INVESTIGATING WHITE MATTER LESION LOAD, INTRINSIC FUNCTIONAL CONNECTIVITY, AND COGNITIVE ABILITIES IN OLDER ADULTS

KARIN KANTAROVICH

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Abstract

Changes to the while matter of the brain disrupt neural communication between spatially distributed brain regions and are associated with cognitive changes in later life. While approximately 95% of older adults experience these brain changes, not everyone who has significant white matter damage displays cognitive impairment. Few studies have investigated the association between white matter changes and cognition in the context of functional brain network integrity. This study used a data-driven, multivariate analytical model to investigate intrinsic functional connectivity patterns associated with individual variability in white matter lesion load as related to fluid and crystallized intelligence in a sample of healthy older adults (n = 84). Several primary findings were noted. First, a reliable pattern emerged associating whole-brain resting-state functional connectivity with individual variability in measures of white matter lesion load, as indexed by total white matter lesion volume and number of lesions. Secondly, white matter lesion load was associated with increased network disintegration and dedifferentiation. Specifically, lower white matter lesion load was associated with greater within- versus between-network connectivity. Higher white matter lesion load was associated with greater between-network connectivity compared to within. These associations between intrinsic functional connectivity and white matter lesion load were not reliably associated with crystallized and fluid intelligence performance. These results suggest that changes to the white matter of the brain in typically aging older adults are characterized by increased functional brain network dedifferentiation. The findings highlight the role of white matter lesion load in altering the functional network architecture of the brain.

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Introduction

Aging increases risk for developing neurodegenerative diseases and accompanying disruptions in mental abilities. Cerebral small vessel disease (CSVD) is the second most prevalent pathology associated with age-related cognitive decline (Debette & Markus, 2010; Griebe et al., 2014). It has been associated with increased risk of stroke, Alzheimer's disease, and other forms of dementia (Barnes et al., 2013; Debette & Markus, 2010; Provenzano et al., 2013; Snowdon et al., 1997). CSVD is characterized by pathological changes in white matter or axonal tissue of the brain (Pantoni, 2010), the role of which is to enable communication between spatially separate brain regions and networks. White matter connections, therefore, form the intrinsic structural architecture in the human brain. These white matter changes can be identified on magnetic resonance imaging (MRI) scans as white matter hyperintensities (WMH) (Black, Gao, & Bilbao, 2009; Wardlaw, Smith, & Dichgans, 2013). Brain imaging studies reveal the presence of one or more WMH in nearly 95% of adults over the age of 45, many of whom do not endorse clinical symptoms (Vernooij et al., 2007).

In addition to these structural brain changes, aging is accompanied by a general shift in cognitive abilities, a trend recently described as the *semanticization of cognition* (Spreng & Turner, 2019). This shift is marked by a decline in cognitive control abilities referred to as fluid intelligence (Park, Polk, Mikels, Taylor, & Marshuetz, 2001; Verhaeghen & Cerella, 2002), in the context of continued accumulation and increased reliance on semantic knowledge, or crystallized intelligence (Park et al., 2001; Verhaeghen, 2003). Fluid intelligence guides novel problem solving and includes the capacity for orienting attentional resources to pertinent aspects of the environment, inhibiting distractions, and flexibly delegating cognitive resources to sustain goal-directed behaviours (Carpenter, Just, & Shell, 1990; Cattell, 1971). Crystallized intelligence

relies on accessing the storage of semantic knowledge about the self and the world that is accumulated over a person's lifetime (Cattell, 1971).

Damage to white matter, as indexed by WMH, leads to a decrease in the healthy neural tissue available for the types of computations required for flexible cofgnitive operations (De Marco, Manca, Mitolo, & Venneri, 2017). Both cross-sectional and longitudinal studies have related the severity of WMH to poorer performance in the age-sensitive domains required for fluid intelligence, including executive functions (Cook et al., 2004; Kramer et al., 2007), episodic memory, working memory (Raz, Rodrigue, Kennedy, & Acker, 2007), and processing speed (Gunning-Dixon & Raz, 2000).

Furthermore, these age-related shifts in cognition mirror local and network-level functional brain changes that are observed in older adulthood (Spreng & Turner, 2019). Large scale brain networks are comprised of anatomically distributed brain regions that are temporally connected and form the intrinsic functional architecture of the brain (Friston, 1994). At the brain network level, functional reductions within-networks and increased connectivity between-networks have been documented across the neurocognitive aging literature (e.g., Chan, Park, Savalia, Petersen, & Wig, 2014; Geerligs, Renken, Saliasi, Maurits, & Lorist, 2014). Converging findings across studies report the default network to be most sensitive to the effects of aging (Grady, 2012). The default network is engaged during internally-driven cognitive processes when access to stored knowledge representations and experiences is required (Andrews-Hanna, Smallwood, & Spreng, 2014). It is comprised of the posterior cingulate cortex, medial prefrontal cortex, inferior parietal lobule, as well as the medial and lateral temporal lobes (Buckner, 2004). Functional connectivity within this network is observed to diminish in older adults (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; see Damoiseaux, 2017; Dennis &

Thompson, 2014; Ferreira & Busatto, 2013 for reviews), and this reduction predicts increased connectivity with the frontoparietal network which is involved in cognitive control (Grady, Sarraf, Saverino, & Campbell, 2016). Therefore, aging is also associated with increased between-network connectivity of the frontoparietal network (Grady et al., 2016). Both the default network and the frontoparietal network have also been observed to exhibit lower network segregation, a measure of within- versus between-network connectivity, (see Chan et al., 2014) in older adults (Grady et al., 2016).

Numerous studies that concurrently examined the changing landscapes of structural and functional brain connectivity found that they are highly correlated and influenced by age (e.g., Betzel et al., 2014; Fjell et al., 2016; Zimmermann et al., 2016; see Damoiseaux, 2017 for review). Although, some inconsistencies in the literature still exist. For example, functional connectivity between brain regions has been observed in the absence of structural connectivity (Damoiseaux & Greicius, 2009; Zimmermann et al., 2016), possibly as a result of indirect structural connections (Damoiseaux, 2017). Meunier and colleagues (2009) have suggested that structural disconnections may lead not only to decreases but also increases in functional connectivity. This phenomenon may be explained by The Compensatory Recruitment of Neural Circuits Hypothesis (CRUNCH) (Reuter-Lorenz & Cappell, 2008), which postulates that the structural and functional brain changes that accompany advancing age, including structural white matter changes, lead to less efficient (‘noisy’) cognitive processing operations, requiring for additional resources to be recruited to compensate for this deterioration of neural networks (Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Li & Rieckmann, 2014; Schmitz, Dixon, Anderson, & De Rosa, 2014).

The relationship between age-related changes in functional connectivity and age-related declines in cognitive abilities remains poorly understood. When controlling for the effects of age, most cross-sectional studies, but not all (Damoiseaux et al., 2017), report that participants with lower functional connectivity within networks also have poorer cognitive outcomes (Andrews-Hanna et al., 2007; Chan et al., 2014; Damoiseaux et al., 2008; Hirsiger et al., 2016). For example, functional connectivity within the default network has been found to be reduced in individuals with memory deficits compared to individuals with preserved memory (Bernard et al., 2015). However, while older adults at risk for CSVD have white matter damage that predicts cognitive decline, particularly in age-sensitive domains (Cook et al., 2004; Gunning-Dixon & Raz, 2000; Kramer et al., 2007; Raz et al., 2007), there is considerable variability in the association between these white matter changes and cognitive ability in older adulthood (Dey, Stamenova, Turner, Black, & Levine, 2016). In other words, white matter changes that only minimally impact brain function may remain clinically 'silent'. To elucidate this phenomenon, it is necessary to examine individual variability in the associations between age-related white matter changes and functional brain changes concurrently, in relation to patterns of cognitive functioning.

To explain the association between structural and functional brain changes and their relationship to behavioural outcomes, a disconnection model of neurocognitive aging has been proposed. Originally stemming from the clinical neurological model of Geschwind (Catani & ffytche, 2005; Geschwind, 1965a, 1965b) and the brain-behaviour model of schizophrenia outlined by Friston (1998), the disconnection hypothesis states that compromise of structural connections (i.e., integrity of white matter) leads to a compromise of functional connections (i.e., brain networks) that have behavioural consequences. As it relates to cognitive aging, the

"disconnected brain" view suggests that progressive degeneration of white matter integrity associated with aging directly affects the functional architecture of the brain, leading to cognitive decline (Antonenko & Floel 2014; Bennett & Madden 2014; Ferreira & Busatto, 2013). In other words, damage to the white matter tracts that form the structural architecture of the brain affects the integrity of functional brain networks by altering neural communication between brain regions (Dey et al., 2016). Understanding how intrinsic shifts in the brain's structural architecture impact the re-organization of functional networks can provide insight into the mechanisms underlying individual variability in cognitive functioning and is critical for distinguishing healthy from potentially pathological aging.

Empirical evidence supporting the disconnection hypothesis comes from animal studies (O'Reilly et al., 2013; van Meer et al., 2010) and in case-studies of individuals with known neurological conditions or trauma (Fridriksson et al., 2013; Johnston et al., 2008; Schonberg et al., 2006; Seghier et al., 2004; Song et al., 2014). Efforts in the present-day literature are being directed towards confirming this for pathologies such as white matter deterioration that are highly prevalent even in typically aging adults (Vernooij et al., 2007).

Langen and colleagues (2017) examined the the location-specific relationship between white matter lesions and resting-state functional connectivity within a population-based setting of middle-aged and older adults. They found that local white matter lesions can decrease tract-specific functional connectivity, both in direct and indirect connections. This study concluded that the brain's structural network architecture allows brain function to be maintained via alternate pathways, even when direct connectivity is compromised. These findings provide support for the disconnection hypothesis at the level of the brain and offer novel insights into the interaction between the spatial topology of white matter lesions and intrinsic functional network

connectivity. However, given that this study did not extend their findings to neurocognitive functioning, it still remains unclear how this impacts age-sensitive cognitive domains such as fluid intelligence.

A recent study (Madden et al., 2017) set out to distinguish various imaging measures to understand how they independently mediate the relationship between age and fluid intelligence in a sample of adults ages 19-79. They reported resting-state functional connectivity of sensorimotor networks, associated with processing speed, were a significant mediator of the age-related decline in cognition. Whereas other imaging measures, including WMHs, did not mediate this relationship. This study provided insight into how age-related structural and functional brain changes are *independently* associated with cognitive abilities. However, it still remains unclear how structural and functional brain changes interact and lead to the emergence of the cognitive deficits seen in older adulthood.

The aim of the present study was to examine how age-related white matter changes impact the functional network integrity of the brain in relation to neurocognitive functioning in a group of healthy older adults. To address the gaps in the literature, this study implemented a two-step approach. First, multivariate modelling was used to measure how WMHs relate to resting-state functional connectivity. Second, this multivariate association between structural and functional connectivity was related to cognitive performance on measures of fluid and crystallized intelligence.

We predicted that the number and size of WMH (i.e., lesion load) would be inversely associated with resting functional connectivity and that the strength of this association would in turn predict cognitive functioning. Specifically, we predicted that increased white matter lesion load would be associated with a global increase in between-network connectivity and a decline in

within-network connectivity, consistent with a dedifferentiation account (Cabeza, 2002; Chan et al., 2014; Grady, 2012; Meunier et al., 2009, 2014; Turner & D'Esposito, 2010). Further, we predicted that the strength of the association between white matter lesion load and resting-state functional connectivity would be more strongly associated with declines in fluid versus crystallized cognitive abilities (Andrews-Hanna et al., 2007; Cole et al., 2012; Ferreira, 2016; Shen et al., 2018).

Methods

Participants

All data for the current study were drawn from a larger neuroimaging and neuropsychological data collection initiative in collaboration with Cornell University known as the Goal-Directed Attention Study. Inclusion criteria included completion of all neuroimaging and neurocognitive protocols, a score of > 26 on the Mini Mental Status Examination (MMSE), no subjective report of cognitive impairment or significant health condition, no history of neurological or active psychiatric disorder, and no current regime of medication known to impact cognition. All procedures were approved by the Institutional Review Boards of York and Cornell Universities.

A total of 88 healthy older adults originally met study criterion. During the white matter hyperintensity segmentation process (see below for details), false positives were noted in the occipital lobe for one participant who was removed from the sample as a result. During the descriptive data analysis (see below) three participants with extreme white matter lesion load were flagged. Given that PLS is known to be highly sensitive to outliers, the decision was made to exclude these participants from further analyses as well. The final sample consisted of 84 participants (47 women, 37 men, $M_{age} = 67.46$, age range: 60-83).

MRI Data Acquisition and Pre-Processing

All neuroimaging data were acquired on a 3T GE Discovery MR750 scanner (General Electric, Milwaukee, United States) with a 32-channel receive-only phased-array head coil at the Cornell Magnetic Resonance Imaging Facility in Ithaca. Each participant underwent an anatomical scan acquired during a 5 m 25 s run using a T1-weighted volumetric MRI magnetization prepared rapid gradient echo [repetition time (TR) = 2530 ms; echo time (TE) = 3.4 ms; inversion time (TI) = 1100 ms; flip angle (FA) = 7°; bandwidth = 195 Hz/pixel; 1.0 mm isotropic voxels, 176 slices]. Anatomical scans were acquired with 2 × acceleration with sensitivity encoding.

Resting-state functional scans were acquired using a multi-echo echo planar imaging (ME-EPI) sequence with online re-construction (TR = 3000 ms; TE's = 13.7, 30, 47 ms; FA = 83°; matrix size = 72 × 72; field of view (FOV) = 210 mm; 46 axial slices; 3.0 mm isotropic voxels). Each participant completed two resting-state multi-echo BOLD functional scans, keeping their eyes open, and blinking and breathing normally in the dimly lit scanner bay. These scans were acquired prior to engagement in any cognitive task functional magnetic resonance imaging (fMRI) experiment. Multi-echo fMRI is a novel data acquisition sequence that assists in eliminating noise components from resting fMRI datasets (Kundu et al., 2013, 2012). Through the acquisition of multiple echoes this method allows for the direct measurement of T2* relaxation rates. Blood-oxygen level dependent (BOLD) signal can then be isolated from non-BOLD noise on the basis of echo time (TE) dependence.

Resting-State Network Definition

Resting-state functional MRI (rs-fMRI) was used as a measure of the intrinsic functional network architecture of the brain (Buckner & Vincent, 2007; Raichle & Snyder, 2007). Rs-fMRI

has proven particularly useful for studying the functional communication between spatially distributed brain regions and their relationship with behaviour (Stevens & Spreng, 2014).

In order to identify functional brain networks, each participant's cortex was separately parcellated into 400 functionally-defined regions. In order for each individual's parcel boundaries to be optimized with respect to their rs-fMRI, the initial group parcellation developed by Schaefer et al., (2018) was refined (Chong et al., 2017). Initialization with a common parcellation produces automatic coherence between parcels across participants. A group sparsity constraint was used to model connectivity so that group similarities could be leveraged in connectivity between parcels while optimizing their boundaries for each participant. Initialization was used with this technique and applied across the entire cohort in groups of 20 unrelated participants with initialization. Past studies validating this method demonstrated improved homogeneity of resting activity within the refined parcels (Chong et al., 2017). In addition, comparisons with task-based localizers showed a dependent decrease in variance of statistical parametric maps within the refined parcels compared to the group-based initialization, marking improved delineation of regions of functional specialization. This approach allows for increased accuracy in estimating individual functional regions while preserving consistency across participants with a standardized topological atlas (Chong et al., 2017). Using the 7 network parcellation by Yeo et al., (2011), each parcel was matched to one of the corresponding networks: visual (VIS), somatomotor (SOM), dorsal attention (DAN), ventral attention (VAN), limbic (LIM), frontoparietal (FPN), and default networks (DN). For each individual in the sample, BOLD time-series for the two 10 m 17 s rs-fMRI scans within each session were temporally standardized by subtracting the mean and dividing it by the standard deviation, and then concatenated. A Pearson correlation coefficient was calculated between each pair of

vertices. To generate the final 400 x 400 functional connectivity matrix, the correlation coefficient matrix was spatially standardized and averaged within and across parcels (Ge et al., 2017). For each participant, the two connectivity matrices that were produced from the two sessions were averaged (Mwilambwe-Tshilobo et al., 2019).

White Matter Hyperintensities

T2- Fluid-Attenuated Inversion Recovery (FLAIR) structural MRI sequences were used to evaluate WMH load volume and quantity. WMH were segmented by the lesion prediction algorithm (LPA) (Schmidt, 2017, Chapter 6.1) as implemented in the Lesion Segmentation Toolbox (LST) version 2.0.15 (www.statistical-modelling.de/lst.html) for Statistical Parametric Mapping (SPM). This algorithm consists of a binary classifier in the form of a logistic regression model. This tool was originally trained to segment white matter lesion data of Multiple Sclerosis patients (Schmidt et al., 2012). Since then, this technique has been reliably implemented in samples of older adults with cardiovascular risk factors and healthy older adults (Birdsill et al., 2014; Maldjian et al., 2013; Wang et al., 2014). As covariates for this model, a lesion belief map showing voxels that appear hyperintense on FLAIR images and that are likely to be part of the white matter was used (Schmidt et al., 2012). In addition, a spatial covariate that takes into account voxel specific changes in lesion probability was implemented. Parameters of this model fit are used to segment lesions in new images by providing an estimate for the lesion probability for each voxel. For the calculation of the lesion probability maps, T2-weighted FLAIR images were used. The resulting output was a probability lesion map in FLAIR space for each participant. Given that FLAIR images can be affected by artifacts such as cerebrospinal fluid pulsation, subject-specific anatomical masks were created using FSL tools (https://fsl.fmrib.ox.ac.uk/fsl/) in order to exclude voxels that were not part of the white matter.

The T1 high-resolution biased corrected images and dilated cerebrospinal fluid masks of each participant were used to create the anatomical masks. The resulting masks excluded the cortical and subcortical gray matter. The masks were then warped to each individual's native FLAIR space. Regions falling outside the mask were excluded from the probability lesion maps. Finally, the masked lesion probability maps were used to calculate the total lesion volumes (in units of milliliters) and the total number of lesions for each participant. Volume and number of lesions values were then computed from the lesion maps. Each participants' raw total lesion volume (TLV) in milliliters (mL) was then divided by their estimated total intracranial volume (eTIV) in mL. Final total lesion volume data (TLV/eTIV) and number of lesions data were converted to within-sample z-scores.

Behavioural Measures of Neurocognitive Functioning

Neurocognitive performance on measures of fluid intelligence (fluid IQ) and crystallized intelligence (crystallized IQ) was assessed to characterize the cognitive abilities of each participant. Assessments of crystallized IQ and fluid IQ were obtained using the Unadjusted Fluid Cognition and Crystallized Cognition Composite Scores from the National Institute of Health (NIH) Toolbox Cognition Battery (http://www.nihtoolbox.org). The NIH Toolbox Cognition Battery includes tests that assess cognitive abilities that are important in adaptive functioning across the lifespan. The Unadjusted Scale Score provides a measure of the participant's overall level of functioning compared with the general population, regardless of age, gender, or other demographic factors. This is done by comparing each test-taker's performance to that of the entire NIH Toolbox representative normative American sample. Higher unadjusted scale scores imply better performance (Slotkin et al., 2012). All behavioural

measures of cognitive functioning in this study were treated as continuous variables. Any mention of high or low scores pertain to the sampling distribution of this specific study.

Assessment of fluid intelligence. In this study, the NIH Toolbox Fluid Cognition Composite Score was used as an indicator for global information processing abilities in novel situations and capacity for new learning (fluid IQ). It is calculated by averaging the normalized scores of each of the fluid IQ measures (Flanker, Dimensional Change Card Sort, Picture Sequence Memory, List Sorting and Pattern Comparison), and then deriving scale scores based on this new distribution (Slotkin et al., 2012).

Assessment of crystallized intelligence. The NIH Toolbox Crystallized Cognition Composite Score was used to measure cognition that relies more heavily on past learning experiences and accumulated knowledge (crystallized IQ) (Weintraub et al., 2013). It is derived by averaging the normalized scores of each of the Picture Vocabulary and Reading Recognition measures, and then deriving scale scores based on this new distribution (Slotkin et al., 2012).

Data Analysis

Partial least squares analysis. Behavioural Partial Least Squares (bPLS) was performed to identify resting-state functional connectivity patterns associated with individual differences in white matter lesion load (total lesion volume and number of lesions). PLS is a multivariate statistical method that relies on a data-driven approach to analyze complex, high dimensional datasets, including neuroimaging data (McIntosh, Chau, & Protzner, 2004; McIntosh & Lobaugh, 2004; McIntosh & Mišić , 2013). bPLS can be used to make inferences about individual differences in the intrinsic connectivity of large-scale neurocognitive networks. It allows for concurrent replication of previous resting-state functional connectivity patterns and explorative investigation of behavioural relationships outside of previously examined networks.

For this reason, it was considered the preferred method of analysis for this study. In this study white matter lesion load values were treated as behavioural variables. bPLS isolates patterns, known as latent variables of LVs, by identifying linear combinations of the original variables (functional connections and behavioural measures) that maximally covary with each other across individuals. These LV's can be understood as optimally-paired functional networks and behavioural phenotypes (Mwilambwe-Tshilobo et al., 2019).

In the present study, two matrices were generated to examine the relationship between resting-state functional connectivity and white matter lesion load (total lesion volume and number of lesions). The arrangement of the X matrix was such that the parcellated functional connectivity matrix for each participant was concatenated, resulting in an 84 x 400 x 400 matrix. The Y matrix was composed of individual scores for total white matter lesion volume and number of lesions for all participants, creating an 84 x 2 matrix. Both matrices were centered and normalized across participants. Singular value decomposition of the cross-correlation matrix X'Y produces multiple mutually-orthogonal LVs. Each LV is composed of three components: (a) a left singular vector which contains weights for each of the white matter lesion load measures; (b) a right singular vector which contains weights for each of the functional connections; (c) a scalar singular value. Effect size is indicated by squared singular values, which are proportional to the covariance between functional connectivity and the white matter lesion load variable (i.e., number, volume) that is accounted for by each LV. The number of LVs is equal to the rank of X'Y which is the number of white matter lesion load variables in the current study (b).

Permutation testing was used to evaluate the significance of each LV, while bootstrap sampling was used to determine its reliability. First, the significance of the pattern of functional

connectivity captured by a given LV was assessed using permutation testing to determine the extent to which the results differ from chance. This was accomplished by computing 500 permutation tests where the sequence of the rows of one of the data matrices (X) was rearranged randomly. Then, the columns of this permuted matrix were correlated with the behavioural Y-matrix and the correlation matrix underwent singular value decomposition (see above). Through this process a distribution of singular values was created under the null hypothesis that there is no relationship between functional connectivity and behaviour. The significance of the LV was estimated by computing the number of times the permuted singular values (covariance explained) was higher in proportion to the observed singular values (significance thresholded at $p < .05$).

Bootstrap resampling was implemented to examine the reliability of weights for individual connections and behavioural variables. This was accomplished by sampling the rows of the X and Y data matrices with replacement, then a resampled correlation matrix (X'Y) was re-computed. The matrix then underwent singular value decomposition and this process was repeated 500 times to estimate a sampling distribution for each singular vector (i.e., connection and white matter lesion load) weight. The ratio between each weight and its bootstrap-estimated standard error was computed to determine which functional connections and white matter lesion load measures (a) contribute considerably to the overall multivariate pattern and; (b) are relatively insensitive to sample composition. Large 'bootstrap ratios' (BSRs) correspond to connections and behaviours that have large weights and narrow confidence intervals. BSRs are equivalent to z-scores if the sampling distribution is approximately unit normal. Brain network connections were considered reliable if the absolute value of the BSR > 3 (approximately $p < .03$) and were visualized using BrainNet Viewer (Xia et al., 2013). A partial correlation analysis

was conducted on the brain connectivity scores with behavioural scores controlling for covariates such as age, gender, and years of education using Statistical Package for Social Sciences (SPSS) version 24.

The degree to which network-level functional connectivity contributes to individual differences in white matter lesion load was examined as well. Separate weighted adjacency matrices were created that reflected the positive and negative PLS weights, respectively. This was done in order to assess the network-level contributions to the connectivity pattern identified by the PLS analysis. The nodes of the graph depict the 400 brain regions defined by the individual parcellation scheme, and the edges depict the BSR weight for each pairwise connection. The matrices were thresholded so that BSRs with an absolute value less than 3 were set to 0. Significant positive BSRs were set to 1, and negative BSRs were set to −1. A 7 x7 matrix was created by quantifying the network-level functional connectivity contributions. More specifically, this was done by computing the mean of the weights of all connections in a specific network. The entire threshold matrix was then subject to permutation testing by re-ordering the network labels randomly (preserving the number of nodes originally assigned to each network) and re-calculating the network averages 500 times to build a sampling distribution under the null hypothesis that network assignment does not contribute to the connectivity pattern. To determine the significance of the pairwise connections from the original 7 x 7 matrix, the number of times the values of the sampling distribution were greater than or equal to the original value were estimated (Shafiei et al., 2019).

Neurocognitive analysis. A partial correlation was conducted to examine the behavioural relationship between cognition (Unadjusted Fluid and Crystallized Cognition Composite Scores) and significant brain connectivity scores, controlling for age, gender, and

years of education. The analysis was performed using SPSS version 24 with statistical significance set at $p < .05$.

Results

Descriptive Data Analysis

Sample characteristics for age, gender, years of education, estimated total intracranial volume in mL (eTIV), total lesion volume in mL, number of lesions, crystallized IQ (indexed by Unadjusted Crystallized Cognition Composite scores), fluid IQ (indexed by Unadjusted Fluid Cognition Composite scores) are shown in Table 1.

Table 1
Sample demographics (n=84)

Gender				
	n	%		
Female	47	56		
Male	37	44		
Variable	Minimum	Maximum	Mean	SD
Age (years)	60	83	67.46	5.74
Education (years)	12	24	17.55	3.08
Crystallized-IQ	113.63	153.95	135.99	10.51
Fluid-IQ	78.21	122.79	94.21	6.83
eTIV (mL)	1094.15	2042.06	1588.71	186.44
Total Lesion Volume (mL)	0	3.04	.92	.74
Number of Lesions	0	18	8.74	4.03

Note. Crystallized-IQ is indexed by Unadjusted Crystallized Cognition Composite scores; Fluid-IQ is indexed by Unadjusted Fluid Cognition Composite scores. eTIV= estimated Total Intracranial Volume; SD = standard deviation.

Pearson correlation based on 1000 bootstrap samples between these behavioural variables identified a positive relationship between total lesion volume and number of lesions ($r(82) = .86$, $p < .001$, 95% CI [0.55, 0.80]). Total lesion volume and number of lesions were both found to be positively correlated with age ($r(82) = .43$, $p = .001$, 95% CI [0.25, 0.60]; $r(82) = .29$, $p = .003$, 95% CI [0.11, 0.47]). In addition, total lesion volume was positively correlated with education,

although the confidence interval here included zero ($r(82) = .24$, $p = .013$, 95% CI [-0.01, 0.12]). Fluid IQ was negatively correlated with total lesion volume ($r(82) = -.26$, $p = .009$ 95% CI [-0.42, -0.57]), number of lesions ($r(82) = -.32$, $p = .002$), and age ($r(82) = -.40$, $p < .001$, 95% CI [-0.55, -0.23]). Positive correlations were revealed between crystallized IQ and age ($r(82) = .30$, $p = .003$, 95% CI [0.12, 0.47]), as well as education ($r(82) = .56$, $p < .001$, 95% CI [0.37, 0.71]). Finally, age and education were positively correlated ($r(82) = .32$, $p = .002$, 95% CI [0.12, 0.49]). No other significant correlations were noted between covariates (see Table 2 for a summary of all results).

Table 2
Pearson Correlation Matrix of White Matter Lesion Load, Cognition, and Demographics

	TLV	Number of Lesions	Age	Education	Crystallized IQ	Fluid IQ
TLV	-					
Number of Lesions	.68** [0.55, 0.80]	-				
Age	.43** [0.25, 0.61]	.29** [0.11, 0.47]	-			
Education	.24* [0.03, 0.45]	0 [-0.21, 0.21]	.32** [0.12, 0.49]	-		
Crystallized-IQ	0.15 [-0.02, 0.33]	0.08 [-0.11, 0.29]	.30** [0.12, 0.47]	.56** [0.37, 0.71]	-	
Fluid-IQ	-.26** [-0.42, -0.06]	-0.18 [-0.35, 0.02]	-.40** [-0.55, -0.23]	-.09 [-0.34, 0.15]	-.05 [-0.22, 0.12]	-

Note. Values in square brackets indicate the 95% confidence interval for each correlation. Crystallized-IQ is indexed by Unadjusted Crystallized Cognition Composite scores; Fluid-IQ is indexed by Unadjusted Fluid Cognition Composite scores. Both number of lesions and total lesion volume (TLV) values were converted to a z-score distribution. Results are based on 1000 bootstrap samples. *p < .05; **p < .01

Intrinsic Resting-state Functional Connectivity Results

Behavioural PLS was used to examine the multivariate relationship between resting-state functional connectivity, total lesion volume, and number of lesions. The analysis identified one significant pattern of connectivity that reliably expressed individual differences in total lesion volume and number of lesions (total lesion volume: r = .82, 95% CI [0.82, 0.87]; number of lesions: r = .82, 95% CI [0.86, 0.71]; permuted p = .04). Both total lesion volume and number of lesions were found to positively correlate with the pattern of brain connectivity of LV 1 (Figure 1A). To ensure the precision of these results, a partial correlation analysis was conducted to test whether the relationship between measures of white matter lesion load and brain connectivity scores remained significant after controlling for age, gender, and years of education. The results remained significant for number of lesions ($r(79) = .81$; $p < .001$) and total lesion volume ($r(79) = .81$, $p < .001$).

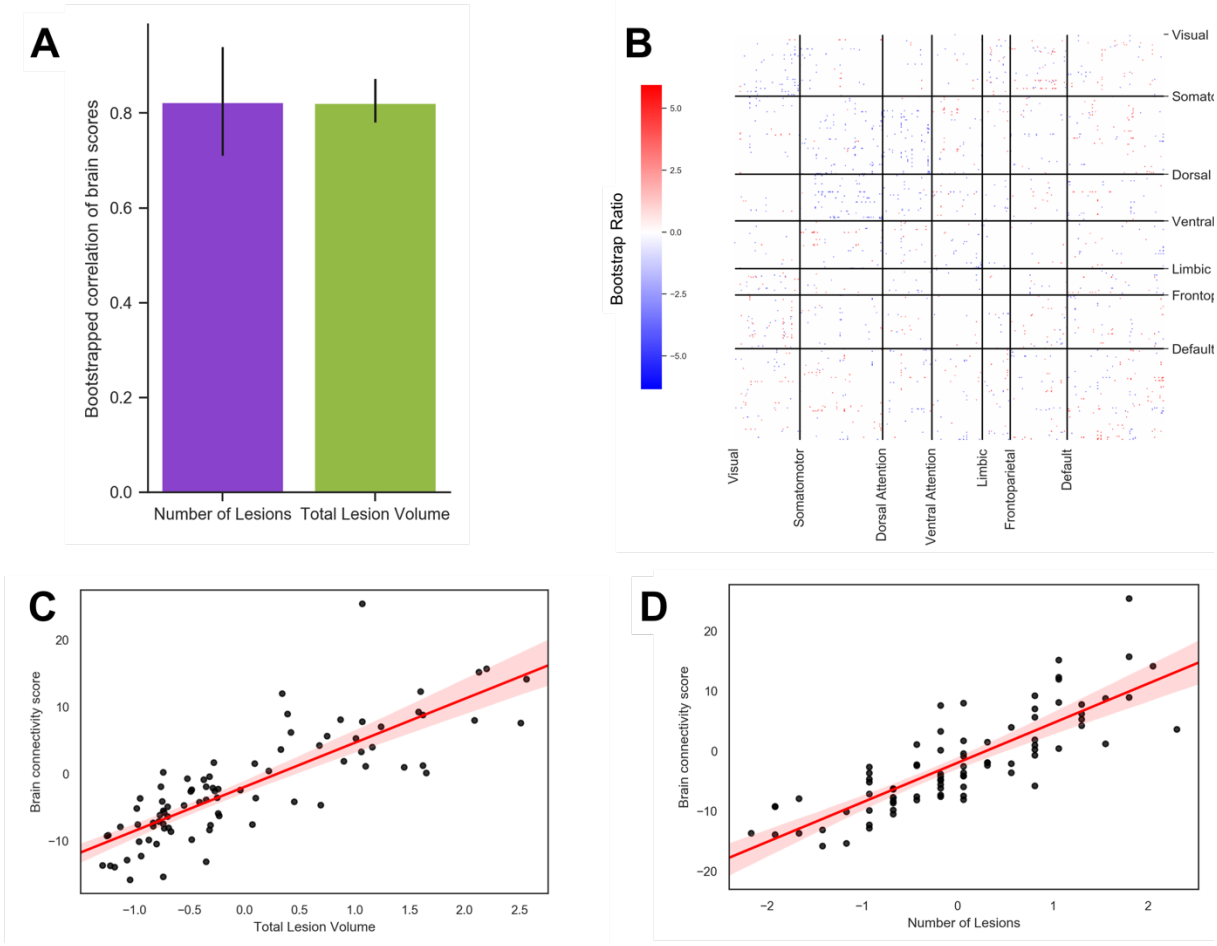

Figure 1. Behavioural PLS results. Analysis revealed one significant latent variable (LV). The functional connections that most reliably express the rsfMRI/white matter lesion load correlations thresholded at bootstrap ratio (BSR) > 3. (A) A bar-graph representation of the correlations between participants' brain connectivity scores and measures of white matter lesion load for LV 1. (B) The correlation matrix of reliable pairwise connections associated with number of lesions and total lesion volume. Scatter plots show the relationship captured by the PLS analysis for individual brain connectivity scores as a function of number of total white matter lesion volume (C) and number of white matter lesions (D).

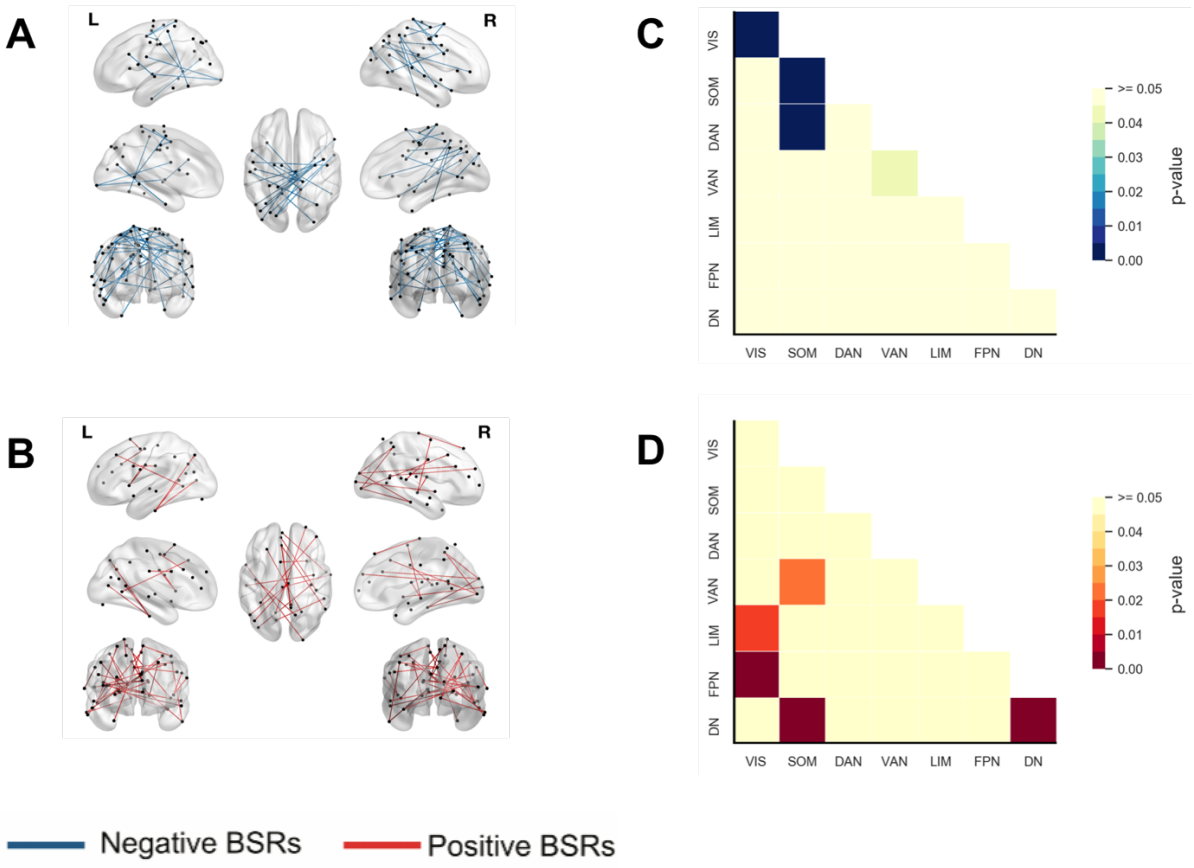

Figure 2. Patterns of connectivity and functional network organization. The pattern of connectivity for LV 1 depicted in (A) blue represent the connectivity weights for LV 1 that covary negatively with white matter lesion load (total lesion volume and number of lesions), while those in (B) red covary positively with white matter lesion load thresholded at a bootstrap ratio (BSR) > 4 for visualization. Nodes that are not connected by edges on lateral surfaces indicate cross-hemisphere connections. Dorsal view of the brain depicts only cross-hemisphere (bilateral) connections. Significant contributions of resting-state network pairs to the connectivity pattern for the (C) negative expression of LV 1 and (D) positive expression of LV 1. VIS = visual; SOM = somatomotor; DAN = dorsal attention; VAN = ventral attention, LIM = limbic, FPN = frontoparietal network; DN = default network.

ROIs that reliably covary with one another are displayed in Figure 2A-B. Overall, the connectivity pattern associated with the negative and positive expression of LV 1 revealed densely interconnected nodes that were more localized within the right hemisphere compared to the left. Participants with lower lesion load (i.e., smaller total lesion volume and a low number of lesions) showed increased posterior connectivity and shorter node-to-node connections (Figure

2A). Participants with higher lesion load (i.e., greater total lesion volume and a high number of lesions) showed more long distance connections between anterior and posterior areas (Figure 2B).

In order to examine the differences in within- and between-network contributions of the seven networks in the Yeo et al. (2011) parcellation scheme, permutation testing was performed on the functional covariance matrix representing the pairwise BSRs for each of the 400 brain regions (Figure 1B).

As shown in Figure 2C, the strongest contributions to the resting-state functional connectivity pattern associated with the negative expression of LV 1 were from the VIS, SOM, DAN, and VAN. For within network connectivity, the VIS ($p < .001$), SOM ($p < .05$), VAN ($p < .05$), and DN ($p < .01$) were found to contribute significantly to the resting-state functional connectivity pattern related to low white matter lesion load (low total lesion volume and low number of lesions). Whereas pairwise connections that contributed most to the between-network connectivity pattern were localized to the DAN and SOM ($p < .001$).

Figure 2D displays the most robust contributions to the resting-state functional connectivity pattern associated with the positive expression of LV 1. Connectivity within the DN ($p < .001$) was found to significantly contribute to the resting-state functional connectivity pattern. However, in general, higher white matter lesion load (high total lesion volume and high number of lesions) was related to greater between-network connectivity. Pairwise connections that contributed the strongest for between network connectivity existed between the VIS with the FPN ($p < .001$) and the LIM ($p < .002$), as well as the SOM with the DN ($p < .001$) and the VAN ($p < .03$).

Neurocognitive Behavioural Analysis

The behavioural relationship between unadjusted fluid IQ and crystallized IQ composite scores and brain connectivity scores of LV 1 was investigated using a partial correlation, controlling for age, gender, and years of education. Results are based on 1000 bootstrap samples. There was no significant relationship found between LV 1 brain scores and crystallized IQ composite scores ($r(79) = -.02$, $p = .897$, 95% CI [−0.19, 1.88]). The association between LV 1 brain scores and fluid IQ composite scores was also non-significant ($r(79) = -.10$, $p = .39$, 95% CI [−0.37, 0.19]).

Discussion

Changes to the white matter of the brain disrupt neural communication between anatomically distributed brain regions and have been associated with cognitive changes in later life. Yet, the association between these markers of neurocognitive aging remains poorly understood. This study used a data-driven multivariate analytical model to investigate patterns of intrinsic functional connectivity associated with individual variability in white matter lesion load in a sample of healthy older adults. This technique allowed for the identification of patterns in whole-brain networks that were reliably associated with two principal measures of white matter lesion load: total lesion volume and number of lesions. These findings were then used to investigate how these emerging patterns relate to cognitive functioning in our sample. Several primary findings were noted. A reliable pattern emerged associating whole-brain resting-state functional connectivity with individual variability in measures of white matter lesion load. Secondly, white matter lesion load was found to be associated with increased network disintegration and dedifferentiation. Specifically, lower white matter lesion load was associated with more within-network connectivity compared to between. In contrast, higher white matter

lesion load was associated with more between-network connectivity compared to within, with the exception of the default network, which showed increased within-network connectivity. In relating these results to cognition, patterns associating functional connectivity and white matter lesion load were not found to be significantly related to performance on measures of crystallized and fluid intelligence.

Overall WMH – Resting-state Functional Connectivity Model

As predicted, a strong and reliable pattern emerged associating whole-brain resting-state functional connectivity with individual variability in the number and total volume of white matter lesions. These effects remained even when accounting for demographic factors, including years of education, gender, and age. This finding contributes to the accumulating evidence for the "disconnection hypothesis" of the aging brain and supports the idea that functional brain changes (i.e., intrinsic functional network connectivity) are strongly related to structural brain changes (i.e., white matter changes) (Antonenko & Floel 2014; Bennett & Madden 2014; Ferreira & Busatto, 2013). However, given that this study was limited by a cross-sectional design, it is not possible to infer causality and establish whether WMH are a causal factor in resting functional connectivity patterns in older adults.

Within- and Between-Network Functional Connectivity

Increases in both number and total volume of white matter lesions were associated with increased functional network disintegration and dedifferentiation. Specifically, lower white matter lesion load was associated with more within- compared to between-network functional connectivity. Networks that exhibited increased within-network connections included: the somatosensory network, visual network, and ventral attention network. Increased between-

network connectivity in participants with lower lesion load was only noted between the dorsal attention network and the somatosensory network.

As expected, higher white matter lesion load was associated with greater between- compared to within-network functional connectivity. Networks that exhibited increased between-network connections with one another included the visual network with the frontoparietal network, the visual network with the limbic network, the somatosensory network with the default network, and the ventral attention network with the somatosensory network. Of note, in addition to exhibiting increased between-network connectivity, the default network also showed increased within-network connectivity among participants with higher lesion load, a finding that was contrary to the study hypotheses. This particular finding is discussed further below.

In general, these results complement observations in the literature reporting shifts in the functional network architecture of the brain in older adulthood away from within-network connectivity and towards between-network connectivity (e.g, Betzel et al., 2014). An explanation for how these functional network connections are influenced by white matter lesion load has been offered by Langen and colleagues (2017), who examined the effects of white matter lesion *location* on the organization of functional networks in the brain. They postulated that when direct connectivity is compromised (i.e., in the face of white matter damage) the brain's structural network architecture allows brain function to be maintained via indirect pathways. Reviews of earlier literature have suggested brain plasticity as a compensatory mechanism that increases connectivity between alternate regions in the face of compromised direct connections (Cabeza, 2002). However, another way of understanding age-related functional network dysconnectivity is in the light of the dedifferentiation process that manifests in older adults (Cabeza, 2002; Grady, 2012; Turner & D'Esposito, 2010). "Dedifferentiation" in aging (Baltes & Lindenberger, 1997;

Li, Lindenberger, & Sikström, 2001; Park et al., 2004) refers to reduced functional specialization of different brain regions and networks for the purpose of being recruited in goal-directed behaviour. Dedifferentiation in older adults has been observed in higher-order systems (Carp et al., 2011b), the ventral visual system (Park et al., 2004, 2012), and motor system (Carp et al., 2011a; Bernard & Seidler, 2012).

Results reported in the current study also align with the notion of functional segregation of brain networks (quantified using graph-theory metrics) in aging. Functional segregation is an extension of the "dedifferentiation" model, where within-network connectivity is reduced in exchange for increased connectivity between networks, and where network modularity is reduced with aging (Meunier et al., 2009, 2014; Chan et al., 2014). Networks with low modularity have sparse connections between the nodes within modules but dense connections between nodes in different modules (Bullmore & Sporns, 2009). In the current study, increases in white matter lesion load were associated with a shift from high within-network connectivity to predominantly between-network connectivity.

Increased Within-Network Connectivity in the Default Network

Contrary to study hypotheses, white matter lesion load was associated with increased within-network connectivity in the default network. A majority of cross-sectional studies of functional network connectivity in aging report decreased within-network connectivity in the default network. However, in the longitudinal literature, default network functional connectivity has been associated with a non-linear trend in older adulthood. In a recent study, Staffaroni and colleagues (2018) found that within-network connectivity in the default network increased from ages 50-70, followed by a plateau around 70, and a subsequent decline as individuals aged further. Their findings remained significant even when accounting for effects of WMH. Given

that the average age of participants within our sample was 67, the work of Staffaroni and colleagues (2018) may provide insight into patterns of increased within-network connectivity in our sample, although it remains unclear why this pattern would be specifically affiliated with increased white matter lesion load. A potential explanation could be that in an effort to compensate, brains with greater lesion load engage more neural resources, leading to increases in brain activity and functional connectivity. This reasoning would align with the CRUNCH model (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005) discussed earlier. To clarify this finding, examining WMH and functional connectivity associations across larger samples and different age-cohorts of older adults (i.e., young, middle, later older adulthood) is necessary. Additional investigations of location-specific effects of WMH on functional brain networks can also provide further insight (see Langen et al., 2017).

Neurocognitive Results

While the findings of this study provide support for the disconnection hypothesis at the level of the brain, there were no significant relationships between individual patterns of lesion load and functional connectivity that were associated with global measures of fluid and crystallized abilities. The link between WMH and declining performance in older adulthood has been established in both cross-sectional and longitudinal studies. The severity of WMH has been associated with diminished performance in age-sensitive domains required for fluid intelligence, including executive functions, episodic memory, and processing speed, among older adults (Cook et al., 2004; Gunning-Dixon & Raz, 2000). Indeed, preliminary analyses of the descriptive data of the current study sample revealed a significant association between total white matter lesion volume and fluid abilities. Fluid intelligence, total lesion volume, as well as the number of lesions were found to be positively associated with age. However, these findings did not translate

when accounting for individual variability in the association of white matter lesion load with resting-state functional connectivity patterns.

Both cross-sectional and longitudinal studies have found decreased functional connectivity within the default network to be associated with poorer cognitive performance (Andrews-Hanna et al., 2007; Bernard et al., 2015; Sala-Llonch et al., 2015; Persson, Pudas, Nilsson, & Nyberg, 2014; Vidal-Pineiro et al., 2014; Ward et al., 2015). Whereas in younger adults increased connectivity in the default network is associated with poorer memory, Fjell and colleagues (2015) have noted a positive correlation between improved memory performance and default network connectivity in older adults. Given that in our study sample, increased lesion load was associated with increased default network connectivity, this may reflect a successful compensatory mechanism and may explain the null-findings. The CRUNCH model posits that older adults may engage cognitive control at lower levels of task load to preserve performance, making age-related differences difficult to detect in behavioural measures where task load is lower than one's cognitive limit despite large differences in underlying processing (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005). Given that the effects of age were accounted for in the current study, it may very well be that the neural architecture supporting these cognitive processes has likely already undergone considerable change even prior to the presentation of any overt decline in these abilities. In other words, it could be the case that at a certain level, compensatory re-organization of functional brain networks in the presence of WMH can mask any observed changes in cognition.

Study Strengths

One strength of this study lies in the fact that both WMH and rs-fMRI data were acquired with consistent scanning parameters during the same scanning session. This study also benefited

from the implementation of a multivariate data-driven analytical model. This approach ensured that the study was free of pre-determined assumptions, thereby avoiding the possible risk of confounding results and interpretations and providing a more comprehensive analysis of patterns.

Study Limitations

Given that the average age of study participants was around 67, this study could benefit from increased sampling across the older adult age-cohort (80+). This is particularly important considering the non-linear trajectory of functional network connectivity across different stages of older-adulthood that has been reported in the longitudinal literature (Ng et al., 2016; Staffaroni et al., 2018). This study could have also benefited from increased statistical power that would allow for the implementation of a meditation analysis in order to provide additional converging evidence.

Future Directions

This study provides a framework for examining individual differences in the intrinsic structural and functional architecture of the brain as they relate to cognitive performance in older adulthood. The next step is to apply complex network analyses such as graph theory to derive metrics that can provide more insight into specific network features. Specifically, graph theory can be used to understand the network re-structuring that occurs in the face of disruptions in structural connectivity due to white matter pathology. Graph theory measures work by quantifying topologies of a systems' network representation. They can provide insight into the segregation and modularity of functional networks, which have been shown in previous studies to be vulnerable to the effects of age (Grady, 2012).

Functional brain networks display spontaneous dynamic fluctuations over scan time (Chang & Glover, 2010; Hutchison et al., 2013). Dynamic functional connectivity provides a

measure of changes in macroscopic neural activity patterns that underlie cognition and behaviour (Hutchison et al., 2013). Given this, another future aim is to use dynamic functional metrics to see how WMH impacts temporal network dynamics.

Future efforts will also be directed at investigating how reliable functional and structural patterns relate to more specific abilities and processes that comprise fluid and crystallized cognition. This can be accomplished by examining the relationships between associations of white matter and functional connectivity in relation to scores on subtests of fluid and crystallized intelligence (e.g., processing speed, executive functions, episodic memory). These methods can be further applied to mapping shifts in the entire neuropsychological profile in the face of age-related white matter disruptions across older adults in different age cohorts (i.e., young, middle, and late adulthood).

Conclusion

The extent of white matter lesion load in healthy older adults was associated with changes to the organization of intrinsic brain networks. However, this relationship was not reflected in individual performance differences on measures of fluid or crystallized intelligence. These findings support the disconnection model of neurocognitive aging at the level of the brain but do not translate to behaviour. This could be a possible indication that changes at the neural level have not yet manifest in behavioural changes as measured by standard neuropsychological assessment tools. The findings of this study mark an important step in understanding the relationship between WMH, intrinsic functional network organization, and cognitive abilities in later life. From a translational perspective, these discoveries can aid the future development and implementation of early preventative therapies. From a basic research perspective, clarifying this

association will allow for greater precision in differentiating healthy and pathological aging cohorts in the study of cognitive aging neuroscience.

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