PRESERVATION OF FUNCTIONAL ORGANIZATION IN ALZHEIMER DISEASE

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Dedicated to Chris and Adrien.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: BACKGROUND

Introduction

Sustaining the complex range and flexibility of human cognition requires brain organization that is dynamic and flexible. In older adults, brain networks undergo a process of dedifferentiation, through which the networks become less functionally specialized relative to earlier in life (Balinksy, 1941; Baltes & Lindenberger, 1997). When dedifferentiation occurs, brain networks are no longer able to act adaptively and do not properly engage and disengage in response to the ever-changing demands of the environment. Thus, flexibility decreases and failures in cognitive processing occur. Despite compelling evidence that dedifferentiation occurs in healthy aging (Goh, 2011; Park et al., 2004), little is known about how Alzheimer Disease (AD) pathology affects this process. Critically, because AD pathology is observed in cognitively normal individuals, determining the relationship between AD-related pathology and dedifferentiation will aid in developing mechanistic explanations of cognitive aging.

Literature Review

As early as infancy, sets of regions begin to form networks that resemble the major functional networks typically present in adults. (Lin et al., 2008; Power, Fair, Schlaggar, & Petersen, 2010). During childhood development these smaller networks, or components, become increasingly segregated from other functionally-unrelated regions close in anatomical space, and more integrated with functionally-related regions in distant space, a property known as "small worldness" (Salvador et al., 2005). A general principle of network organization is that communities or modules of components in children and adolescents are arranged by anatomical proximity whereas communities in adults reflect functional relationships (Cao et al., 2014). This "local to distributed" characterization of networks has important implications for understanding

the development of the organizational structure of networks and how this progression is mirrored in cognitive abilities (Fair et al., 2009).

By the time individuals reach the latter decades of life, much of the beneficial small world organization has begun to unravel (Onoda & Yamaguchi, 2013). Deterioration of functional connectivity within major brain networks accelerates with increased age. However, age-related changes in functional connectivity are not isolated to connections *within* networks. Critically, strong anticorrelations, or negative relationships *between* some brain networks are needed to successfully carry out cognitive tasks. For example, the anticorrelation between the default mode network (DMN) and dorsal attention network (DAN) decreases at rest in older relative to younger adults (Spreng, Stevens, Viviano, & Schacter, 2016). When anticorrelations weaken, networks more easily become activated simultaneously, which leads to competition for cognitive resources, and consequently lower cognitive performance (Anticevic et al., 2012; Cabeza et al., 2004; Mennes et al., 2010; Mueller et al., 2013; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009; Weissman, Roberts, Visscher, & Woldorff, 2006). Combined, the diminished integrity of within-network functional connectivity and between-network anticorrelation indicate a breakdown in the intrinsic functional architecture of the brain that is consistent with dedifferentiation (Spreng et al., 2016).

Dedifferentiation in the Aging Brain

Dedifferentiation-centered hypotheses posit that alterations in functional organization arise due to global deficits in neural transmission, which in turn lead to the decreased specialization of neural representations (Baltes & Lindenberger, 1997; Goh, 2011; Li, Lindenberger, & Bäckman, 2010; Rajah & D'Esposito, 2005). The dedifferentiation model was initially introduced after observation that from younger to older adulthood there is an increasing

correlation between intelligence and sensory acuity (Baltes & Lindenberger, 1997). Subsequent studies have corroborated (de Frias, Lövdén, Lindenberger, & Nilsson, 2007; Wilson, Segawa, Hizel, Boyle, & Bennett, 2012) and expanded upon this account to include evidence of decreased specialization of neural systems (Dennis & Cabeza, 2011; Goh, 2011; Park et al., 2004). The dedifferentiation model is of particular importance to understanding neural function, as it provides a strong link between behavioral and brain-based theories of cognitive aging (Park & Reuter-Lorenz, 2009).

Neural activation patterns reflecting dedifferentiation, such as regional over-recruitment, have been demonstrated in task and resting-state neuroimaging studies and are thought to contribute to age-related changes in neural activation patterns. It is well established that compared to younger adults, older adults frequently over-recruit, or activate additional brain regions, during cognitive and behavioral tasks (Baltes & Smith, 2003; Barulli & Stern, 2013; Grady, 2008; Park & McDonough, 2013; Reuter-Lorenz & Park, 2010). Age-related over-recruitment is typically observed in prefrontal regions and may present as 1-over-activation in the same regions as younger adults, 2- activation in additional regions not activated by younger adults, or 3- additional activation in equivalent regions contra-lateral to the side activated in younger adults (Grady, 2008; Park & McDonough, 2013; Reuter-Lorenz & Park, 2010). The dedifferentiation model hypothesizes that over-recruitment, presenting in any of these 3 manifestations, arises as a consequence of decreases in the specialization of cortical areas, which in turn leads to the decreases in the specialization of cognitive abilities (Baltes & Lindenberger, 1997; Goh, 2011; Li, Lindenberger, & Sikström, 2001; Rajah & D'Esposito, 2005).

In addition to over-recruiting prefrontal regions, cognitively normal older adults are more likely than younger adults to demonstrate patterns of task-related under-recruitment and non-

selective recruitment, or the recruitment of task-irrelevant areas (Cabeza, 2002; Grady, 2008; Logan, Sanders, Snyder, Morris, & Buckner, 2002; Maillet & Rajah, 2014; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Lustig, 2005; Schneider-Garces et al., 2008). Given that under-recruitment can be reversed with supportive task conditions, it has been hypothesized that under-recruitment reflects ineffective utilization of prefrontal resources, as opposed to an absence of resources (Logan et al., 2002). Conversely, non-selective recruitment may reflect more deleterious and irreversible effects of cognitive decline in advanced aging, as the dedifferentiation model postulates (Logan et al., 2002).

While task fMRI is useful for identifying which regions are activated during tasks, resting-state fMRI is an informative tool for capturing dynamic and spontaneous neural activity of the brain (Buckner, Andrews-Hanna, & Schacter, 2008; Damoiseaux et al., 2006; Fox et al., 2005; Mennes et al., 2010; Sheline & Raichle, 2013). Studies examining the brain have revealed that intrinsic activity is highly correlated between regions that are functionally related, even in the absence of external stimuli (Fox et al., 2005). Two primary analysis methods are used to examine spontaneous brain activity. The first method measures the characteristics of the resting state signal within specific regions of the brain (e.g., regional homogeneity and amplitude of low frequency fluctuations; Zou et al., 2008). The second method assesses the relationship within and between brain networks using functional connectivity measures. Both resting-state analysis methods reveal diminishing functional connectivity between regions with increasing age. This is especially true of regions within the DMN (Damoiseaux et al., 2008; Grady, Sarraf, Saverino, & Campbell, 2016; Koch et al., 2010; Wu et al., 2011), which exhibits less activity during attention-demanding tasks, and more activity during wakeful rest, introspective and unconstrained thought, and mind-wandering (Fox et al., 2005; Mennes et al., 2010; Spreng,

Sepulcre, Turner, Stevens, & Schacter, 2013; Spreng et al., 2016; Tomasi & Volkow, 2012). However, age-related reductions in functional connectivity are not isolated to the DMN. Decreased functional connectivity is also observed within theDAN, frontoparietal control network (FPC), and salience network (SAL; Grady et al., 2016; He et al., 2014; Li et al., 2015; Tomasi & Volkow, 2012). Interestingly, regions comprising the DMN, DAN, and FPC are also typically over-recruited during cognitive tasks in healthy older adults compared to young adults, suggesting that deteriorating functional networks contribute to the abnormal activation patterns observed during cognitive tasks in aging.

In addition to traditional resting-state analytic methods, graph theory-based approaches have increasingly been applied to resting state fMRI data to characterize the topological organization of the brain and its networks (Bullmore & Sporns, 2009, 2012; Rubinov & Sporns, 2010; Smith, 2012). Because they do not require a priori hypotheses, data-driven approaches are particularly beneficial for generating models for data when there is no existing or satisfactory model available. Graph theory-based analyses of functional connectivity have led to important revelations about organizing principles of the human brain, as well as the conditions under which the brain functions most efficiently (Bassett, Zurn, & Gold, 2018; Bullmore & Sporns, 2012; Rubinov & Sporns, 2010). Brain organization principles affect not only network functioning, but also behavior and cognitive performance. Thus, when organization is adversely altered, as arises in pathological aging and AD, cognitive and affective functioning suffers.

AD Pathology and Functional Organization of the Brain

AD, the most common cause of dementia, is defined by the presence of amyloid-beta plaques and tau tangles (Holtzman, Morris, & Goate, 2011; Jack & Holtzman, 2013). In cerebrospinal fluid (CSF), the presence of amyloid is reflected by decreased levels of Aβ42 and

increased levels of tau in individuals with AD, compared with cognitively normal older adults (Galasko et al., 1998; Kapaki, Kilidireas, Paraskevas, Michalopoulou, & Patsouris, 2001). Pathological biomarkers can be detected up to two decades before the onset of cognitive symptoms (Jack et al., 2013). Due to the discrepancy between pathology accumulation and clinical symptom onset, it is imperative to detect AD biomarkers and identify effective intervention targets as early as possible. AD was traditionally staged using clinical assessments such as the Clinical Dementia Rating Scale (CDR; Morris, 1993) because amyloid and tau have not always been observable pre-mortem. The CDR is derived from semi-structured interviews with the individual in question as well as someone close to them. It assesses cognition and daily functioning and designates the individual between CDR 0-3 (CDR 0 = cognitively normal; CDR 0.5 = very mild impairment; CDR 1 = mild impairment; CDR 2 = moderate impairment; and CDR 3 = severe impairment; Morris, 1993).

Although AD is typically staged using clinical assessments such as the CDR, recent efforts have been made to stage AD using the pathological biomarkers (e.g., amyloid and tau) that characterize the disease (Jack et al., 2018). Specifically, the National Institute on Aging and the Alzheimer's Association have outlined a research framework that stages AD through the presence of amyloid (A), tau (T), and neurodegeneration or neuronal injury ((N); Jack et al., 2018). This framework additionally allows for the distinction between biomarker profiles that are specific to AD (i.e., A+ with or without the presence of T+ and/or N+) versus those that are not (i.e., A-, even in the presence of T+ and/or N+). However, it should be noted that although a pathologic profile may be specific to AD (i.e., A+), it may not be sufficient for the development of AD. Tau is additionally needed for AD to be present. Due to the continuous nature of the ATN

framework, new biomarkers beyond ATN can be added as they are identified. The ATN framework therefore grounds AD diagnosis in biology rather than behavioral observations.

AD is often described as a disconnection syndrome due to the observed alterations in structural and functional connectivity of brain regions resulting from accumulations of amyloid and tau (Brier et al., 2012; Delbeuck, Linden, & Collette, 2003; Greicius, Srivastava, Reiss, Menon, & Raichle, 2004; Khazaee, Ebrahimzadeh, & Babajani-Feremi, 2015). The first brain network with dysfunction identified in AD was the DMN, which is also the first network to display elevated irregular amyloid accumulation, tau deposition, and synaptic dysfunction (Buckner et al., 2008; Sheline & Raichle, 2013). Individuals with mild AD demonstrate decreased functional connectivity of regions within DMN and between the DMN and specific attention networks (Sorg et al., 2007; Zhong et al., 2014). Notably, functional abnormalities in the DMN typically appear even before most AD-related structural brain changes, highlighting the importance for early detection of breakdowns in functional connectivity and organization (Brier et al., 2012; Sheline & Raichle, 2013).

Review of the literature on resting state networks in pathological aging leads to the conclusion that changes in functional brain network connectivity arise in a systematic pattern. For example, Brier and colleagues (2012) demonstrated that functional connectivity decreases from CDR 0 to 1 in networks other than the DMN. Specifically, from CDR 0 to CDR 0.5 within-network correlations decreased in FPC, DAN, and sensory-motor (SM) networks, but increased in the SAL network. By CDR 1, within-network connectivity in each of these networks, including SAL, was significantly lower than CDR 0 and CDR 0.5. Between-network anticorrelations also consistently decreased with AD progression, suggesting widespread loss of network integrity (Brier et al., 2012).

Topological changes in organization of the brain, such as loss of small-worldness (Sanz-Arigita et al., 2010), increased dedifferentiation (Brier et al., 2014), and alterations in regional centrality (i.e., number of interactions between a particular brain region and many other regions; (Khazaee, Ebrahimzadeh, & Babajani-Feremi, 2017), have been observed with increasing CDR status . Brain networks are most effective at carrying out cognitive and behavioral tasks when organized in a small-world fashion (i.e., regions are more segregated from other functionally-unrelated regions close in space and more integrated with functionally-related regions in distant space). When properties of segregation and integration begin to break down, individuals are no longer able to function optimally. Furthermore, when regions that are (typically) densely interconnected become less interconnected, the network to which the regions belong is more likely to become widely distributed (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). This property, known as the assortativity coefficient, is indicative of how vulnerable a network is to threats such as AD pathology, cellular degeneration, and cerebrovascular damage (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). Thus, as networks become more widely distributed and less assortative, they become less resilient to neural insult. Given that networks lose interconnections with increasing CDR status it is important to determine whether individuals with greater AD pathology are more susceptible to deterioration of networks long term, and if so, at which stage ATN of AD.

Accumulations of amyloid and tau are associated with the rampant breakdowns of functional organization in the aging brain (Gordon et al., 2018; Hedden et al., 2009; Sheline et al., 2010; Sheline & Raichle, 2013). These findings are observed not only in CDR 0.5+ individuals , but also in cognitively normal adults (CDR 0) harboring pathological biomarkers, particularly amyloid (Brier et al., 2014). Thus, it is reasonable to hypothesize that AD-related

biomarkers causally contribute to the dedifferentiation of functional networks in older adults with and without a clinical diagnosis of AD. However, most research on dedifferentiation has not taken into account whether participants harbor pathological biomarkers, and instead focuses on whether the individual is "cognitively normal" by clinical standards (e.g., CDR 0). Investigating neural dedifferentiation using the ATN framework will elucidate to what extent dedifferentiation occurs as a part of healthy aging versus how much occurs due to AD-related pathology. Furthermore, characterizing the process of dedifferentiation as a function of AD biomarkers will help inform mechanistic explanations of healthy and pathological cognitive aging and also aid in determining the most effective targets and staging for therapeutic interventions. For example, if the accumulation of amyloid is associated with the greatest increase in dedifferentiation, it will provide evidence for the potential benefit of pharmacological treatments that target amyloid deposition.

CHAPTER 2: AIMS AND HYPOTHESES

Despite the well-established functional organization alterations and dedifferentiation in older adults, little is known about how the process differs as a function of Alzheimer pathological biomarkers, irrespective of clinical diagnosis or behavioral presentation. The primary aim (Aim 1) of the proposed study was to compare ATN group differences in measures of network dedifferentiation (i.e., segregation) and vulnerability to threat (i.e., assortativity coefficient). Secondary aims were to: 2) Assess and compare the relationship between amyloid-beta and dedifferentiation to the relationship between tau and dedifferentiation; 3) Assess the relationship between network dedifferentiation and vulnerability to threat.

To carry out the above aims, graph theory-based methods were employed to compute the degree of network segregation and assortativity for each individual with respect to the ATN framework (i.e., biomarker free (A-T-N-); amyloid positive only (A+T-N-); amyloid positive and tau and/or neurodegeneration positive (collectively called A+T+N+); amyloid negative, but tau and/or neurodegeneration positive (collectively called A-T+N+); Jack et al., 2018) to characterize biomarker status. For the sake of this study, the A+T+N+ group broadly encompasses AD specific pathologic profiles, including individuals who were A+T+N-, A+T-N+, or A+T+N+. In contrast, for the sake of this study, the A-T+N+ group broadly encompasses non-AD specific profiles, including individuals who were amyloid negative irrespective of tau or neurodegeneration status (i.e., A-T+N-, A-T-N+, or A-T+N+). For Aim 1, I hypothesized that segregation and assortativity would be lower in individuals harboring pathologic biomarkers (i.e., A+T-N-, A+T+N+, and A-T+N+ groups) compared to biomarker free individuals (A-T-N-). For Aim 2, I expected that decreases in segregation would be correlated with lower CSF amyloid and higher CSF tau, irrespective of ATN status. I also expected that the relationship between

segregation and amyloid would be significantly stronger than the relationship between segregation and tau. Lastly, for Aim 3, I expected that network segregation and assortativity would be positively correlated.

CHAPTER 3: METHOD

Participants

Data were obtained from individuals enrolled in memory and aging studies at the Alzheimer's Disease Research Center (ADRC) at Washington University in St. Louis, MO (Berg et al., 1998). Participants were at least 40 years old and classified as either CDR 0, 0.5, or 1. To be retained for the present analyses, participants' neuroimaging, CSF, and neuropsychological data had to be collected within three years of one another. Individuals with any major comorbid neurological or neuropsychological disorder, such as major depression, cerebrovascular disease, or traumatic brain injury, were excluded from the analyses. It should be noted that age data was missing for 28 individuals. Furthermore, there was a significant age difference between ATN groups ($F(3, 401)=2.92$, $p<0.001$, eta squared=0.10) such that the A+T+N+ and A-T+N+ groups were older than the A-T-N- group (all ps<0.001). The A+T+N+ group was also older than the A-T+N+ group ($p<0.001$; see **Table 1** for group means and participant characteristics).

Clinical Assessment

All CDRs were obtained from assessments by experienced clinicians trained in the use of the CDR. The CDR is used to determine whether dementia is present and, if so, to stage its severity. When using global scores, a CDR of 0 indicates that the individual is still "cognitively normal" while CDR 0.5 and CDR 1 indicate very mild and mild AD, respectively (Morris, 1993). All participants with a CDR > 0 had a clinical diagnosis of dementia of the Alzheimer's type in accordance with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (Brier et al., 2012; Buckner et al., 2009b; McKhann et al., 1984; Sperling et al., 2009).

Table 1. Participant characteristics by ATN status.

	A-T-N-	**A+T-N-**	**A+T+N+**	**A-T+N+**
N	168	105	88 (A+T+N-: 76; A+T-N+: 10; A+T+N+: 2)	71 (A-T+N-: 55; A-T-N+: 13; A-T+N+: 3)
Age[1] mean (SD)	64.2 (8.1)	66.0 (8.5)	71.1 (7.0)	68.9 (7.3)
Age[1] range	45-78	42-83	50-82	48-81
% Female	64%	50%	47%	51%
Mean CSF aβ42 (SD)	1633.0 (392.2)	768.5 (224.2)	691.4 (213.8)	1957.0 (734.7)
Mean CSF tau (SD)	184.9 (37.0)	162.5 (47.6)	353.5 (139.7)	299.6 (85.8)
Mean neurodegeneration (i.e., standardized cortical signature) (SD)	0.266 (0.84)	0.005 (0.88)	-0.389 (1.09)	-0.181 (1.17)

[1] Age data were missing for 28 individuals.

National Institute on Aging ATN Framework

While the CDR is often used for a clinical diagnosis of AD, there has been a recent push and growing movement to diagnose and stage AD in biology-driven way. The National Institute on Aging and the Alzheimer's Association have proposed a research framework that stages AD through the presence of A, T, and N; Jack et al., 2018). Accordingly, individuals were categorized as either A-T-N-, A+T-N-, A+T+N+, or A-T+N+. CSF amyloid positivity was defined by a concentration of Ab42 < 500 pg/mL (Morris et al., 2010; Wang et al., 2013), CSF tau positivity was defined as concentration of t-tau > 440 pg/mL (Morris et al., 2010), and neurodegeneration positivity was defined by the presence of cortical thinning or diminished cortical signature in individuals with the presence of biomarkers compared to biomarker free

individuals (see Dickerson et al., 2009 and Wang et al., 2015 for description of cortical signature).

CSF Analysis

CSF (20-30 mL) was collected by lumbar puncture (LP) using a 22-gauge Sprotte spinal needle (Geisingen, Germany). LPs were performed in the morning after overnight fasting by a trained neurologist. CSF was aliquoted (500 ul) into polypropylene tubes and was free of visible blood contamination. After collection, samples were gently inverted and frozen at -84°C. CSF was analyzed for Ab42 and tau by enzyme-linked immunosorbent assay (Innotest; Innogenetics, Ghent, Belgium; see Fagan et al., 2006 for additional details).

Image Acquisition

Imaging was performed using a 3.0 Tesla Siemens (Erlangen, Germany) MRI scanner equipped with a 12-channel head coil. For atlas registration, a high-resolution 3-dimensional sagittal T1 magnetization-prepared rapid gradient echo (MP-RAGE) anatomical image was acquired with the scanning parameters of repetition time (TR) = 2400 ms, echo time (TE) = 16 ms, inversion time = 1000 ms, flip angle = 8°, 176 slices, slice thickness = 1.00 mm, acquisition matrix = 256 x 256, and 1 mm isotropic voxels. For rs-fcMRI atlas registration, high-resolution 3-dimensional oblique axial spin density and/or T2-weighted fast spin echo structural images were acquired using slice tilts and positions computed by slice pre-registration with the scanning parameters of TR = 3200 ms, echo time TE = 455 ms, acquisition matrix = 256 x 256, and 1 mm isotropic voxels. Functional images were collected using a gradient spin-echo sequence (TR = 2200 ms, TE = 27 msec, field of view = 256 mm, flip angle = 90°, 4 mm isotropic voxels, and 36 slices) sensitive to the BOLD contrast (T2* weighting). Two 6 minute rs-fcMRI runs (164 volumes per run) were acquired during which participants were instructed to fixate on a visual

crosshair and not fall asleep. Further image acquisition details were reported by Brier and colleagues (2012, 2014).

rs-fcMRI Preprocessing

rs-fcMRI images were processed by adjusting all volumes for slice timing and realignment. Functional images were intensity scaled to acquire a mode value of 1000, to facilitate assessment of voxel-wise variance for quality assurance (Ojemann et al., 1997). Normalization was performed using composition affine transforms to align the rs-fcMRI volumes with the T2-weighted and magnetization-prepared rapid gradient echo images, and images were resampled to a voxel size of 3 mm x 3mm x 3mm followed by spatial smoothing with a Gaussian kernel of 6 mm full width at half maximum (FWHM). Data were also temporally filtered to remove linear trends over each run and to retain frequencies below 0.1 Hz. Finally, global signal regression (GSR) was conducted to reduce spurious variance by regressing out nuisance signal from white matter and CSF (Fox, Zhang, Snyder, & Raichle, 2009). Further preprocessing details were reported by Brier and colleagues (2012, 2014).

Quality Assurance

Although GSR can mitigate the impact of motion and physiological noise, additional steps are needed for quality assurance, as the effects of motion can persist after regression of the movement covariate (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). To address this issue, volumes with excessively high (0.4 mm framewise displacement) movement over time were removed without replacement (Power et al., 2012). Only individuals with <20% excluded frames were retained.

ROIs

Two hundred and sixty-four (5 mm radius) regions of interest (ROIs) were placed throughout the brain based on previously published work (Power et al., 2011). ROIs were selected because they have been previously validated as adequately sampling various RSNs and sufficiently cover cortical and subcortical structures, excluding the cerebellum. Correlation matrices were calculated by extracting the mean BOLD time course from each ROI. The Pearson correlation coefficient (r) was computed between the time course of a single ROI and all other ROIs, and then Fisher z(r) transformed (see Brier et al., 2012, 2014).

Graph Theoretical Analysis

For the present study, graph analyses were used to examine functional brain network organization. In graph theory-based models, networks are represented as a graph consisting of vertices (or nodes) and edges, or connections between nodes (see **Figure 3**; Bullmore & Sporns, 2009; Bullmore & Sporns, 2012; Rubinov & Sporns, 2010). For assortativity, binary, or undirected (i.e., no causal direction implied), graphs were created and indicate whether or not an edge exists, which in turn indicates whether relationship between nodes exists.

In the present study, nodes are represented by ROIs and their edges are represented by the time series correlation matrix among ROIs. The undirected graphs were created separately for each individual using the following steps. First, a 264 x 264 correlation matrix comprised of time courses for each ROI to every other ROI was created. Second, edges for assortativity were defined using threshold values based on connection density, or the ratio of the number of connections in a network to the total number of connections possible. In order to determine the existence of edges for the assortativity coefficient, a threshold of 0.05 was applied to the time series correlation matrix. Past research has demonstrated that real cortical networks display

connection densities in this range (Jalili, 2017). When the correlation (r) exceeds the threshold, an edge, or connection between two nodes, exists. If r does not exceed the threshold, no edge exists. After the threshold value was determined, a 264 x 264 adjacency matrix was computed from the correlation matrix for each individual, where each cell contains a binary value (0, 1) denoting whether edge strength surpassed the connection density threshold. Lastly, segregation values (as detailed below) were computed in R (version 3.5.1; R Foundation for Statistical Computing) and network assortativity (as detailed below) was calculated using the GRETNA toolbox for Matlab (Wang et al., 2015).

Graph Network Indices

Functional Segregation

Functional segregation in the brain allows for specialized cognitive processing to occur within groups of brain regions that are densely interconnected (see **Figure 3**). The purpose of segregation measures is to quantify the presence of these groups, which are often referred to as modules. Within functional networks, the presence of modules suggests segregated neural processing of operations, as modules often map to specialized functional areas (Rubinov & Sporns, 2010). Thus, lower segregation values reflect a reduction in the specialization of networks. Segregation was computed by taking the difference of the mean between-network correlation from the average within-network correlation as a proportion of average within-network correlation (Chan et al., 2014):

$$\text{Segregation} = \frac{\bar{Z}_{Within} - \bar{Z}_{Between}}{\bar{Z}_{Within}}$$

where $\bar{Z}_{Within}$ is the mean z-transformed correlation between ROIs within a network and $\bar{Z}_{Between}$ is the mean z-transformed correlation between ROIs between networks (Chan et al.,

2014). This computation of segregation is particularly useful because it allows for positive *and* negative connections (i.e., anticorrelations) to contribute to the characterization of the graph.

Assortativity

Assortativity indicates the degree to which densely connected nodes connect to other densely connected nodes on opposite ends of a link. In GRETNA (Wang et al., 2015), assortativity is the correlation between the degrees of all nodes on two opposite ends of a link. A positive assortativity coefficient reflects central nodes (or hubs) that are more interconnected. Conversely, a negative assortativity coefficient reflects nodes that are less interconnected. Networks with negative assortativity are more likely to be widely distributed and are therefore more vulnerable to threat (Bullmore & Sporns, 2010; Rubinov & Sporns, 2010).

Analyses

Statistical analyses assessed 1) ATN group differences in measures of network segregation and assortativity; 2) the relationship between amyloid-beta and segregation, and between tau and segregation, as well as differences in strength of associations; and 3) the relationship between segregation and network assortativity. To test hypothesis 1, graph theoretical indices (i.e., segregation and assortativity) were computed for each individual. To determine how biomarker status impacts segregation and assortativity, a MANOVA was conducted with biomarker status (i.e., A-T-N-, A+T-N-, A+T+N+, and A-T+N+) as the independent variable and the graph theory indices (i.e., segregation and assortativity coefficients) as the dependent variables. Bonferroni corrected follow-up tests were used to discern where biomarker status group differences exist, correcting for multiple comparisons. To test hypothesis 2, a two-stage hierarchical regression model was performed with CSF amyloid entered at stage 1 as a predictor of whole-brain segregation, and CSF tau added at stage 2. Finally, to test

hypothesis 3, network segregation and assortativity were correlated using a one-tailed Pearson's r.

Because differences in segregation may be observed at the network-level rather than global level, exploratory follow-up analyses were also performed. Specifically, ANOVAs were conducted for each of the major association networks: DMN, SAL, DAN, FPC, cingulo-opercular network, ventral attention network, and memory network (Power et al., 2011). Again, ATN status was the independent variable and network segregation was the dependent variable. Additional ANOVAs with age as a covariate were conducted for significant models. Pearson's r correlation analyses were also used to assess the relationships of whole-brain segregation and assortativity to age.

Power Analysis

A power analysis was conducted in G*Power (Erdfelder, Faul, & Buchner, 1996) to determine sample size was based on Aim 1, a multivariate analysis of variance (MANOVA) with independent variable of biomarker status (4 levels: A-T-N-, A+T-N-, A+T+N+, and A-T+N+) and dependent variables of segregation and assortativity, at an alpha of 0.05, a power level of 0.80, and a medium effect size of f = 0.25. Power analysis indicated that an overall sample of 68 (17 per group) would provide sufficient statistical power to detect significant effects. Power analyses also indicated that to obtain an adequate sample size to detect prediction and correlations (i.e., Aims 2 and 3) at an alpha of 0.05, a power level of 0.80, and a medium effect size of r=0.30 and R^2=0.15 64 participants are needed for correlations and 43 participants are needed for prediction. The present sample of 432 exceeds this number.

CHAPTER 4: RESULTS

Whole-brain segregation and assortativity do not differ as a function of ATN status

Results from the MANOVA indicated that there was no main effect of ATN status on segregation or assortativity (see **Table 2**), $F(3,428)=1.18$, $p=0.31$, Pillai's Trace=0.02.

Table 2. Mean whole-brain segregation and assortativity by ATN status.

	A-T-N-	**A+T-N-**	**A+T+N+**	**A-T+N+**
Mean Segregation (SD)	1.01 (0.02)	1.00 (0.02)	1.01 (0.02)	1.00 (0.02)
Mean Assortativity (SD)	0.36 (0.11)	0.35 (0.11)	0.34 (0.09)	0.34 (0.11)

CSF amyloid and tau do not predict whole-brain segregation

Results of the two-stage hierarchical regression indicated that neither stage 1 with amyloid ($R^2=0.00$, $F(1,430)=0.16$, $p=0.69$) nor stage 2 with tau ($R^2=0.01$, $F(2,429)=1.58$, $p=0.21$) predicted whole-brain segregation.

Whole-brain segregation and assortativity are positively correlated

A one-tailed Pearson's r correlation analysis was performed to assess the relationship between segregation and assortativity. Results demonstrated that segregation and assortativity were positively correlated, $r(430)=0.11$, $p=0.02$ (see **Figure 1**).

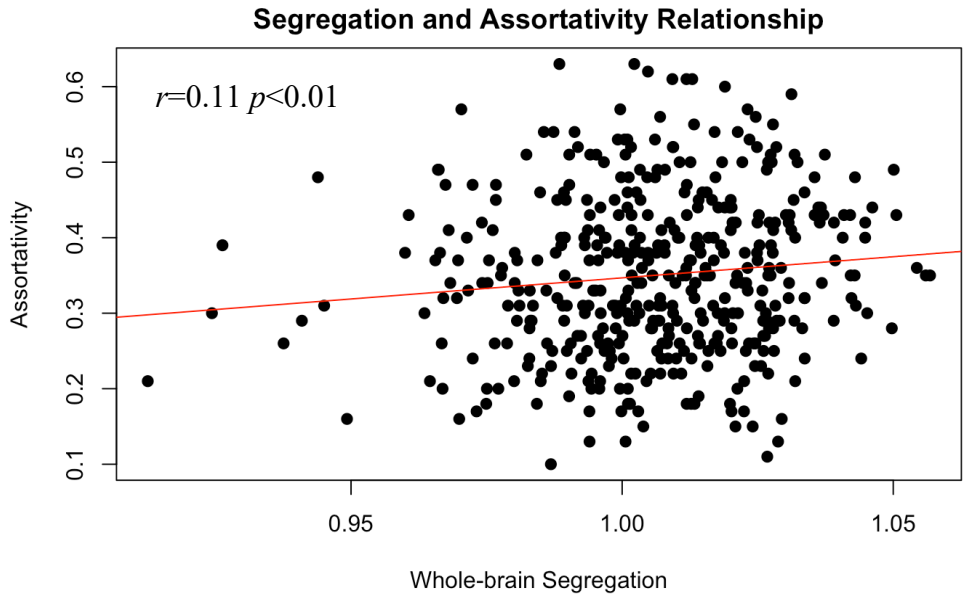

Figure 1. Positive relationship between whole-brain segregation and assortativity.

Segregation of Default Mode and Salience networks differ by ATN status

Of the 7 individual networks assessed, only DMN ($F(3,428)=5.35$, $p=0.001$, eta squared=0.04) and SAL ($F(3,428)=3.28$, $p<0.05$, eta squared=0.02) demonstrated a main effect of ATN status on segregation (all other Fs(3,428)<1.57, all ps>0.35, all eta squared<0.01) .

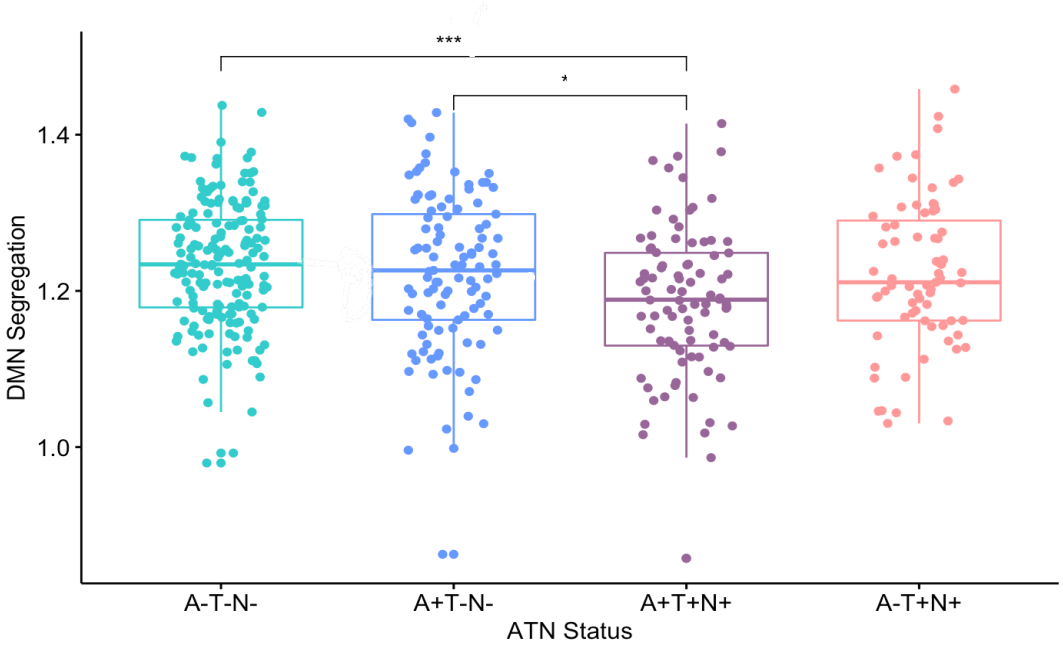

Figure 2. Mean Default Mode network (DMN) segregation greater in A-T-N- and A+T-N- than A+T+N+. ***=$p<0.001$, *=$p<0.05$.

Segregation of the DMN (see **Figure 2**) was greater in the A-T-N- (*M*=1.23, *SD*=0.08) group than in the A+T+N+ (*M*=1.19, *SD*=0.09; *p*<0.001, Cohen's d=0.56), and in the A+T-N- (*M*=1.22, *SD*=0.09) than in the A+T+N+ group (*p*<0.05, Cohen's d=0.37). All other comparisons between ATN groups did not surpass threshold for significance (*p*s>0.07). The main effect of ATN status on DMN segregation remained significant after controlling for age (*F*(3,397)=3.12, *p*<0.05, eta squared=0.02). Furthermore, there was also a significant effect of age (*F*(1,397)=4.43, *p*<0.05, eta squared=0.01) on DMN segregation although there was no interaction between ATN status and age (*F*(3,397)=1.83, *p*=0.14, eta squared=0.01).

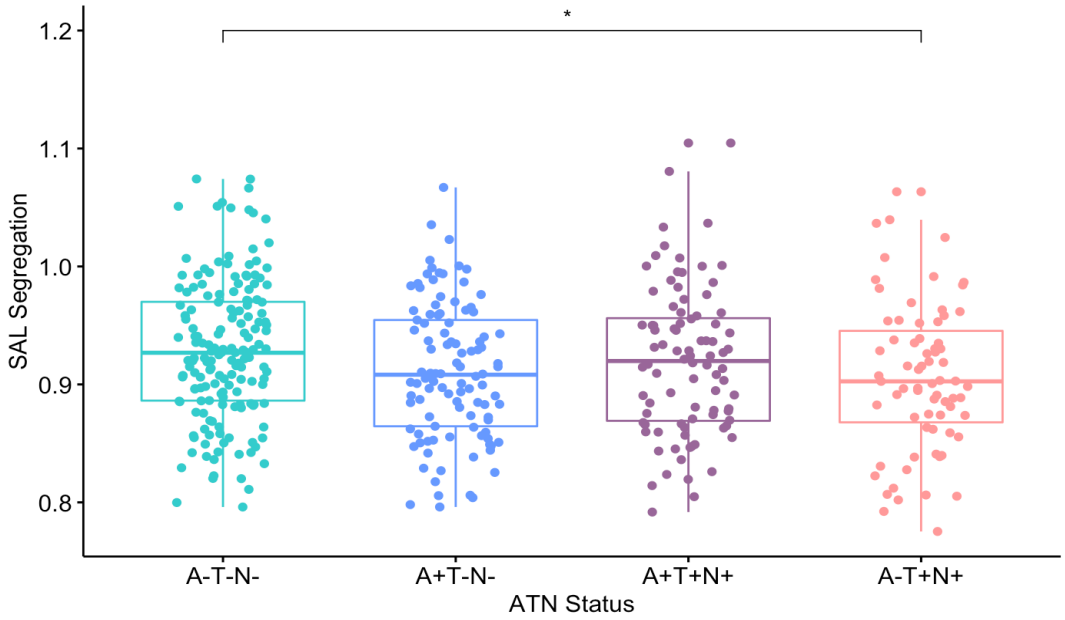

Figure 3. Mean Salience network (SAL) segregation greater in A-T-N- than A-T+N+. *=*p*<0.05.

Segregation of the SAL (see **Figure 3**) was greater in the A-T-N- (*M*=0.93, *SD*=0.06) group than in the A-T+N+ (*M*=0.91, *SD*=0.06; *p*<0.05, Cohen's d=0.38). All other comparisons between ATN groups did not surpass threshold for significance (*p*s>0.08). The main effect of ATN status on SAL segregation remained significant after controlling for age (*F*(3,397)=3.75, *p*=0.01, eta squared=0.03). There was no effect of age (*F*(1,397)=0.94, *p*=0.33, eta

squared=0.002) on DMN segregation or interaction between ATN status and age ($F(3,397)=1.95$, $p=0.12$, eta squared=0.01).

Segregation and assortativity are negatively correlated with age

Results from the Pearson's r correlation analyses indicate that both segregation ($r(403)= -0.15$, $p<0.01$) and assortativity ($r(403)= -0.15$, $p<0.01$) are negatively related to age; assortativity and segregation both decrease with aging (see **Figure 4**).

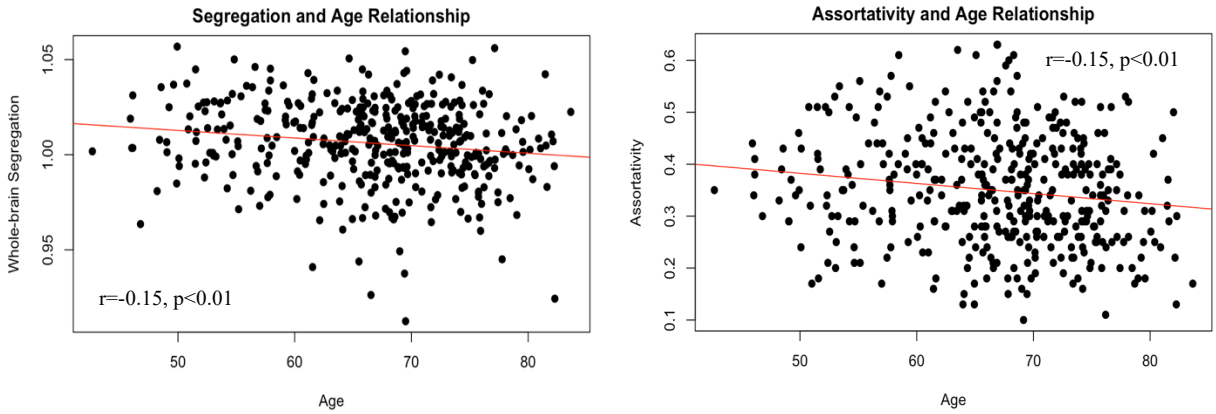

Figure 4. Segregation and assortativity decrease with age.

CHAPTER 5: DISCUSSION

The primary purpose of the present study was to characterize changes in brain functional organization in relation to AD biomarkers. Specifically, this study compared differences in measures of network dedifferentiation and vulnerability to threat (i.e., segregation and assortativity, respectively) using the ATN framework. Secondary goals included assessing the relationship among network dedifferentiation, vulnerability, tau, and amyloid burden Overall, it was expected that whole-brain dedifferentiation and vulnerability to threat would be positively related, and that each would differ as a function of ATN positive status (i.e., A+T-N-, A+T+N+, and A-T+N+) compared to biomarker negative individuals. Results demonstrated that dedifferentiation increases as vulnerability increases, however, dedifferentiation and vulnerability do not differ by ATN status, nor are they associated with CSF amyloid or tau. Follow-up exploratory analyses revealed that both dedifferentiation and vulnerability to threat increase with age, and that any effects of AD biomarkers on dedifferentiation are specific to particular networks (DMN and SAL), indicating that AD pathology does not have an effect on global organizational properties.

Of greatest interest was the question of whether there is a difference in functional organization between older adults harboring amyloid-beta versus those who do not. Chan and colleagues (2014) found that dedifferentiation (represented by graph-theoretical segregation measures) increases with age; however, their study did not take into account whether older adults were amyloid (or tau) positive. In contrast, Brier and colleagues (2014) demonstrated that although dedifferentiation, as measured by the network clustering coefficient, was not affected by age, dedifferentiation was greater in cognitively normal individuals (CDR 0) with CSF amyloid burden compared to those without. The present study combined methods from both of

these studies by utilizing the segregation formula employed by Chan and colleagues (2014), while taking into account AD biomarker status from Brier (2014), and additionally considering relationship to network vulnerability. Results from the present study largely support findings from Chan and colleagues (2014) suggesting that, at the global level, dedifferentiation is an aging-related process.

Despite a lack of effect of ATN status on global dedifferentiation and vulnerability to threat, there was evidence of network-specific alterations in functional organization. The DMN, which demonstrated greater dedifferentiation with increasing pathology, typically undergoes functional changes earlier than other brain functional networks (Brier et al., 2012; Sheline & Raichle, 2013), and is also the first network to display elevated levels of amyloid accumulation, tau depositions, and synaptic dysfunction (Buckner et al., 2008; Sheline & Raichle, 2013). The present results support this pattern of findings and demonstrate that functional organization of DMN deteriorates with elevated levels of amyloid and tau and increased neurodegeneration. Specifically, DMN dedifferentiation was greater in individuals with AD pathology compared to biomarker free and amyloid-only individuals. This finding suggests that although DMN dedifferentiation is specific to AD, it occurs later in the ATN staging. Thus, amyloid accumulation is not sufficient for altering organization; individuals must also demonstrate tau burden and/or neurodegeneration.

The salience network additionally demonstrated greater dedifferentiation in individuals with tau and neurodegeneration compared to biomarker free individuals, however, this effect was not specific to AD. Compared to healthy older adults (i.e., CDR 0), individuals with very mild AD (i.e., CDR 0.5) often display increases in functional connectivity within SAL, which are then followed by decreases in functional connectivity later in the disease (i.e., CDR > 0.5; Balthazar

et al., 2014; Brier et al., 2012). Conversely, functional connectivity between SAL and other functional networks remains stable until later in the disease progression (Brier et al., 2012). The dedifferentiation (i.e., segregation) formula utilized in the present study requires greater between network connectivity compared to within network connectivity in order for dedifferentiation to be present. It is therefore possible that hyperactivity of SAL observed in the literature led to relatively stable dedifferentiation values across groups except those with non-AD pathology. Interestingly, research has demonstrated that while SAL functional connectivity is enhanced in AD, it is diminished in frontotemporal dementia (Zhou et al., 2010), thus lending support to the hypothesis that the observed changes in SAL are not specific to AD and instead are present in individuals with differing or co-contaminant disease.

Collectively, the present pattern of results suggests that either a) dedifferentiation due to AD pathology only arises in specific association networks, or b) dedifferentiation due to AD pathology arises at different points in AD progression such that additional networks would demonstrate increased dedifferentiation at later clinical stages of the disease. As noted previously, AD related changes in functional connectivity arise in a systematic pattern- while the DMN is the first network to demonstrate functional alterations, additional networks also demonstrate reduced functional connectivity with increased disease severity (Brier et al., 2012). It is therefore possible that although some individuals in the present study had accumulated sufficient biomarker burden (i.e., amyloid, tau, and neurodegeneration), they may not yet have experienced significant cognitive decline, suggesting that most of the association networks' functional organization remained largely stable, possibly due to highly effective cognitive reserve (Stern, 2006). Given that other researchers have demonstrated altered organizational characteristics in individuals with confirmed AD (de Haan et al., 2009; Khazaee et al., 2017), it

is most plausible that additional network dedifferentiation would be observed with increased disease severity.

There is evidence that dedifferentiation may reflect reductions in white matter, dopaminergic signaling, or both (Abdulrahman, Fletcher, Bullmore, & Morcom, 2017; Goh, 2011). White matter integrity and dopaminergic systems diminish in old age (Backman, Nyberg, Lindenberger, Li, & Farde; Madden, Bennett, & Song, 2009). The decrease in white matter and dopaminergic integrity are further accelerated in later stages of AD (Martorana & Koch, 2014; Medina et al., 2006). Both mechanisms have also been linked to decreases in functional connectivity, suggesting a common cause for decreased global integrity and increased dedifferentiation across systems, especially as AD severity progresses (Burzysnka et al., 2015; Greicius et al., 2008; Nagano-Saito et al., 2008).

Limitations and Future Directions

There are several methodological and conceptual limitations that are important to consider when interpreting results from the present study. First, results were based on cross-sectional data. In order to make sound inferences about within-person changes in dedifferentiation, longitudinal data are needed. Second, models of dedifferentiation have important implications for cognitive functioning. Although cognitive performance was not considered in this study, it is reasonable to assume that increases in dedifferentiation and pathology burden would be reflected in performance on cognitive tasks. Future research should investigate the precise interaction between dedifferentiation, pathology, and cognition. Lastly, past studies have yielded mixed results in regard to AD related changes in functional organization. For example, while some have demonstrated increased dedifferentiation (i.e., decreased clustering coefficient) in AD compared to cognitively normal older adults (Brier et al.,

2014; Dai et al., 2019), others have found no difference between cognitively normal older adults and those with AD (Sanz-Arigita et al., 2010). Discrepancies in results are likely due to a number of factors including differences in graph theory metric computations, sample size, and AD staging (i.e., ATN vs CDR). To fully reconcile these differences, future studies should vary computations (e.g., thresholds, weighted vs. unweighted) while taking into account biomarker as well as cognitive status.

Conclusions

Results from the present study demonstrate that as dedifferentiation increases, networks become more vulnerable to threat. Furthermore, although dedifferentiation and vulnerability to threat increase with age, they remain largely unaffected by AD pathology. This observation provides a relatively optimistic view and suggests that there are aspects of functional organization that are preserved until the end stages of AD. Thus, while functional organization remains intact, individuals may be able to maintain certain aspects of cognitive functioning despite accumulation of pathological biomarkers. By investigating neural dedifferentiation using the ATN framework, this study aids in informing mechanistic explanations of healthy and pathological cognitive aging.

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