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Intelligence moderates the relationship between age and inter-connectivity of resting state networks in older adults

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ABSTRACT

Age-related changes in the interactive behavior of default mode network (DMN) with other resting state networks are poorly understood. We hypothesized that age would positively correlate with *inter*-network connectivity in late life and intellectual functioning was expected to moderate this relationship. The sample consisted of 48 community-dwelling older adults with resting state functional magnetic resonance imaging data. Global *inter*-connectivity between DMN and 9 other resting state networks was calculated using a novel computational framework based on machine learning. Intellectual functioning (intelligence) was estimated using the Wechsler Test of Adult Reading. A significant, positive relationship was found between age and global *inter*-network connectivity ($r = 0.31$, $p = 0.029$). Moderation analyses yielded a significant age × intelligence interaction term ($p = 0.003$), such that intelligence attenuated the relationship between age and global *inter*-network connectivity. Taken together, these results suggest that age is positively associated with global DMN desegregation, possibly due to dedifferentiation or compensation. Intellectual functioning moderates this relationship, such that more intelligent older adults maintain a segregated DMN profile.

1. Introduction

The concept of "cognitive reserve" (CR) was developed to account for non-linear relationships between levels of brain pathology and functional status (Stern, 2002, 2009, 2012). In essence, CR refers to differences in cognitive efficiency, capacity, and flexibility that influence an individual's ability to cope with neural insult (Barulli and Stern, 2013). Commonly used proxy measures for this construct include educational attainment, occupational complexity, socioeconomic status, crystalized intelligence, and leisure activity engagement (Stern, 2002). Older adults with high CR have been found to maintain cognitive function at a comparable level to counterparts with low CR despite greater levels of gray matter atrophy (Boots et al., 2015), white matter hyperintensities (Brickman et al., 2011), and amyloid pathology (Vemuri et al., 2015). In addition, older adults with fewer years of education have an increased risk of dementia relative to more educated peers (odds ratio: 2.61; Meng and D'Arcy, 2012).

Task-based functional magnetic resonance imaging (fMRI) has been used to investigate potential neural mechanisms underlying CR. Among healthy older adults, CR has been positively associated with network efficiency during cognitive task performance (Stern, 2012). More concretely, greater CR is associated with less fMRI activation on tasks assessing visual episodic memory (Solé-Padullés et al., 2009), speech comprehension (Bosch et al., 2010), working memory (Bartrés-Faz et al., 2009), and non-verbal recognition (Stern et al., 2003). In the face of gray matter atrophy, older adults with high CR better maintain efficiency in primary networks during cognitive performance and require less support from alternative networks (Steffener et al., 2011).

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In contrast to task-based fMRI, resting state fMRI is collected while participants lie passively in the scanner and measures temporal correlations in spontaneous blood-oxygen-level-dependent signal fluctuations between spatially distributed brain regions (Binder et al., 1999; Biswal et al., 1995; Cordes et al., 2000; Fox and Raichle, 2007; Hampson et al., 2002; Xiong et al., 1999). Old age, even in the absence of overt pathology, is associated with a number of changes in resting state functional connectivity (for reviews, see Baldassarre and Corbetta, 2015; Sala-Llonch et al., 2015). The default mode network (DMN), which has hub regions in medial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobule, has received the most attention in the literature (Buckner et al., 2008; Greicius et al., 2003; Mazoyer et al., 2001; Raichle et al., 2001; Shulman et al., 1997). Generally speaking, older adults show reduced connectivity strength between seed regions within DMN (e.g., anterior-posterior disconnections) relative to young adults (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Mevel et al., 2013). Problems deactivating or suppressing DMN activity during performance of externally oriented cognitive tasks have also been observed (Park et al., 2010; Spreng and Schacter, 2012). Such age-related changes in DMN have meaningful cognitive correlates (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Mevel et al., 2013; Persson et al., 2014).

More recent findings suggest that old age is associated with enhanced connectivity between separate resting state networks that show segregation earlier in the lifespan (Betzel et al., 2014; Chan et al., 2014; Geerligs et al., 2015; Song et al., 2014; Voss et al., 2010). For example, Geerligs et al. (2015) found older adults to show reduced modularity of DMN relative to young adults, specifically characterized by reduced connectivity within DMN coupled with increased connectivity to other functional networks. The authors related these findings to dedifferentiation theory, which holds that the brain exhibits less functional specialization with advancing age (Baltes and Lindenberger, 1997). In turn, resting state network desegregation correlates with episodic memory dysfunction, amyloid burden, and tau pathology (Brier et al., 2014; Chan et al., 2014). Resting state network desegregation has also been observed in age-related neurodegenerative conditions, including Alzheimer's and Parkinson's disease (Brier et al., 2014; Göttlich et al., 2013).

A limited body of research suggests that proxy measures of CR influence functional connectivity in old age. Among healthy older adults, educational attainment was positively associated with functional connectivity between anterior cingulate cortex and several brain regions, including hippocampus, posterior cingulate cortex, inferior frontal lobe, and angular gyrus (Arenaza-Urquijo et al., 2013). In turn, anterior cingulate cortex functional connectivity was positively related to measures of verbal fluency and delayed recall (r = 0.45–0.61; Arenaza-Urquijo et al., 2013). CR—operationalized as a composite score of education, occupation, predicted intelligence based on vocabulary, and lifetime engagement in leisure, social, cognitive, and physical activities—has also been found to positively correlate with task-induced deactivations of DMN during passive speech comprehension in cognitively normal older adults (Bosch et al., 2010). The opposite pattern (i.e., a negative correlation) was observed in older adults with mild cognitive impairment (MCI) and Alzheimer's disease, which the authors interpreted to reflect greater subjective task difficulty among more impaired participants (Bosch et al., 2010). More recently, CR (education, occupation, and leisure activity engagement) was found to positively relate to functional connectivity within the cognitive control network (Franzmeier et al., 2016) and the posterior cingulate cortex of the DMN (Bozzali et al., 2015) in older adults with MCI and Alzheimer's disease, respectively.

Taken together, the available literature suggests a relationship between CR proxies and functional connectivity in healthy and pathologically aging populations. However, relatively few studies have been conducted on this topic and the research to date has focused largely on the effect of CR proxies *within* specific functional networks (e.g., DMN). To the authors' knowledge, no studies have considered how sociobehavioral proxy measures assumed to covary with reserve constructs, such as intellectual functioning (Stern et al., 2018), may influence the interactive behavior *between* distinct resting state networks. A novel computational framework for analyzing fMRI data was recently developed and validated that is particularly well suited to fill this gap in the literature (Ge et al., 2016; Jiang et al., 2015; Lv et al., 2015a, b, c; Makkie et al., 2015; Zhao et al., 2016). This framework—referred to as the Holistic Atlases of Functional Networks and Interactions (HAFNI) system—uses machine learning principles to measure the interactive behavior of brain activities that otherwise may be obscured using traditional, general linear model, subtraction-based analyses (Logothetis, 2008; Lv et al., 2015b, c). An important distinction between HAFNI and the more commonly used independent component analysis (ICA) method is that the latter assumes independence of different functional network components despite findings that fMRI signals are often spatially overlapping and interacting (Daubechies et al., 2009; Lee et al., 2011). HAFNI does not make this assumption and has thus demonstrated greater consistency and reliability in identifying functional brain networks than ICA, especially when networks exhibit substantial spatial overlap (Lv et al., 2015a). For example, it was recently demonstrated that while ICA methods perform relatively well when functional networks exhibit minor levels of spatial overlap, sparse dictionary learning methods including HAFNI consistently perform well, even when the spatial overlap between functional networks is moderate or higher (see Zhang et al., 2018). HAFNI is sensitive to subtle but meaningful network disruptions in various clinical conditions, including mild traumatic brain injury (Lv et al., 2016), autism spectrum disorder (Zhao et al., 2016), and prenatal alcohol exposure (Lv et al., 2015c).

The present study applied the HAFNI system to resting state fMRI data to achieve 2 major aims. The first was to extend the literature on the relationship between age and *inter*-network connectivity profiles in community-dwelling older adults. In light of well-documented disruptions of DMN during the aging process, even among healthy older adults without overt pathology (Sheline and Raichle, 2013), our investigation focused on the interaction of DMN with other established resting state networks in the neuroscience literature (Smith et al., 2009). Based on findings that *inter*-connectivity changes in old age are not restricted to interactions between DMN and any single functional network (e.g., Geerligs et al., 2014, 2015; Spreng and Schacter, 2012; Voss et al., 2010), the present analyses focused on the interactive behavior of DMN with other resting state networks on a global (aggregate) level. Exploratory analyses were conducted to investigate the relationship between age and *inter*-connectivity on an individual network level. The second aim was to evaluate whether estimated intellectual functioning (intelligence) moderates the relationship, if any, between age and global *inter*-network connectivity. Consistent with the bulk of the available literature, age was hypothesized to positively relate to between-network interactions, such that the oldest old in our sample would show the greatest desegregation of DMN with other resting state networks. Intelligence was expected to confer resilience to the effects of age on global *inter*-network connectivity and therefore attenuate this relationship in moderation analyses.

2. Material and methods

2.1. Participants

The present study was ancillary to a larger clinical trial evaluating the influence of dietary factors on various visual and neurocognitive outcomes (e.g., see Hammond et al., 2017; Lindbergh et al., 2018). Study volunteers included community-dwelling older adults (64–86 years old) recruited from the area via electronic mailing lists, flyers, and newspaper advertisements. Exclusionary criteria were left-handedness, traumatic brain injury, macular degeneration, gastric conditions that may interfere with nutrient absorption, corrected visual acuity worse than 20:40, MRI incompatibility, Geriatric Depression Scale (GDS) total score >19, or neurological disorder. Individuals with a current or prior history of psychiatric/neuropsychiatric illness (based on self-report or the report of a reliable collateral informant) were also excluded. Structural MRI images were reviewed to screen out individuals with significant brain abnormalities, such as structural lesions, substantial cerebrovascular disease (e.g., infarctions, extensive leukoaraiosis), tumor, and hydrocephalus. In addition, participants were required to be functionally independent and without evidence of dementia, including a Clinical Dementia Rating (CDR) global score <1.0 (Morris, 1993). The present analyses were conducted on 48 individuals who met these criteria and had resting state fMRI data from the baseline (pre-intervention) assessment visit of the larger clinical trial. Participants were compensated with $100 for their time and effort. The study was approved by the University of Georgia Institutional Review Board, informed consent was obtained from every participant, and the tenets of the Declaration of Helsinki were consistently upheld by all study personnel.

2.2. Measures

2.2.1. CDR

The CDR is a semi-structured interview with the participant and a reliable collateral informant (e.g., family member) that provides a global measure of cognitive and functional status (Morris, 1993). An overall CDR score can be calculated based on performance across 6 domains impacted by Alzheimer's and other age-related neurodegenerative diseases, including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Global scores can be calculated using the Washington University online algorithm (https://biostat.wustl.edu/~adrc/cdrpgm/index.html) and range from 0 to 3, with higher scores corresponding to greater levels of impairment (0 = normal, 0.5 = questionable impairment, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia). Participants with CDR global scores of 1 (mild dementia) or greater were excluded from analyses.

2.2.2. Wechsler Test of Adult Reading

The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) involves reading a list of 50 words with irregular pronunciations due to atypical grapheme to phoneme relationships. An estimate of intellectual functioning can be calculated by algorithmically combining the examinee's word reading score with demographic variables, including age, education, race, sex, and geographic region. The WTAR is a valid and reliable instrument with high test-retest correlations (i.e., >0.90; Green et al., 2008; Strauss et al., 2006; Wechsler, 2001; Whitney et al., 2010).

2.2.3. GDS

The GDS was administered as a gross screener for significant levels of depressive symptoms (Yesavage et al., 1983). The GDS is a self-report measure containing 30 yes/no questions that focus on the affective and cognitive aspects of depression. Somatic symptoms that are often attributable to aging rather than mood disturbance are minimized (Smarr and Keefer, 2011). Greater scores indicate greater levels of depression (0–9 = normal; 10–19 = mild; 20–30 = severe).

2.3. Neuroimaging

2.3.1. MRI acquisition

A General Electric (Waukesha, WI) 3T Signa HDx MRI system was used to acquire the structural and functional neuroimaging data. The structural protocol consisted of a 3-dimensional T1-weighted fast spoiled gradient recall echo sequence [repetition time (TR) = 7.5 ms; echo time (TE) = <5 ms; field-of-view (FOV) = 256 × 256 mm matrix; flip angle = 20°; slice thickness = 1.2 mm; 154 axial slices] with total acquisition time of 6 minutes and 20 seconds. One hundred seventy-six images were collected that provided coverage from the brainstem to the top of the head. The functional (resting state) protocol consisted of a T2*-weighted single shot echo planar imaging sequence [TR = 5000 ms; TE = 25 ms; 90° radiofrequency (RF) pulse; acquisition matrix = 128 × 128; FOV = 220 × 220 mm; in-plane resolution = 220/128 mm; slice thickness = 2 mm; 60 interleaved axial slices] with total acquisition time of 9 minutes and 25 seconds. One hundred thirteen volumes, providing coverage of the cortical surface and cerebellum, were acquired axially and aligned to each participant's anterior commissure-posterior commissure line. The first 5 volumes were discarded as "dummy scans" to allow longitudinal magnetization to reach equilibrium. Although the TR for the echo planar imaging sequence was longer than typically used in the literature, the number of volumes and scan length of this protocol provide adequate resolution and statistical reliability/power (e.g., see Birn et al., 2013; Kalcher et al., 2012). In addition, empirical manipulation studies have suggested minimal differences in resting state fMRI findings when varying temporal resolution from 2500 to 5000 ms (Van Dijk et al., 2010). A TR of 5000 ms has been successfully implemented within the HAFNI framework in previously published work (Lindbergh et al., 2019).

During scanning, a blank dark-gray screen was displayed via goggles compatible with the MRI environment (Resonance Technology Inc, Northridge, CA). Participants were instructed to close their eyes and relax while lying as still as possible and not falling asleep. To further minimize head motion, foam pads were used to stabilize participants' heads.

2.3.2. Data analyses

Functional MRI of the Brain (FMRIB) Software Library (FSL; Jenkinson et al., 2012) was used to implement a standard preprocessing pipeline for resting state fMRI data detailed elsewhere (Lv et al., 2015a, b, c, 2016). Briefly, the pipeline included skull removal, motion correction, slice time correction, spatial smoothing (full-width-at-half-maximum = 5 mm), global drift removal, and registration to Montreal Neurological Institute space. Motion Correction FLIRT (FMRIB's Linear Image Registration Tool) (MCFLIRT) in FSL was used as a motion correction tool to improve between-volume registration, as described in detail by Jenkinson et al. (2002). MCFLIRT is widely used in fMRI research, including within the Human Connectome Project (Marcus et al., 2013; Smith et al., 2013). Furthering handling of motion effects and other sources of noise within the data was achieved within the HAFNI framework and is detailed below. The resting state data were also subject to band-pass filtering (0.01–0.1 Hz), which helps remove noise referable to the vascular system and other potential non-neural confounds within the data. Voxel signals from individual subject brains were normalized to mean = 0 and standard deviation (SD) = 1.

The HAFNI framework was employed using a temporal concatenated sparse coding approach that permits group-wise analysis of

functional networks and their interactions (Lv et al., 2016). The HAFNI framework has been validated previously and the interested reader is referred online (http://hafni.cs.uga.edu/) and to several published studies for a detailed description of the methodology (Ge et al., 2016; Lv et al., 2015a, b, c, 2016). To briefly summarize here, a 2-dimensional (voxel number × time series) signal matrix is created for each subject by extracting and aggregating whole-brain fMRI signals. The concatenated signal matrices are then subject to an online dictionary learning and sparse coding algorithm (Mairal et al., 2010) that factorizes the data into a time series signal dictionary matrix (D) and a coefficient matrix (A). D is organized into columns that correspond to activities of learned functional networks ("atoms"). Meanwhile, the rows in A provide a mapping of the functional networks to their location within the brain volume by preserving the original signal matrix's spatial voxel organization. Seeing as groups of participants comprise the input for the online learning, it is possible to create group-level networks with shared spatial profiles. "Small" dictionaries corresponding to each subject can also be derived from the concatenated dictionary matrix (D). It is thus possible to quantify local dynamics at the individual subject level while still being able to perform group-level statistical comparisons because of the network correspondence resulting from the common spatial networks.

For the interested reader, Mairal et al. (2010) provides an elaborated description of the publically available dictionary learning/spare representation algorithms used here. Briefly, an empirical cost function is applied to each raw data sample (x_i) :

$$f_n(D) \triangleq \frac{1}{n}\sum_{i=1}^{n} \ell(x_i, D)$$

where a "sparse" solution to the coefficient vector α_i is produced by the loss function (ℓ):

$$\ell(x_i, D) \triangleq \min_{\alpha_i \epsilon \mathbb{R}^m} \frac{1}{2} \parallel x_i - D\alpha_i \parallel_2^2 + \lambda \parallel \alpha_i \parallel_1$$

At the same time, the columns within D are constrained to prevent arbitrarily large values:

$$C \triangleq \left\{ D \epsilon \mathbb{R}^{t \times m} \; s.t. \forall \; j \; = \; 1, \ldots m, \; d_j^T d_j \leq 1 \right\}$$

The dictionary size, m, and regularization parameter, λ, are 2 important variables to select within the context of machine learning and unfortunately there are no established "gold standards" in the field. In the present study, these 2 parameters were selected *a priori* based on prior experiments showing that a dictionary size of 500 and a λ of 1.5 perform well within the HAFNI framework (e.g., Lv et al., 2015a, b). Although it is possible that slightly different results may have been obtained upon selecting different values, it has previously been demonstrated (e.g., Lv et al., 2015a, b) that HAFNI results are highly consistent and reliable across a range of dictionary sizes (e.g., 100–600) and regularization parameters (e.g., 1.0–2.0).

The dictionary atoms corresponding to DMN and 9 other resting state networks (visual medial, visual occipital, visual lateral, cerebellum, sensorimotor, auditory, executive control, right frontoparietal, and left frontoparietal) that are well-established in the neuroscience literature (Smith et al., 2009) were then identified for each subject. This was accomplished quantitatively by calculating spatial overlap rate similarity (ORS) using a validated approach (Zhao et al., 2016) with network templates provided by Smith et al. (2009). More specifically,

$$\mathrm{ORS} \; = \; \sum_{k=1}^{|V|} \frac{\min(V_k, W_k)}{\frac{(V_k + W_k)}{2}}$$

where V corresponds to the Smith et al. (2009) resting state network template and W represents the network learned in our sample. The minimum activation value between spatially corresponding voxels (k) in V and W is divided by the average activation value of the same voxel pair and summed. Greater ORS values thus represent greater correspondence between volume maps in terms of activation intensity and spatial location within the brain. In the rare incidences (<0.05%) that the same atom was identified as the best representation of more than one network (e.g., DMN and executive control), that data point was excluded from subsequent analyses.

An advantage of the HAFNI framework is that the dictionary learning and sparse coding technique can be used to identify and remove the effects of motion and other sources of noise (e.g., non-neuronal physiology and scanner artifacts) within the data, as described previously (e.g., Lv et al., 2016, 2017). Specifically, motion effects and other noise components are "learned" within HAFNI as separate dictionary atoms, which can then be excluded from subsequent analyses. In the present study, analyses were restricted to 10 atoms corresponding to well-established functional networks in the neuroscience literature; the other 490 atoms (out of 500) effectively captured the full range of nuisance effects within the data and were excluded. This data-driven approach to de-noising the data is conceptually similar to the ICA-based FIX method used in the Human Connectome Project (see Salimi-Khorshidi et al., 2014).

Consistent with procedures used elsewhere (Ge et al., 2016; Lv et al., 2016; Zhao et al., 2016), *inter*-network connectivity could then be quantified by calculating Pearson correlation coefficients between the time series of the atom corresponding to DMN and each atom corresponding to the other 9 resting state networks. Averaging across these correlations yielded a measure of global *inter*-network connectivity.

The hypothesized positive relationship of older age to global DMN desegregation was tested in a zero-order bivariate correlation between age and aggregate *inter*-connectivity scores. The relationship between age and DMN *inter*-connectivity on an individual network level (i.e., separately for each of the 9 resting state networks) was similarly evaluated in exploratory bivariate correlational analyses. All bivariate correlation coefficients are reported as Pearson's r values.

Moderation analysis was conducted using the regression-based approach in Hayes (2013) PROCESS macro (Version 2.16.3) for IBM SPSS (Version 23.0). Age was entered as a continuous independent variable (X), intelligence (estimated intellectual functioning) as a continuous moderator (M), and age × intelligence as the interaction term (XM). Aggregate *inter*-network connectivity scores served as the dependent variable (Y). The statistical model can thus be represented by the following linear equation: $Y = i + b_1X + b_2M + b_3XM + e_y$, where i refers to the intercept, e refers to the error term, and b refers to the regression coefficients. To probe a significant interaction term, the conditional effect of X (i.e., age, treated continuously) on Y (i.e., *inter*-network connectivity, treated continuously) at low (1 SD below the mean), moderate (the mean), and high (1 SD above the mean) values of M were evaluated through simple slopes analysis (Hayes, 2013). Because all moderation analyses employed multiple regression techniques, including the simple slopes analyses (see Hayes, 2012, 2013), corresponding results are reported as regression coefficients (b values) that take into account the influence of all other predictors within the model (Cohen et al., 2003).

3. Results

3.1. Descriptive statistics

Basic characteristics of the sample, including age, race, sex, and educational attainment, are presented in Table 1. Global *inter*-

Table 1
Descriptive statistics

Variable	Mean (SD) or % age
Age (Y)	72.29 (6.25)
Race (% Caucasian)	100.00
Sex (% female)	58.30
Education (Y)	16.40 (3.12)
WTAR (predicted FSIQ)	114.38 (7.94)
Inter-network connectivity	0.03 (0.09)

Key: FSIQ, full-scale intelligence quotient; *Inter*-network connectivity, aggregate correlation among default mode network activity and visual medial, visual occipital, visual lateral, cerebellum, sensorimotor, auditory, executive control, right frontoparietal, and left frontoparietal network activity; SD, standard deviation; WTAR, Wechsler Test of Adult Reading.

network connectivity scores and WTAR performance are also displayed in Table 1. Although the majority of the sample had CDR global scores of 0, 5 participants fell within the questionable impairment range (CDR = 0.5). Accordingly, primary analyses were repeated with CDR scores in the model to evaluate and control for a potential influence of cognitive status on our results (see below).

3.2. Age and inter-network connectivity

Consistent with prior work (e.g., Lv et al., 2015a, b), a dictionary size of 500 yielded a readily recognizable DMN in our sample (Fig. 1).

As predicted, the bivariate correlation analysis indicated that age positively and significantly related to global *inter*-network connectivity ($r = 0.31$, $p = 0.029$). The size of this effect could be characterized as "medium" in magnitude (Cohen, 1992). Of note, the relationship between age and global *inter*-network connectivity remained statistically significant upon controlling for CDR status in the model ($p = 0.047$).

Exploratory analyses were conducted to evaluate the extent to which age correlated with *inter*-connectivity between DMN and each of the other 9 resting state networks at an individual network level. Correlations were positive and small-to-medium in magnitude for visual occipital ($r = 0.219$, $p = 0.135$), visual lateral ($r = 0.221$, $p = 0.132$), cerebellum ($r = 0.179$, $p = 0.225$), sensorimotor ($r = 0.310$, $p = 0.032$), and left frontoparietal ($r = 0.205$, $p = 0.167$) networks (see supplementary materials). Age effects were close to 0 for visual medial ($r = 0.034$, $p = 0.818$), auditory ($r = 0.023$, $p = 0.877$), executive control ($r = -0.003$, $p = 0.983$), and right frontoparietal ($r = -0.089$, $p = 0.551$).

3.3. Moderation analyses

With respect to moderation, the overall regression model containing age (X), intelligence (M), and age × intelligence (XM) significantly accounted for variance in global *inter*-network connectivity (Y), $F(3, 44) = 7.95$, $p \leq 0.001$, $R^2 = 0.21$. Although the effects of age [$b = 0.0033$, $t(44) = 1.97$, $p = 0.055$] and intelligence [$b = -0.0009$, $t(44) = -0.79$, $p = 0.433$] were non-significant in the overall model, the age × intelligence interaction term was statistically significant [$b = -0.0005$, $t(44) = -3.14$, $p = 0.003$]. This pattern indicated that a moderating effect was present.

To probe the interaction, simple slopes analysis revealed that the conditional effect of age on *inter*-network connectivity was statistically significant at low levels (1 SD below the mean) of intelligence [$b = 0.0070$, $t(44) = 3.89$, $p \leq 0.001$]. In contrast, the conditional effects of age were non-significant at average [$b = 0.0033$, $t(44) = 1.97$, $p = 0.055$] and high (1 SD above mean) levels of intelligence [$b = -0.0005$, $t(44) = -0.21$, $p = 0.832$]. Fig. 2 visually depicts the raw data with regression-based slopes at different levels of intellectual functioning.

The moderation analyses were repeated with CDR as a covariate in the model to control for potential effects of cognitive status. The overall regression model remained significant [$F(4, 43) = 2.99$, $p = 0.029$, $R^2 = 0.22$] and the individual effects of age [$b = 0.0037$, $t(43) = 1.86$, $p = 0.07$] and intelligence [$b = -0.0013$, $t(43) = -0.84$, $p = 0.406$] remained non-significant. Intelligence continued to moderate the relationship between age and global *inter*-network connectivity, as evidenced by a statistically significant age × intelligence interaction term [$b = -0.0005$, $t(43) = -2.43$, $p = 0.019$]. Simple slopes analysis similarly revealed that the conditional effect of age on *inter*-network connectivity was statistically significant at low levels of intelligence [$b = 0.0077$, $t(43) = 3.09$, $p = 0.003$], but not at average [$b = 0.0026$, $t(43) = 1.25$, $p = 0.219$] or high [$b = 0.0002$, $t(43) = 0.09$, $p = 0.928$] intelligence levels.

3.4. Sensitivity analysis

Given prior literature that depression may influence functional connectivity (e.g., Veer et al., 2010), a sensitivity analysis was conducted to evaluate whether excluding individuals ($n = 2$) with mild levels of depression (GDS scores = 10–19) meaningfully altered our findings. In the subsample of participants without mild depressive symptoms ($n = 46$), age continued to significantly and positively relate to global *inter*-network connectivity ($r = 0.348$, $p = 0.018$). The overall results of the moderation analysis were also similar [$F(3, 42) = 3.65$, $p = 0.02$, $R^2 = 0.21$] and the age × intelligence interaction term remained statistically significant [$b = -0.00043$, $t(42) = -2.09$, $p = 0.04$]. As was observed in the overall sample, the simple slopes analysis demonstrated that the conditional effect of age on *inter*-network connectivity was statistically significant at low levels of intelligence ($b = 0.0072$, $p = 0.003$), but not at average ($b = 0.0029$, $p = 0.17$) or high ($b = 0.0009$, $p = 0.721$) intelligence levels.

4. Discussion

As hypothesized, the present results suggest a positive relationship between older ages and global *inter*-connectivity of DMN with other resting state networks. This finding is consistent with the small number of prior studies that have evaluated age-related changes in the interactive behavior of functional networks in the resting state (e.g., Geerligs et al., 2014, 2015; Spreng and Schacter, 2012; Voss et al., 2010). The present results extend this literature by demonstrating that estimated intellectual functioning (intelligence) significantly moderates the relationship between older ages and *inter*-network connectivity. More specifically, the relationship between age and global DMN desegregation is attenuated among older adults with high levels of intelligence.

The mechanism responsible for age-related increases in global *inter*-network connectivity remains an open question. As noted by others (e.g., Geerligs et al., 2015), it is possible that resting state network desegregation can be explained by dedifferentiation theory and reflects reduced functional specialization of the aging brain (Baltes and Lindenberger, 1997). Processes of dedifferentiation have been observed on task-based fMRI as less specific (more diffuse) activation in various brain regions (e.g., parietal and frontal) during cognitive task performance (Carp et al., 2011; Kalkstein et al., 2011) and are thought to be driven by age-related declines in dopaminergic system modulation (Li et al., 2001).

Alternatively, or perhaps in combination, increased between-network interactions in old age could reflect a compensatory process. As elaborated in the Scaffolding Theory of Aging and Cognition (Reuter-Lorenz and Park, 2014), the aging brain adaptively

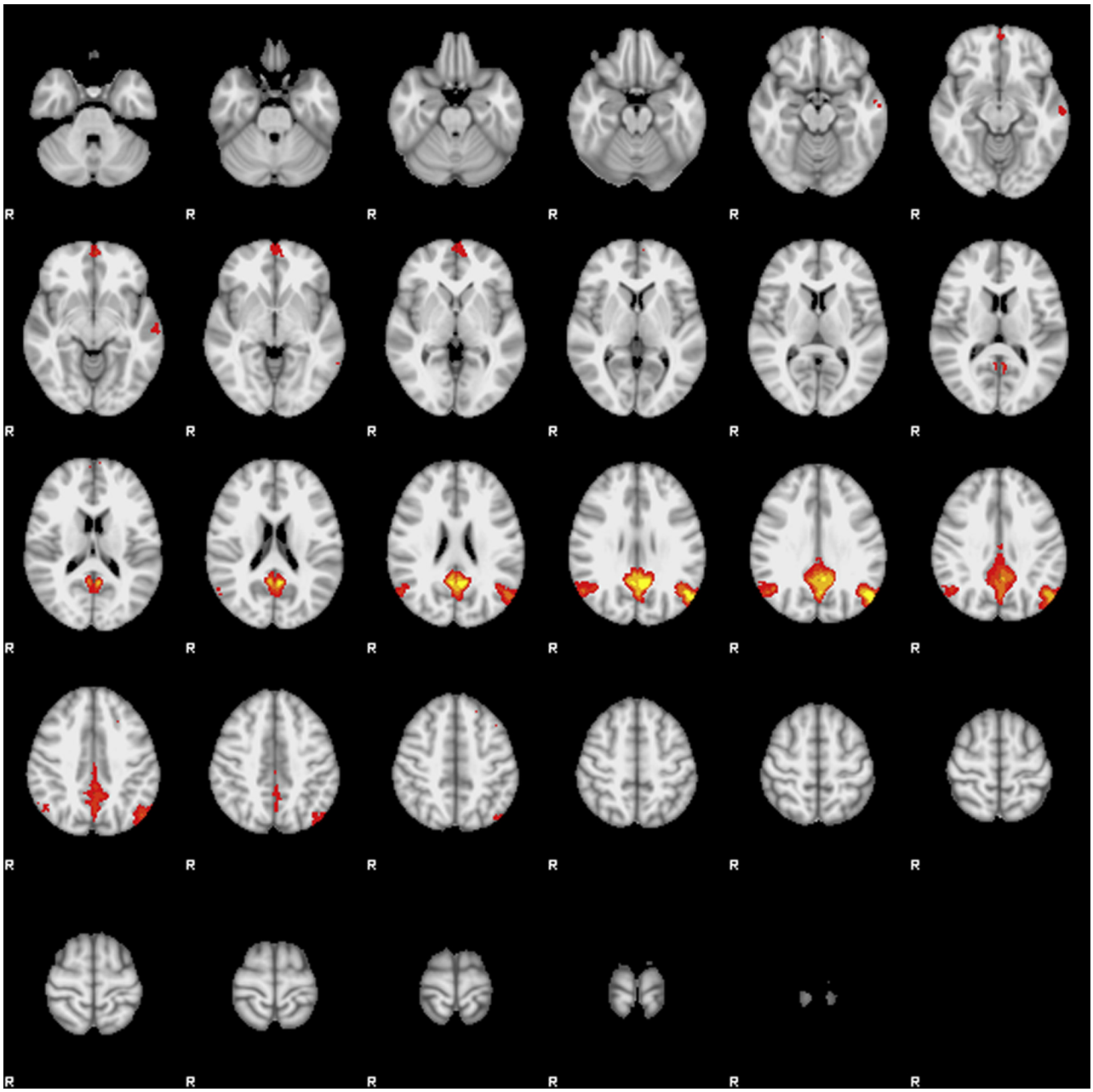

Fig. 1. Default mode network learned in the present sample.

reorganizes and enlists support from supplementary neural circuitry to counteract the effects of age-related structural and functional deterioration. In this context, increased *inter*-network connectivity may represent a form of positive neuroplasticity. Hemispheric Asymmetry Reduction in Older Adults (Cabeza, 2002), Compensation-Related Utilization of Neural Circuits Hypothesis (Reuter-Lorenz and Cappell, 2008), and Posterior-Anterior Shift with Aging (Davis et al., 2008) are all models that have arisen to characterize the compensatory recruitment pattern seen on task-based fMRI. The compensatory recruitment pattern on resting state fMRI is less well studied or understood. Increased between-network functional connectivity in cognitively normal older adults has generally been interpreted as compensatory (Betzel et al., 2014; Elman et al., 2016), though the research base is quite sparse. From a theoretical standpoint, given the vulnerability of DMN to early stages of pathobiological processes (Sheline and Raichle, 2013) such as amyloid deposition (Mintun et al., 2006), it may be particularly advantageous for DMN to solicit support from other networks and engage alternative pathways for information flow. This may manifest in the resting state as enhanced *inter*-network connectivity.

Interestingly, exploratory analyses suggested that the global effect of age on *inter*-connectivity was driven primarily by enhanced correlations of DMN to visual occipital, visual lateral, cerebellum, sensorimotor, and left frontoparietal networks. In contrast, *inter*-connectivity of DMN to visual medial, auditory, executive control, and right frontoparietal networks appeared to be relatively less associated with age. This suggests a nuanced pattern of age-related changes in between-network interactions, with some networks evidencing greater reorganization in connective synergy with DMN than others. Still, the effects of age on *inter*-network connectivity tended to be larger when *inter*-network connectivity

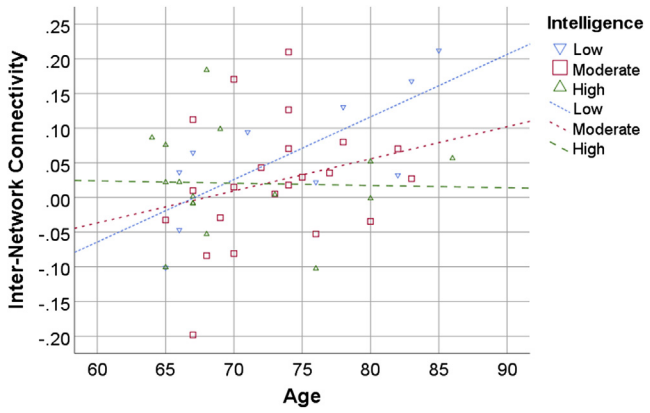

Fig. 2. Simple slopes analysis. Raw data are plotted with regression-based slopes corresponding to the conditional effect of age on *inter*-network connectivity at moderate (within 1 standard deviation of the mean), low, and high levels of estimated intellectual functioning. *Inter*-network connectivity is defined as the aggregate correlation between default mode network activity and visual medial, visual occipital, visual lateral, cerebellum, sensorimotor, auditory, executive control, right frontoparietal, and left frontoparietal network activity.

was measured on a global level (i.e., averaged across networks) versus an individual network level. This may reflect that our global measure of *inter*-network connectivity, which combined data across multiple networks, provides a relatively more sturdy and robust index of age-related functional reorganization. Future research is warranted to further explore the nuances of age-related *inter*-connectivity changes at an individual network level, including investigating whether there are any meaningful clinical correlates.

To the authors' knowledge, the present study represents the first attempt to evaluate whether intelligence moderates the interactive behavior between distinct resting state networks. The finding that older adults with greater levels of estimated intellectual functioning maintain DMN segregation may reflect a "brain maintenance" effect (Nyberg et al., 2012). Brain maintenance involves the idea that the primary determinant of successful aging is the absence of brain pathology at various levels of the central nervous system (e.g., cellular, neurochemical, white matter, gray matter, and neural network). In essence, older adults who avoid age-related neural decline require less compensatory reorganization, display similar patterns of brain activation to younger adults, and ultimately exhibit preserved cognitive and functional abilities (Nyberg et al., 2012; Reuter-Lorenz and Park, 2014). These individuals are considered to have greater neurobiological efficiency given a reduced need to recruit additional neural resources to meet task demands (Duverne et al., 2008). Applied to the present findings, it is possible that more intelligent older adults are resistant to age-related neuropathological processes and thus maintain a more efficient, "youth-like," resting state functional connectivity profile. Relatedly, Santarnecchi et al. (2015) conducted a resting state fMRI study of healthy adults (mean age = 34, range = 20–60) and demonstrated that individuals with higher levels of intelligence show greater brain resilience to simulated attacks on neural network nodes, seemingly due to a more distributed processing capacity. Accordingly, older adults with higher levels of intelligence at baseline may have a more robust processing capacity, which confers resilience to the effects of aging on functional connectivity and reduces the need for between-network compensatory reorganization.

There are some limitations to the present study that deserve consideration. Although there is evidence that medications can influence resting state functional connectivity patterns (e.g., McCabe and Mishor, 2011), medication use was not controlled for in our analyses and may have influenced our results. The sample was relatively small, entirely Caucasian, and well educated. Moving forward, it will be important to replicate our findings with larger sample sizes characterized by greater diversity in race, ethnicity, and levels of intellectual functioning. Relatedly, the present study was conducted on a functionally independent, community-dwelling older adult population. It is possible that the relationship between age and *inter*-network connectivity, as well as the moderating effect of intelligence, could manifest differently in the face of frank neurodegenerative disease. For example, it was recently demonstrated that high CR older adults with MCI show *greater* resting state functional connectivity within the cognitive control network than low CR counterparts with MCI (Franzmeier et al., 2016). Although the overall pattern of our results did not change upon controlling for cognitive status as measured by the CDR, future research may benefit from a focus on "purer" samples of typically aging older adults compared to older adults with biomarker-confirmed neurodegenerative conditions (e.g., Alzheimer's disease).

Longitudinal designs will be helpful to determine whether functional connectivity differences associated with intellectual functioning, both within and between resting state networks, are pre-existing or reflect a compensatory process. The cross-sectional nature of the present analyses prevents conclusions regarding the extent to which older adults with high intelligence had more segregated resting state networks at baseline (i.e., prior to old age) or are more resistant to age-related functional connectivity changes. Finally, it will be important to examine whether *inter*-network connectivity levels, and changes in these levels across time, have cognitive and functional correlates. In a similar vein, it may be worthwhile to evaluate the potential of *inter*-network connectivity profiles to serve as a novel biomarker of underlying neurodegeneration and predictor of future functioning.

Despite its limitations, the present study advances the literature by replicating and extending previous findings showing a relationship between age and functional connectivity in late life. To the authors' knowledge, it is the first of its kind to demonstrate that intellectual functioning moderates the effect of age on the interactive behavior of functional networks in the resting state.

Disclosure

This research project was ancillary to a larger study funded in part by Abbott Nutritional Products (Columbus, OH, USA; research grant to Hammond, Renzi-Hammond, and Miller) and the University of Georgia's Bioimaging Research Center (Athens, GA, USA; administrative support to Miller). DSM Nutritional Products (Switzerland) provided supplements and placebos for the larger study. Miller was an employee of Abbott Nutrition during a portion of the grant period while holding a joint appointment at the University of Georgia. Hammond has consulted for Abbott Nutrition. No other potential conflicts of interest exist for any of the study authors, including Puente, Lindbergh, Mewborn, Terry, Lv, Liu, and Zhao. The study design and writing of the report, as well as the collection, analysis, and interpretation of the data, were all completed independently of supporting agencies. The decision to submit the article for publication was approved by Abbott Nutritional Products.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.02.014.

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