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Gray Matter Volume Covariance Networks Associated with Social Networks in Older Adults

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Abstract

Extensive social networks are associated with better physical, mental, and cognitive health in aging, but the underlying brain substrates remain largely unexplored. Voxel-based morphometry and multivariate statistics were used to identify gray matter volume covariance networks associated with social networks in 86 older adults without dementia (*M* Age = 75.20 years, 53% women). Gray matter networks associated with the number of high-contact social roles and the total number of network members were identified after adjusting for age, sex, education, global health, and total intracranial volume – and shared nodes included medial, lateral and orbital prefrontal, hippocampal, precuneus, insular, and cingulate regions. Greater expression of these gray matter networks was associated with better memory scores on the Free and Cued Selective Reminding Test. A more distributed network was associated with high-contact social roles than total number of networks members – also extending into amygdala and entorhinal cortex. Thus, high-contact social roles and total number of network members in older adults are associated with gray matter networks composed of regions previously linked to memory and affected by both healthy aging and Alzheimer disease – and high-contact social roles are more strongly associated with brain structures than the total number of network members.

Keywords

Social Networks; Aging; Neuroimaging; Multivariate Statistics

Introduction

Extensive social networks and high levels of social support are associated with better physical, mental, and cognitive health outcomes in older adults (Barnes, De Leon, Wilson, Bienias, & Evans, 2004; Berkman, 1984; Ertel, Glymour, & Berkman, 2008; Fratiglioni, Paillard-Borg, & Winblad, 2004; Holt-Lunstad, Smith, & Layton, 2010; House, Landis, & Umberson, 1988; Kawachi & Berkman, 2001; McNeill, Kreuter, & Subramanian, 2006; Pillemer & Holtzer, 2016; Seeman, Lusignolo, Albert, & Berkman, 2001; Yeh & Liu, 2003). Yet, the brain substrates associated with social networks and social support remain largely

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unexplored, particularly in older adults. A *social network* is a social structure of interactions and relationships – including family members, friends, and coworkers – and *social support* is the perceived or actual level of support provided to an individual by their social network (Antonucci, 1990). Extensive social networks are associated with a reduced risk for morbidity and mortality (Berkman, 1984; Holt-Lunstad et al., 2010; House et al., 1988), and increased participation in physical activities (for a review see (McNeill et al., 2006)). Extensive social networks are also associated with reduced levels of depressive symptoms and anxiety (for a review see (Kawachi & Berkman, 2001)). In addition, extensive social networks and high levels of social support in older adults are associated with better cognitive functions, and a reduced risk for cognitive decline, Alzheimer's disease (AD) and related dementias (Barnes et al., 2004; Bassuk, Glass, & Berkman, 1999; Ertel et al., 2008; Fratiglioni et al., 2004; Pillemer & Holtzer, 2016; Seeman et al., 2001; Yeh & Liu, 2003). A better understanding of the brain substrates associated with social networks and social support in older adults – potentially modifiable factors of physical, mental, and cognitive health – has the potential to inform the development of interventions for improving a number of different health outcomes in aging.

The brain substrates associated with social networks and social supports in older adults are not well-understood. Prior studies of predominantly young and middle-aged adults, however, have observed associations between social networks and social support and the structure of medial prefrontal cortex (Lewis, Rezaie, Brown, Roberts, & Dunbar, 2011; Powell, Lewis, Roberts, García-Fiñana, & Dunbar, 2012), the structure and function of the amygdala and the entorhinal cortex (Bickart, Wright, Dautoff, Dickerson, & Barrett, 2011; Von Der Heide, Vyas, & Olson, 2014), functional connectivity between amygdala and superior temporal sulcus, medial temporal lobe, anterior cingulate, orbitofrontal, and medial prefrontal cortex regions (Kevin C Bickart, Mark C Hollenbeck, Lisa Feldman Barrett, & Bradford C Dickerson, 2012), as well as white matter integrity of the genu of the corpus callosum (Molesworth, Sheu, Cohen, Gianaros, & Verstynen, 2015). These regions have been previously associated with a number of physical, mental, and cognitive processes in older adults, including physical exercise, depression, emotion, memory, social processing, cognitive decline and dementia (Bherer, Erickson, & Liu-Ambrose, 2013; Du et al., 2003; Gutchess, Kensinger, & Schacter, 2007; Pennanen et al., 2004; Rodrigue & Raz, 2004; St. Jacques, Dolcos, & Cabeza, 2010; Whalen, Shin, Somerville, McLean, & Kim, 2002).

We recently examined functional connectivity associated with social networks in 28 older adults without dementia (65–87 years (Pillemer, Holtzer, & Blumen, 2017)), using resting-state functional magnetic resonance imaging (fMRI) and the social network index (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997). We found that functional connectivity in several well-established resting-state networks, previously linked to a number of visual, motor, speech and other language functions, were associated with the number of high-contact social roles (including spouse, parent, child, child-in-law, close relative, close friend, religious group member, student, employee, neighbor, volunteer and group member) and the total number of network members – including the sensory-motor, visual, vestibular/insular and left fronto-parietal resting-state networks. We also found that the number of high-contact social roles were more strongly associated with functional connectivity in the lateral prefrontal components of the left fronto-parietal resting-state network, while the total

number of network members were more strongly associated with functional connectivity in the medial prefrontal components of the left fronto-parietal resting-state network. We concluded that a) linking social networks in older adults to functional connectivity in several resting-state networks is consistent with that extensive social networks and social support have been linked to a number of positive physical, mental, and cognitive health outcomes, and that b) the functional brain networks associated with the number of high-contact social roles and the total number of network members largely overlap, but also differ, particularly in the prefrontal cortex.

Although resting-state fMRI is a valuable tool for linking social networks in older adults to connectivity in well-established functional networks, normal and pathological aging is associated with structural deterioration in different brain regions that, in turn, are distributed across different functional networks (Kalpouzos et al., 2009; Raz et al., 1997; Thompson et al., 2003). We also know that the relationship between brain function and structure is not clear-cut or one-to-one (Kopell, Gritton, Whittington, & Kramer, 2014; Park & Friston, 2013). In normal aging, for example, the greatest gray matter atrophy is observed in prefrontal cortex regions – including dorsolateral and orbitofrontal regions – yet, considerable atrophy is also observed in sensorimotor, occipital, and insular regions (Kalpouzos et al., 2009; Raz et al., 1997). Entorhinal, hippocampal and amygdala regions, however, are relatively spared in normal aging (Thompson et al., 2003). By contrast, in older adults with AD, the greatest gray matter atrophy is observed in entorhinal, hippocampal, and other medial temporal regions, with relative sparing of frontal and sensorimotor regions until the later stages of the disease (Thompson et al., 2003). Thus, determining whether the structural brain substrates of social networks are particularly affected or relatively spared in normal aging and AD could inform us about who will be more or less likely to benefit from interventions aimed at strengthening social networks and social support. Further linking these brain substrates to key cognitive functions affected by normal aging and AD, including processing speed, memory, and executive functions, would provide additional information regarding this issue.

The aim of the current study was to examine the structural brain networks of social networks in older adults without dementia – and how they relate to processing speed, memory, and executive function. Voxel-based morphometry methods and multivariate covariance-based statistics were used to identify gray matter covariance patterns or ‘networks’ associated with both high-contact social roles and the total number of network members (Cohen et al., 1997). Unlike traditional univariate approaches to neuroimaging analysis that evaluate gray matter volume (or functional activation) on a voxel-by-voxel basis, multivariate covariance-based approaches to neuroimaging analysis evaluate the correlation or covariance between gray matter volume (or functional activation) between different brain regions, and can therefore be more straightforwardly interpreted as neural networks (Habeck & Stern, 2010). Multivariate covariance-based approaches to neuroimaging analysis also typically involves some form of data reduction (analogous to a principal components analysis) and do not require a priori modeling or hypotheses – thereby avoiding the multiple comparison problem of traditional univariate analyses and increasing statistical power (Ashby, 2011; Habeck et al., 2008; Habeck, Krakauer, et al., 2005; Habeck & Stern, 2010). In addition, multivariate covariance-based networks have been shown to be highly reproducible across different data

sets of older adults (Bergfield et al., 2010; Habeck et al., 2008). Thus, multivariate covariance-based statistics offers a potentially sensitive and reproducible approach for identifying gray matter covariance networks associated with the number of high-contact social roles and the total number of network members in older adults without dementia. A network-based approach is also more appropriate than traditional univariate approaches because social networks and social support have been associated with a number of physical, mental and cognitive health outcomes in aging, and we hypothesized that both the number of high-contact social roles and the total number of network members would be associated with fairly distributed networks of gray matter volume. Our multivariate approach also permitted us to adjust for potential confounders, including age, sex, education, global health, and total intracranial volume. Finally, the expressions of these gray matter networks associated with the number of high-contact social roles and the total number of network members could also be correlated with neuropsychological assessments of processing speed, memory, and executive function.

Methods

Participants.

We examined gray matter covariance patterns related to the social network index (Cohen et al., 1997), and their associations with specific cognitive functions, in 86 community-dwelling of older adults without dementia who had undergone magnetic resonance imaging (MRI) from a larger study called the Central Control of Mobility in Aging (CCMA) study at Albert Einstein College of Medicine, Bronx, NY (Holtzer, Wang, & Verghese, 2014)]. Inclusion criteria for the larger CCMA study were 1) 65 years and older, 2) plan to be in the area for next three or more years, 3) able to speak English, and 4) ambulatory. Additional inclusion criteria for the current sub-study was willingness to undergo MRI. Persons with dementia were excluded from the CCMA study based on the telephone-based memory impairment screen (score of <5 (Lipton et al., 2003) Ascertain Dementia 8-item Informant Questionnaire AD-8 score >1(Galvin et al., 2005) or clinical case conferences using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (Association, 2000). Other exclusion criteria included, serious chronic or acute illness (e.g. cancer), any medical condition or chronic medication use (e.g., neuroleptics) that would compromise safety or affect cognitive functioning or terminal illness with life expectancy less than 12 months, progressive degenerative neurologic disease (e.g. Parkinson's disease), hospitalized in the past 6 months for severe illness or surgery, severe auditory or visual loss, active psychoses or psychiatric symptoms and living in nursing home. Additional exclusion criteria for the current sub-study was MRI contraindication. Key MRI contraindications were vascular stents (7%), pacemakers (4%) and joint replacements (4%). The participant characteristics of the current sample are summarized in Table 1.

Social Network index.

The Social Network Index (SNI; (Cohen et al., 1997)) was used to assess the *total number of high-contact social roles* that a respondent interact with at least biweekly (SNI-1), and the *total number of network members* that a respondent interact with at least biweekly (SNI-2). The maximum number of high-contact social roles a respondent can have is 12 and these

include: spouse, parent, child, child-in-law, close relative, close friend, religious group member, student, employee, neighbor, volunteer and group member (1 point is assigned for each type of relationship). The SNI-2 score reflects the total number of people whom the respondent has contact with at least bi-weekly, and is obtained by summing up the number of people across the 12 domains.

Measures and Covariates.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS (Randolph, Tierney, Mohr, & Chase, 1998) was used to assess overall cognitive function (Total Index). *Processing speed* and *executive function* was assessed with the Trail Making Test: Time to complete Part A (TMT:A (Reitan, 1978)), and Time to complete Part B minus time to complete Part A (TMT:B-A), respectively. *Memory* was assessed with the Free and Cued Selective Reminding Test: Total Free Recall (FCSRT (Buschke, 1973)), a reliable predictor of dementia (Grober, Lipton, Hall, & Crystal, 2000; Grober, Sanders, Hall, & Lipton, 2010). Finally, a global health status score (range 0 to 10) was obtained from dichotomous ratings (presence or absence) of physician diagnosed diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, chronic obstructive pulmonary disease, and angina or myocardial infarction (Verghese, Holtzer, Lipton, & Wang, 2009).

MRI Data Acquisition.

MRI scanning was performed using a Philips 3T Achieva Quasar TX multinuclear MRI/MRS (Magnetic Resonance Spectroscopy) system equipped with a Dual Quasar High Performance Gradient System, 32-channel broadband digital RF system, Quadrature T/R Head Coil, RapidView reconstructor, Intera Achieva ScanTools Pro R2.5 Package, NetForum and ExamCards, and SENSE parallel imaging capability. Standard three-dimensional T1-weighted images were acquired using axial 3D-MP-RAGE (magnetic prepared rapid acquisition gradient echo) parameters over a 240 mm field of view (FOV) and 1.0 mm isotropic resolution, TE = 4.6 ms, TR = 9.9 ms, α = 8o, with SENSE factor 2.5. A neuroradiologist reviewed each MRI to verify that there were no clinically significant findings for any of the participants.

MRI Pre-Processing.

T1-weighted images were first manually re-oriented to the anterior commissure – posterior commissure line, and then pre-processed in using SPM8 (Wellcome Department of Cognitive Neurology) that was implemented with MATLAB R2016b (Mathworks, Natick, MA). Each structural MRI image was analyzed using Voxel-Based Morphometry (VBM) and segmented into Gray Matter (GM), White Matter (WM), and Cerebrospinal Fluid (CSF), using the unified segmentation procedure, Diffeomorphic Anatomical Registration Through Exponentiated Line Algebra (DARTEL; (Ashburner, 2007; Ashburner & Friston, 2005)). DARTEL ensures proper inter-subject alignment by modeling the shape of the brain using three parameters for each voxel. DARTEL simultaneously aligns gray matter and white matter to produce a study-specific and increasingly crisp template to which the data are iteratively aligned. For each participant, DARTEL produces a GM map, a WM map and a CSF map in the same space as the original T1-weighted image, where each voxel is assigned

a probability. These probability maps were first manually examined to ensure proper segmentation, and then spatially normalized (Friston et al., 1995) into Montreal Neurologic Institute (MNI) space. Finally, these probability maps were spatially smoothed with an isotropic Gaussian kernel, full-width-at half-maximum = 8 mm. Only GM probability maps were used in the upcoming multivariate analyses.

Group-Level Covariance Analyses.

Multivariate analyses were performed to identify gray matter covariance patterns or networks associated with SNI-1 (total number of high-contact social roles) and SNI-2 (total number of network members), in two separate statistical models. Both models were adjusted by age, sex, education, total intracranial volume, and global health status (see Table 1). Multivariate analyses were implemented using the principal components analysis (PCA) suite, http://www.nitrc.org/projects/gcva_pca (Habeck, Rakitin, et al., 2005; Habeck & Stern, 2007; Moeller & Strother, 1991). Gray matter probability maps were first masked with a gray matter mask supplied by SPM to only include voxels with > 20% probability of being gray matter. A principal components analysis (PCA) was then performed after participant means were subtracted from each voxel, in order to generate a set of principal components and their associated participant-specific (or pattern) expression scores. Participant-specific expression scores reflect the degree to which a participant displays a particular component or pattern. The gray matter volume covariance patterns associated with the social network index were then computed by regressing the participant-specific factor scores from the best linear combination of principal components (PCs) – selected using the Akaike information criteria (Burnham & Anderson, 2002) – against SNI-1 or SNI-2. The stability of the voxels in each GM volume covariance pattern associated with a social network index were then tested using 1,000 bootstrap resamples (Efron & Tibshirani, 1994). Voxels with bootstrap samples of $[Z] > +1.96$ or < -1.96, $p < .05$ (.025 in each tail) were considered significant. These group-level covariance analyses allowed us to identify key nodes in the gray matter volume covariance networks (Habeck, Krakauer, et al., 2005; Habeck & Stern, 2007; Steffener, Brickman, Habeck, Salthouse, & Stern, 2013) associated with SNI-1 and SNI-2.

Note that covariance patterns obtained from any multivariate analysis assigns positive and negative weightings (or loadings) to each voxel (or variable) included in the analysis (Habeck et al., 2008), and that both positively and negatively weighted regions contribute to the derived covariance patterns (Habeck et al., 2008; Spetsieris & Eidelberg, 2011; Steffener et al., 2013). Within the context of the current study, keep in mind that positively-weighted regions show relatively *more volume* with increasing scores on a social network index (total number of high-contact social roles or total number of network members), while negatively-weighted regions show relatively *less volume* with increasing scores on a social network index.

Results

The mean age of participants was 75.20 years (± 5.60). On average they had 15.66 years (± 3.56) of education, and 53% of participants were female. The mean total index score on

the RBANS was 93.19 (± 13.20), indicative of average global cognition. The mean global health status score was 1.24 (±0.99), indicative of good health. On average, participants reported 5.26 (± 1.44) total number of high-contact social roles in their social network (SNI-1), and a total of 22.98 (± 21.79) individuals in their entire social network (SNI-2). There was no difference in SNI-1 and SNI-2 score as a function of gender: on average males reported 5.28 (± .26) total number of high-contact social roles and 22.13 (± .3.56) individuals in their entire social network, while females reported 5.26 (±.18) total number of high-contact social roles and 23.72 (±3.15) in their entire social network, $t(84) = .04$; $p = .96$ and $t(84) = .33$, $p = .73$, respectively.

Multivariate covariance-based analyses revealed a gray matter covariance network associated with both SNI-1 and SNI-2. These gray matter covariance networks were composed of both shared and distinct brain regions (see Figure 1a, Figure 1b and Table 2). We also found that greater expression of these gray matter covariance patterns linked to SNI-1 and SNI-2 were associated with better memory, as assessed with Total Free Recall on the FCSRT. We describe these results in more detail below.

Gray matter covariance network associated with total number of high-contact social roles (SNI-1).

The gray matter volume covariance pattern associated with SNI-1 scores was constructed from two principal components, and accounted for 17% of the variance in gray matter volume ($R^2 = .17$). Positively weighted regions included superior, middle and inferior frontal (medial, lateral, and orbitofrontal) regions, inferior and middle temporal regions (including parahippocampal, hippocampal, entorhinal and amygdala) as well as precuneus, precentral (primary motor), insular, cingulate (anterior, posterior and mid-cingulate) thalamic, pallidum, brain stem (pons and ventral tegmental area) and cerebellar (VIII and IX) regions. Negatively weighted regions included superior and inferior occipital, superior and inferior temporal, middle and inferior frontal (particularly lateral inferior and orbitofrontal), as well as postcentral (primary somatosensory) and cerebellar (particularly Crus I and VIIb) regions. We also found that greater expression of this gray matter covariance pattern linked to SNI-1 was associated with better memory as assessed with Total Free Recall scores on the FCSRT, Pearson's $r = .28$, $p = .01$, but not with processing speed (Trails A; Pearson's $r = .19$, $p = .09$) or executive functions (Trails B-A, Pearson's $r = .16$ $p = .16$).

Gray matter covariance network associated with total number of network members (SNI-2).

The gray matter volume covariance pattern associated with SNI-2 scores was constructed from two principal components, and had an R^2 of .29 (i.e. accounted for 29 % of the variance in gray matter volume) Positively weighted regions included superior, middle and inferior frontal cortex (medial, lateral, and orbitofrontal), inferior temporal, and medial temporal (parahippocampal and hippocampal) regions, as well as precuneus, precentral, insular, cingulate (anterior and middle), thalamic, brain stem (ventral tegmental area) and cerebellar (VIII & IX) regions. Negatively weighted regions included supplementary motor, primary motor (precentral gyrus) and primary somatosensory (postcentral gyrus) regions, superior occipital, superior middle and inferior frontal gyrus (particularly medial and orbitofrontal), as well as inferior temporal, precuneus, and cerebellar (Crus II) regions. We

also found that greater expression of this gray matter covariance pattern linked to SNI-2 was associated with better memory, Pearson's $r = .28$, $p = .01$, but not with processing speed (Pearson's $r = .17$, $p = .12$) or executive functions (Pearson's $r = .14$, $p = .22$)

Discussion

The current study is the first to examine gray matter volume covariance patterns associated with social networks in a reasonably sized sample of older adults without dementia. We identified gray matter volume covariance patterns associated with total number of high-contact social roles and total number of network members that were composed of both shared and distinct regions (see Figure 1a and 1b). We also found that greater expression of these gray matter covariance patterns linked to total number of high-contact social roles and total number of network members were associated with better memory, but not with processing speed or executive function. We discuss the implications of these results in more detail next.

A distributed pattern of gray matter volume is associated with total number of high-contact social roles.

The gray matter volume of a widely distributed pattern of brain regions was associated with total number of high-contact social roles in the current study of older adults without dementia. Key nodes in this pattern were medial, lateral, and orbital prefrontal cortex, medial temporal (hippocampal, parahippocampal, entorhinal and amygdala), precuneus, insular cingulate (anterior, middle and posterior), and brain stem (pons and ventral tegmental area) regions (see Figure 1a and Table 2). Medial, lateral and orbital prefrontal, entorhinal, and amygdala regions were previously linked to social networks and social support in predominately young and middle-aged adults (Kevin C. Bickart, Mark C. Hollenbeck, Lisa Feldman Barrett, & Bradford C. Dickerson, 2012; Bickart et al., 2011; Lewis et al., 2011; Powell et al., 2012; Von Der Heide et al., 2014). Hippocampal and entorhinal regions are particularly affected in early Alzheimer's disease (Thompson et al., 2003), while prefrontal cortex and insular regions are particularly affected in normal aging (Kalpouzos et al., 2009; Raz et al., 1997). Key functions associated with precuneus are visuospatial imagery, memory, and self-related mental representations (Cavanna & Trimble, 2006). The cingulate cortex plays an important role in a number of cognitive and emotional processes, including executive function, memory, and negative affect (Botvinick, Cohen, & Carter, 2004; Bush, Luu, & Posner, 2000; Shackman et al., 2011; Spaniol et al., 2009; Wagner, Shannon, Kahn, & Buckner, 2005). Finally, key functions associated with the insula are drives and emotions; yet recent studies suggest that insular regions are also important for maintaining executive function and attentional processes (Menon & Uddin, 2010), as well memory awareness in normal aging and AD (Cosentino et al., 2015). Taken together, these results suggest that the structural brain substrates associated with total number of high-contact social roles in older adults without dementia are composed of regions that undergo both age-related and AD-related changes, have been linked to social networks and social support in young and middle-aged adults, and are linked to a number of cognitive and emotional processes – including memory processes. Note also that many of these regions – including amygdala, hippocampal, orbitofrontal, medial prefrontal, and anterior cingulate regions - are part of the

mesocorticolimbic dopamine system that originates in the ventral tegmental area, which was also a part of the network associated with total number of high-contact social roles (see Table 2). The mesocorticolimbic dopamine system is critical for reward-related learning and memory, and is also impaired in AD (Arias-Carrión, Stamelou, Murillo-Rodríguez, Menéndez-González, & Pöppel, 2010; Burns, Galvin, Roe, Morris, & McKeel, 2005; Gibb, Mountjoy, Mann, & Lees, 1989; Nobili et al., 2017).

A more restricted pattern of gray matter volume is associated with the total number of network members.

The gray matter volume of a similar, yet more restricted, pattern of brain regions was associated with total number of network members than total number of high-contact social roles in the current study of older adults without dementia. Shared nodes included medial, lateral and orbital prefrontal cortex, hippocampal, precuneus, insular and cingulate regions (see Figure 1b and Table 2). Unlike the total number of high-contact social roles, however, the total number of network members was not associated with gray matter volume in amygdala and entorhinal cortex regions. This finding tells us that the total number of high-contact social roles are more strongly associated with gray matter volume than the total number of network members. Nevertheless, total number of network members, like total number of high-contact social roles, were associated with gray matter volume in regions that undergo both age-related, AD-related changes to the structure of the brain, and have been previously linked to memory, social networks, and social support. (Kevin C. Bickart et al., 2012; Bickart et al., 2011; Burgess, Maguire, & O'Keefe, 2002; Kalpouzos et al., 2009; Lewis et al., 2011; Powell et al., 2012; Raz et al., 1997; Thompson et al., 2003; Von Der Heide et al., 2014).

Gray matter networks associated with the total number of high-contact social roles and the total number of network members are correlated with memory performance, but not with processing speed and executive function.

Greater expression of the gray matter covariance patterns associated with total number of high-contact social roles and total number of network members were associated with better memory performance in this study of older adults without dementia. This finding is consistent with that key nodes in these gray matter networks – particularly hippocampal regions, but also precuneus and anterior cingulate cortex – play important roles in memory (Burgess et al., 2002; Cavanna & Trimble, 2006; Spaniol et al., 2009). The expression of the gray matter covariance networks associated with the total number of high-contact social roles and the total number of network members, however, were not associated with a measure of processing speed (Trails A) and a measure of executive function (Trails B-A) in this sample of older adults without dementia. These findings are inconsistent with that key nodes in these gray matter networks, particularly medial, lateral and orbital prefrontal regions, have been linked to both executive functions and processing speed in general and performance on the trail making test in particular (Alvarez & Emory, 2006; Bowie & Harvey, 2006; Demakis, 2004; Eckert, Keren, Roberts, Calhoun, & Harris, 2010; Elderkin-Thompson, Ballmaier, Hellemann, Pham, & Kumar, 2008; Koechlin, Ody, & Kouneiher, 2003; Lee, Habeck, Razlighi, Salthouse, & Stern, 2016; Miller & Cohen, 2001). Future investigations are needed to determine the reliability and the generalizability of these

correlations, and lack thereof - in different older adult populations, using the same, different, and potentially more challenging tests of processing speed, memory, and executive functions. Future investigations are also needed to determine if and how increasing the total number of high-contact social roles and/or total number of network members will be helpful for improving memory in normal and pathological aging.

Strengths, Limitations and Recommendations for Future Research.

There are important strengths, weaknesses, and implications of the current study findings. Identifying gray matter covariance networks associated with high-contact social roles and total number of network members in a physically-healthy and cognitively-normal sample of community-dwelling older adults with an appropriately adjusted, yet sensitive, multivariate analytic approach are the key strengths of the current study. This approach allowed us to identify gray matter covariance networks associated with both total number of high-contact social roles and total number of network members in older adults, which were composed of regions a) particularly affected in healthy aging and AD, b) previously linked to social networks and social support in young and middle-aged adults, and c) previously linked to a number of cognitive and emotional processes – including memory. This approach also allowed us to examine the relative distribution of the gray matter covariance patterns associated with total number of high-contact social roles and the gray matter covariance pattern associated with total number of network members. A more distributed pattern of gray matter volume was associated with total number of high-contact social roles than total number of network members, which tells us that high-contact social roles is more strongly associated with brain structure than total number of network members. Finally, this approach allowed us to examine the relationship between the expression of the gray matter covariance patterns associated with total number of high-contact social roles and total number of network members and different cognitive functions. The gray matter networks associated with total number of high-contact social roles and total number of network members in the current study of older adults were linked to a measure of memory, but not processing speed and executive functions.

Several limitations of the current study findings should also be considered. First, the results of the current study findings from older adults without dementia may not be generalizable to older adults with AD and related dementias. Thus, future studies of larger and more cognitively diverse populations of older adults are needed to determine the generalizability and/or define the boundaries of the current study findings. Second, the social network index employed in the current study did not consider if older adults had positive or negative relationships with the people in their social network. Although older adults are generally more satisfied with their social relationships than younger adults (Luong, Charles, & Fingerman, 2011), a recent study suggest that while positive social support from children is associated with a reduced risk of dementia, negative social support from children and other immediate family members is associated with an increased risk for the dementia (Khondoker, Rafnsson, Morris, Orrell, & Steptoe, 2017). Thus, additional studies are needed to explore potential similarities and differences between the brain substrates associated with positive and negative social relationships and social support in healthy aging and AD. Third, in the absence of longitudinal neuroimaging data the directionality of the relationship

between gray matter volume, total number of high-contact social roles, and total number of network members remain unclear. It is also unclear what changes these brain substrates and social network indices undergo during healthy aging and AD, and how they may influence cognitive decline. Longitudinal studies that simultaneously examines trajectories of structural brain changes, cognitive function, total number of high-contact social roles, and total number of network members are needed to clarify these relationships.

Conclusions

This study suggest that total number of high-contact social roles and total number of network members in older adults are associated with gray matter networks, which include brain regions that are affected by both healthy and AD-related aging. This study also suggests that greater expression of these networks are associated with memory performance. Finally, this study suggests that the total number of high-contact social roles is more strongly associated with brain structure than the total number of network members.

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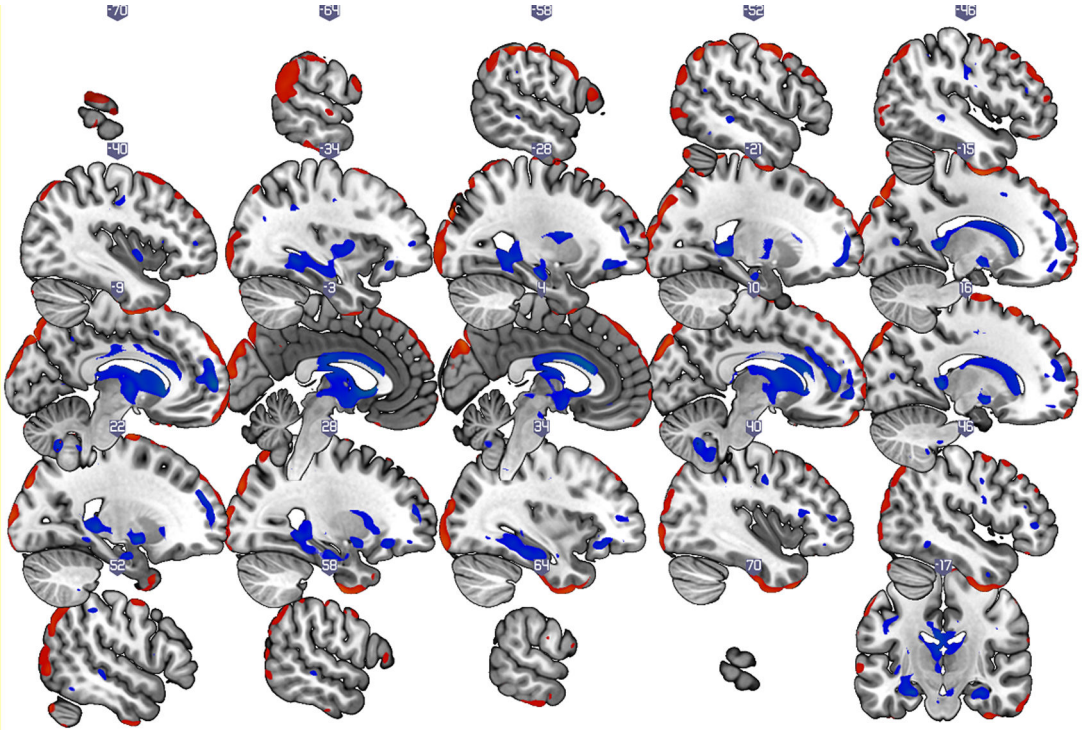

Figure 1a:

Gray matter covariance patterns associated with the SNI-1 score (total number of high-contact roles of a respondent) in older adults without dementia. Shown are thresholded Z-loadings at |Z|>1.96 $p < .05$ (.025 in each tail). Positively weighted regions are displayed in blue, implying relatively *larger* volumes with SNI1-score. Negatively weighted regions are displayed in red, implying relatively *smaller* volumes with SNI1–1 score. All results are adjusted for age, sex, education, total intracranial volume, and global health status.

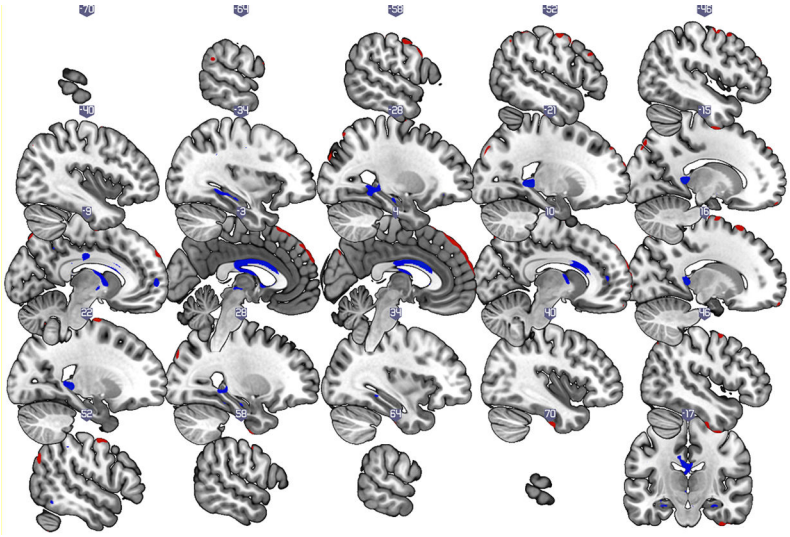

Figure 1b:

Gray matter covariance patterns associated with the SNI-2 score (total number of individuals in a respondent's social network) in older adults without dementia. Shown are thresholded Z-loadings at |Z|>1.96 $p < .05$ (.025 in each tail). Positively weighted regions are displayed in blue, implying relatively *larger* volumes with SNI2-score. Negatively weighted regions are displayed in red, implying relatively *smaller* volumes with SNI-2 score. All results are adjusted for age, sex, education, total intracranial volume, and global health status.

Table 1.

Demographic, social and cognitive characteristics of 86 older adults without dementia.

	M (SD)	Range
Age (years)	75.20 (5.60)	65–91
Gender (% female)	53% (N/A)	N/A
Education (years)	15.66 (3.56)	7–28
Global Health Status Score *	1.24 (.99)	0–4
SNI-1 Score **	5.26 (1.44)	1–9
SNI-2 Score ***	22.98 (21.79)	2–143
Trails A	44.35(16.77)	23.72–108.5
Trails B minus A	77.05(55.59)	16.13–261.9
Total Free Recall	30.88 (7.13)	7–46

* Global health status score (range 0–10) obtained from dichotomous rating (presence or absence) of diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, chronic obstructive pulmonary disease, angina, and myocardial infarction.

** SNI-1 score: total number of high-contact roles of a respondent (Cohen et al., 1997)

*** SNI-2 score: total number of individuals in a respondent's social network (Cohen et al., 1997)

Table 2.

Peak voxels and Corresponding Brain Regions of Clusters with Positive and Negative Pattern Weights. Positively-weighted regions show relatively *more volume* with increasing scores on a social network index (high-contact social relationships or overall social network size), while negatively-weighted regions show relatively *less volume* with increasing scores on a social network index. For large clusters (>5,000 voxels), the peak of each cluster is listed first, and then other regions within the cluster are named in parentheses. $$PARABREAKHERE$$ Threshold z = ± 1.96, p <.05, k >10 voxels.

High-Contact Social Relationships (SNI-I)

Brain Region(s)	X	Y	Z	z-value	k (cluster size)
Positive					
Superior Frontal Gyrus (medial; large cluster extending into cingulate cortex, caudate, putamen, globus pallidus, thalamus, hippocampal, entorhinal cortex and amygdala regions)	−8	59	6	2.7900	73954
Parahippocampal gyrus (large cluster extending into hippocampus, entorhinal cortex, and amygdala)	15	−36	4	2.5933	9368
Cerebellum (VIII)	9	−61	−41	2.4623	1947
Precentral Gyrus	−45	−18	28	2.2012	1022
Middle Temporal Gyrus	−48	−38	−8	2.3611	670
Cerebellum (VIII)	−9	−64	−43	2.4306	499
Supramarginal Gyrus	54	−36	46	2.3558	479
Precentral Gyrus	41	−6	38	2.3945	456
Inferior Frontal Gyrus	43	28	13	2.2894	445
Brain Stem (Ventral Tegmental Area)	6	−18	−19	2.1764	412
Middle Temporal Gyrus	55	−30	−4	2.3831	381
Medial Frontal Gyrus (orbital)	1	35	−12	2.3583	336
Inferior Temporal Gyrus	47	−48	−13	2.1871	333
Middle Cingulate Gyrus	12	0	46	2.1936	289
Calcarine Sulcus	−14	−74	10	2.2368	270
Precuneus	−33	−45	33	2.2335	263
Inferior Frontal Gyrus (lateral)	−44	33	20	2.2685	240
Supplementary Motor Area	−13	14	47	2.3237	209
Middle Frontal Gyrus	48	−1	21	2.3186	208
Inferior Frontal Gyrus (lateral)	46	38	3	2.2620	161
Middle Frontal Gyrus (orbital)	29	48	−10	2.1721	140

Superior Frontal Gyrus	16	53	−13	2.1423	128
Cerbellum (IX)	−9	−48	−47	2.1600	111
Precentral Gyrus	−13	−24	54	2.2378	109
Calcarine Sulcus	15	−76	12	2.2075	94
Inferior Frontal Gyrus	45	1	−37	2.2726	76
Middle Temporal Gyrus	−50	−55	19	2.1592	74
Precentral Gyrus	20	−33	52	2.2133	64
Inferior Temporal Gyrus	−53	−53	−17	2.0404	64
Inferior Parietal lobule	−48	−47	47	2.0931	63
Precuneus	−10	−53	41	2.1673	53
Middle Occipital Gyrus	−32	−68	27	2.1778	51
Insula	−37	20	8	2.1219	45
Precentral Gyrus	43	−17	31	2.0984	44
Superior Frontal Gyrus	17	34	48	2.0631	44
Brain Stem (pons)	8	−19	−32	2.0244	43
Posterior Cingulate Gyrus	12	−17	37	2.0524	35
Superior Temporal Gyrus	−44	−20	−1	2.1107	34
Inferior Frontal Gyrus (lateral)	−48	34	6	2.1159	27
Calcarine Sulcus	−8	−60	5	2.0647	26
Calcarine Sulcus	18	−89	5	2.0209	26
Pallidum	18	7	1	1.9957	26
Insula	36	−14	−3	2.0065	22
Precentral Gyrus	−18	−33	53	2.1050	19
Superior Parietal Gyrus	34	−45	60	2.1036	19
Superior Frontal Gyrus (oribital)	−19	19	−12	2.0547	14
Superior Occiptal	−17	−90	4	2.0197	14
Putamen	−26	17	−5	2.0054	13
Supramarginal Gyrus	−58	−37	33	2.0670	11
Inferior Frontal Gyrus (lateral)	52	13	11	2.0409	10
Middle Cingulate Gyrus	−14	−8	52	2.0217	10
Negative					
Superior Occipital Gyrus (large cluster extending into cuneus and precuneus regions)	−24	−90	32	−2.7946	92005

Inferior Temporal Gyrus	−26	−9	−51	−2.6839	4395
Inferior Temporal Gyrus	26	−6	−49	−2.6520	7715
Cerebellum (Crus I)	51	−74	−31	−2.4052	1029
Cerebellum (Crus I)	−54	−67	−34	−2.3282	1007
Inferior Parietal Lobule	−67	−34	−24	−2.3267	1222
Inferior Frontal Gyrus (lateral)	−56	23	17	−2.3187	372
Inferior Frontal Gyrus (lateral)	−47	47	10	−2.3185	243
Postcentral Gyrus	67	−13	24	−2.3071	290
Inferior frontal Gyrus (orbital, medial)	−6	22	−29	−2.2751	567
Middle Frontal Gyrus	44	2	59	−2.2714	1650
Inferior Temporal Gyrus	68	−27	−26	−2.2274	1703
Postcentral Gyrus	58	−19	52	−2.1976	177
Inferior Occipital Gyrus	−52	−71	−2	−2.1876	1177
Superior Temporal Pole	−28	25	−26	−2.1767	75
Inferior Frontal Gyrus (orbital)	44	32	−21	−2.1621	131
Middle Frontal Gyrus	46	26	43	−2.1362	729
Inferior Frontal Gyrus (orbital)	15	41	−30	−2.1339	78
Inferior Frontal Gyrus (lateral)	−55	37	5	−2.1308	156
Inferior Frontal Gyrus (lateral)	58	28	6	−2.1274	128
Inferior Parietal Lobule	56	−41	56	−2.1171	237
Inferior Frontal Gyrus (orbital)	−12	45	−31	−2.1047	38
Inferior Frontal Gyrus (orbital)	26	22	−25	−2.0948	25
Postcentral Gyrus	−46	−21	66	−2.0938	22
Precuneus	−2	−56	35	−2.0634	16
Inferior Frontal Gyrus (orbital, medial)	8	16	−27	−2.0578	50
Supramarginal Gyrus	66	−26	39	−2.0526	49
Precentral Gyrus	65	8	17	−2.0458	75
Precentral Gyrus	−68	−17	29	−2.0438	35
Precentral Gyrus	−1	−25	80	−2.0433	41
Inferior Temporal Gyrus	66	−47	−13	−2.0361	108
Postcentral Gyrus	−49	−22	64	−2.0304	27
Inferior Frontal Gyrus (orbital)	31	66	−14	−2.0171	36

Middle Temporal Gyrus	−61	−65	2	−2.0068	40
Superior Temporal Gyrus	71	−18	5	−1.9868	12
Middle Frontal Gyrus (orbital)	−29	61	−15	−1.9820	20
Inferior Temporal Gyrus	−67	−48	−12	−1.9788	12

Overall Social Network Size (SNI-II)

Brain Region(s)	**X**	**Y**	**Z**	**z-value**	**k**
Positive					
Parahippocampal gyrus (large cluster extending into hippocampal regions)	−19	−42	2	2.2970	19825
Hippocampus	20	−35	1	2.2889	2336
Superior Frontal Gyrus (medial)	−10	60	2	2.1813	336
Medial Frontal Gyrus (orbital)	8	59	−3	2.0941	62
Hippocampus	28	−17	−19	2.0911	177
Inferior Frontal Gyrus (orbital)	−29	35	−11	2.0810	143
Anterior Cingulate Gyrus	−7	32	23	2.0732	66
Inferior Temporal Gyrus	51	−55	−15	2.0703	139
Precuneus	−9	−53	42	2.0649	30
Anterior Cingulate Gyrus	10	47	10	2.0624	154
Inferior Frontal Gyrus (lateral)	48	0	22	2.0605	31
Medial Frontal Gyrus (orbital)	1	33	−12	2.0547	61
Supramarginal Gyrus	52	−38	46	2.0515	46
Insula	−38	−1	−3	2.0510	65
Precentral Gyrus	−36	−10	38	2.0390	163
Superior Frontal Gyrus	20	53	24	2.0342	62
Brain Stem (Ventral Tegmental Area)	5	−18	−18	2.0279	34
Cerebellum (VIII)	−7	−65	−43	2.0219	41
Lingual Gyrus	21	−42	−9	2.0102	16
Middle Temporal Gyrus	54	−29	−4	1.9987	10
Superior Frontal Gyrus (orbital)	−16	52	−12	1.9960	19
Thalamus	19	−3	−9	1.9921	27
Superior Frontal Gyrus (orbital)	−19	58	−2	1.9879	13
Cerebellum (IX)	8	−61	−45	1.9705	10
Negative					

Superior Frontal Gyrus (supplementary motor area)	22	−6	76	−2.2634	5200
Precentral Gyrus	−48	−4	57	−2.2460	1456
Superior Occipital Gyrus	−25	−89	33	−2.2375	662
Inferior Temporal Gyrus	−44	−5	−49	−2.1814	364
Inferior Temporal Gyrus	26	−7	−50	−2.1635	440
Middle Frontal Gyrus	52	−2	54	−2.1611	728
Angular Gyrus	54	−68	30	−2.1595	275
Superior Frontal Gyrus	17	20	65	−2.1374	378
Inferior Temporal Gyrus	43	−13	−41	−2.1351	1138
Superior Parietal Gyrus	−29	−73	56	−2.1341	151
Inferior Frontal Gyrus (lateral)	−48	47	10	−2.1108	104
Precuneus	−12	−59	74	−2.1048	492
Superior Frontal Gyrus	19	59	37	−2.0949	131
Superior Parietal Gyrus	14	−76	57	−2.0945	470
Paracentral Lobule	−19	−22	79	−2.0835	528
Inferior Frontal Gyrus (orbital,medial)	−14	62	−21	−2.0816	51
Supplementary Motor Area	−5	7	71	−2.0812	54
Cerebellum (Crus II)	53	−60	−47	−2.0733	44
Superior Frontal Gyrus	−15	7	72	−2.0718	92
Inferior Frontal Gyrus (orbital, medial)	14	65	−20	−2.0689	91
Superior Frontal Gyrus	−21	66	24	−2.0640	86
Superior Occipital Gyrus	28	−87	35	−2.0554	113
Angular Gyrus	50	−60	51	−2.0530	185
Middle Frontal Gyrus	−30	11	66	−2.0459	111
Superior Frontal Gyrus	−17	40	56	−2.0407	17
Middle Frontal Gyrus	−43	46	28	−2.0407	107
Middle Frontal Gyrus (lateral)	−51	27	33	−2.0343	62
Angular Gyrus	−51	−61	48	−2.0330	26
Middle Frontal Gyrus	−45	10	55	−2.0281	165
Middle Frontal Gyrus (lateral)	30	28	57	−2.0242	37
Superior Parietal Gyrus	10	−59	73	−2.0202	175
Cuneus	2	−78	36	−2.0164	79

Supramarginal Gyrus	−64	−47	27	−2.0141	73
Postcentral Gyrus	−54	−45	56	−2.0122	59
Superior Parietal Gyrus	−41	−67	55	−2.0110	19
Superior Parietal Gyrus	−27	−43	75	−2.0083	22
Inferior Parietal Gyrus	−57	−29	53	−2.0076	26
Inferior Parietal Gyrus	−39	−76	44	−2.0015	12
Superior Parietal Gyrus	−24	−63	66	−1.9998	15
Inferior Temporal Gyrus	33	4	−52	−1.9956	12
Inferior Frontal Gyrus (orbital)	−23	69	−8	−1.9897	12
Orbitofrontal Gyrus (medial)	6	72	−2	−1.9853	63
Middle Frontal Gyrus	27	63	28	−1.9848	15