ROIs, the data from which correlations are calculated is orthogonal to the data from which voxels are selected. Relevant voxels were based on the most active voxels evoked by the language task stimuli, which assumes time-invariance. Following this step, task-evoked responses were regressed from the data, yielding the resultant residuals used to calculate correlations. It is

arguable that the task-residual time series are statistically independent from the time series used to determine the relevant voxels. The threat of circularity is essentially a risk of type I error, or the acceptance of spurious results. In any given analysis, decisions are made to strike a balance between avoiding type I and type II errors. In the present study, the risk of type II error would come from a neglect of reducing the ROI to voxels most relevant to the task. For the purposes of this study, we needed to identify the specific voxels that would show the most response to the task and thus offer block by block variability. Failure to do so would reduce the signal to noise ratio and potentially lead to the acceptance of null results.

The second level in which the voxel selection procedure threatens to introduce bias is during the task-residual versus resting state comparison. It is possible that the most relevant voxels for the task-residual data are not the same voxels to generate correlations for resting state data. In this regard, the analysis is biased towards finding significant or stronger correlations in task-residual data than resting state data. An alternative analytic approach to circumvent this bias would be to use a seed-based functional connectivity approach. However, a number of studies have used task-based analyses as a means to interrogate resting-state connectivity (Wang et al., 2013; Cole et al., 2010). Hence, this method is well established in extant literature. Additionally, the use of both semantic and phonemic categories enabled the language voxels to be more broadly defined than a single stimulus class would offer. Thus, it can be argued that the voxels used to define the language system represented core or general language functions (as opposed to a unique or specific stimulus) which may be closer analog to general language connectivity in resting state data.

4.5   Conclusion

The present findings indicate that functional connectivity using task-residual data is a viable approach to characterizing the functional architecture of long-range connections. In addition to capturing spontaneous and intrinsic fluctuations, task-residuals afford greater specificity of network coherence than resting state data. Furthermore, alterations in intrahemispheric functional connectivity can be observed at midlife between domain-general intention/attention regions. Future studies should continue to explore changes across the adult lifespan to better understand differential patterns of brain network efficiency and disruption.

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