Older adults with smaller and less complex social networks show deficits in medial temporal cerebrovascular reactivity

Evelyn Chang, MA[1], Arunima Kapoor, MSc[1], Trevor Lohman, PhD[2], Shubir Dutt, PhD[3], John Paul M. Alitin, BA[2], Isabel J. Sible, MA[4], Jean K. Ho, PhD,[4] Aimée Gaubert, BA[2], Anna E. Blanken, PhD[5,6], Mara Mather, PhD[2,4,8], Xingfeng Shao, PhD[9], Danny J.J. Wang, PhD[9], Daniel A. Nation, PhD[2,10]

[1]Department of Psychological Science, University of California, Irvine, Irvine, CA, USA; [2]Leonard Davis School of Gerontology, University of Southern California, Los Angeles, CA, USA; [3]Memory and Aging Center, Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA; [4]Department of Psychology, University of Southern California, Los Angeles, CA, USA; [5]San Francisco Veterans Affairs Healthcare Center, San Francisco, CA; [6]Department of Psychological and Behavior Sciences, University of California, San Francisco, San Francisco, CA; [7]Leonard Davis School of Gerontology, University of Southern California, Los Angeles, CA, USA; [8]Department of Biomedical Engineering, University of Southern California, Los Angeles, CA, USA; [9]Stevens Neuroimaging and Informatics Institute, University of Southern California, Los Angeles, CA, USA; [10]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

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Correspondence: Daniel A. Nation, Ph.D.
Leonard Davis School of Gerontology, University of Southern California
3715 McClintock Ave., Los Angeles, CA 90089
(213)740-5156
danation@usc.edu

Social isolation is associated with increased risk for stroke and cognitive decline.[1] Although existing research has proposed neuroimmune system dysregulation as a possible underlying mechanism,[1] few studies have investigated cerebrovascular mechanisms in connection to social isolation. Cerebrovascular reactivity (CVR) denotes the ability of cerebral blood vessels to regulate cerebral blood flow (CBF) through dilation or constriction in response to stimuli.[2] The present study examined CVR in response to hypercapnia in select brain regions implicated in social cognition, specifically the hippocampus, parahippocampal gyrus, amygdala, entorhinal cortex, superior frontal gyrus, medial orbitofrontal cortex, anterior cingulate cortex, inferior parietal cortex and precuneus. We hypothesized that lower social network size and complexity would be associated with reduced CVR in these regions.

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Independently living older adults were recruited from the community. Exclusion criteria included history of stroke, dementia, major depression, and other illnesses or medications affecting the central nervous system. Study protocol was approved by the USC and UCI Institutional Review Board. All participants gave informed consent and were financially compensated. Cohen's Social Network Index (SNI) evaluated social network size and complexity. Participants reported the total number of individuals they had high contact (≥1x per 2 weeks) with for 12 different social roles. Network size was defined by total number of individuals reported, while network complexity was defined by total number of roles with ≥1 high-contact relationship. Depression was evaluated by Geriatric Depression Scale (GDS). Number of vascular risk factors (VRFs), including hypertension, diabetes, hypercholesterolemia, coronary artery disease, smoking, atrial fibrillation and history of transient ischemic attack, were all assessed by medical history.

Hypercapnia (vasodilatory stimulus) was induced using a 15s breath-hold task while cerebral blood flow was obtained using a pseudo-continuous arterial spin labeling (pCASL)-MRI (Siemens Prisma 3T). Details on neuroimaging procedures are previously described.[2] Cerebrovascular reactivity was quantified as the percent change in CBF per unit change in $etCO_2$ and calculated using the following formula:

$$CVR\ (\%\Delta CBF / \Delta mmHg\ etCO_2) =$$

$$[100 * (CBF_{maximum} - CBF_{minimum}) / CBF_{minimum}] / (etCO_{2\ maximum} - etCO_{2\ minimum})$$

Regional mean CVR values were extracted for all regions of interest (ROI).

All analyses were performed using R Version 4.2.3. Social network size and complexity (independent predictors) were related to CBF and CVR to hypercapnia using multiple linear regression for each ROI, controlling for age and sex. Sensitivity analysis further controlling for vascular risk factors, depression and education. Significance threshold was $p < 0.05$ and Benjamini-Hochberg false discovery rate (FDR) adjustment was applied at q value of .05.

Six participants were excluded from the CVR analysis for non-adherence to the breathing task. Sixty-nine older adults (mean age 69.0±7.1SD, range 60-89; 65.2% female; education 16.7±2.2SD; GDS 4.2±4.2SD; VRFs 1.4±1.0SD) were included in analyses. Neither network size nor network complexity were found to be associated with CBF in any of the brain regions.

Social network size was associated only with CVR in the hippocampus, while social network complexity was associated with CVR in the hippocampus, right amygdala, right entorhinal cortex, and right parahippocampal gyrus (Figure 1). These associations persisted after adjusting for vascular risk factors, depression and education and when robust standard error estimates were utilized. However, after FDR analysis, only network complexity remained

significant with CVR in the hippocampus (left: adjusted p=0.038; right: adjusted p=0.038) and right amygdala (adjusted p=0.038).

The current study found that older adults with smaller social network size and complexity exhibited attenuated cerebral vasodilatory response in regions previously implicated in social cognition. Importantly, all participants were free of any history of stroke, and all findings persisted after sensitivity analysis, indicating a specific relationship between CVR deficits and social network metrics. Findings could suggest that CVR deficits contribute to the increased risk of stroke in socially isolated individuals.

The present study revealed correlations between CVR and social network size and complexity in brain regions previously implicated in social cognition, but also cognitive decline.[3] Network complexity showed the strongest association with CVR in the hippocampus, a region important for processing contextual information.[3] Associations between regional CVR and social network parameters also occurred mainly in the right hemisphere, consistent with prior studies implicating the right hemisphere in social cognition.[4]

Resting CBF in these regions was not correlated with social network parameters, suggesting that the observed correlations with CVR are specific to cerebrovascular function and not merely the result of changes in neuronal metabolism. This is consistent with studies in experimental animal models and humans linking social isolation to changes in biomarkers of vascular dysfunction.[5] However, further investigation is warranted given the limited sample size. It remains unclear from this cross-sectional study whether the association is causal, whether CVR deficits in these regions contribute to social deficits that result in isolation, or whether social isolation causes deficits in CVR within these regions. Additional study limitations include the use of a self-report measure that may be subject to recall or self-reporting bias. Future studies

are warranted to gain further insight into cerebrovascular mechanisms underlying increased stroke risk in socially isolated individuals.

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Disclosures

None.

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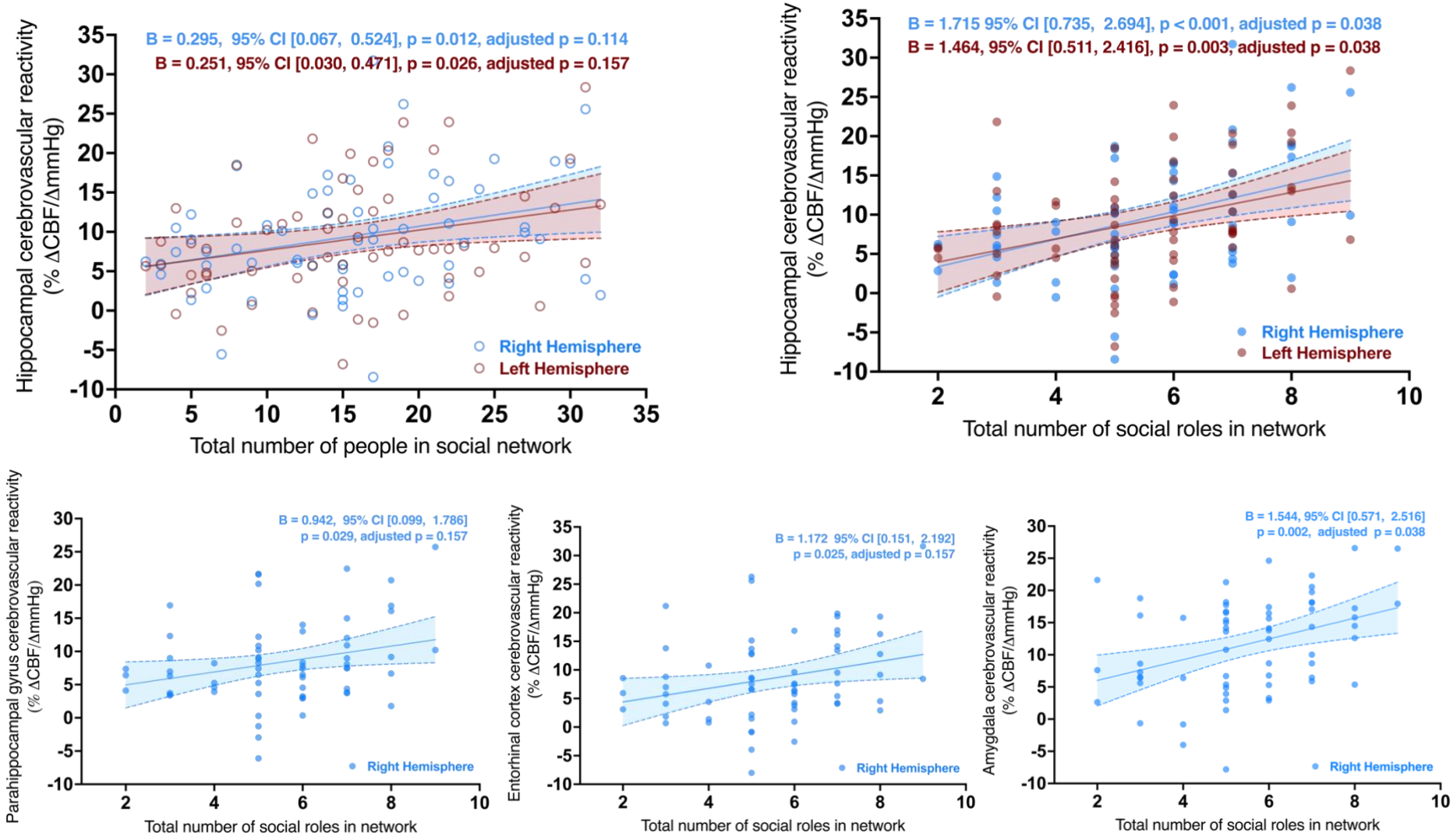
Figure 1. Regression plots show associations between CVR and social network size and complexity.



***Note*: B estimates are adjusted for age and sex.**