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Right hemisphere stroke is linked to reduced social connectedness in the UK Biobank cohort

Katherine O'Connell[1]✉, Abigail A. Marsh[2] & Anna Seydell-Greenwald[3]

Social connectedness is fundamental to health and life satisfaction. Empathic capacities that support social connections are commonly impaired following damage to the brain's right hemisphere, but how these acquired socio-emotional deficits correspond to real-world social outcomes remains unclear. Using anatomical brain imaging and behavioral data from a large sample of stroke survivors included in the UK Biobank ($n = 209$), we link damage to regions of the right hemisphere involved in emotion recognition to lower social relationship satisfaction and higher loneliness. The effect was driven by lesions to the right anterior insula and not explained by stroke extent and motor function; it was further corroborated by an exploratory analysis of social decline in a few participants for whom data were available from before and after a stroke to the right anterior insula ($n = 3$; comparison $n = 13$). These correlational findings provide new insight into the role of the right hemisphere in maintaining social connections and bear important implications for treatment and rehabilitation post-stroke.

Keywords Stroke, UK Biobank, Social connectedness, Social activity, MRI, Brain imaging, Anterior insula

Right hemisphere stroke is associated with notably poor quality of life and low functional independence, even compared to left hemisphere stroke[1–3]. Unlike people living with a left hemisphere stroke injury, right hemisphere stroke survivors typically retain normal language function and use of their dominant hand. Why, then, do right hemisphere strokes lead to comparatively poor outcomes? One explanation could be their relation to empathic and emotion perception deficits[4–11] which receive little clinical attention[11–13] and have been shown to have behavioral relevance[14]. In neurologically healthy adults, empathic processes such as detecting and responding to emotional features of speech (i.e., prosody) and facial expressions engage brain regions including right posterior superior temporal gyrus/sulcus, inferior frontal gyrus, and anterior insula[15–19]—areas that are frequently damaged by stroke[20].

Right hemisphere strokes affecting posterior superior temporal gyrus/sulcus, inferior frontal gyrus, and anterior insula are linked to lower performance in laboratory-based emotion tasks. Strokes to right posterior superior temporal gyrus/sulcus impair both emotion perception[5,21] and prosody[22]. Strokes to right anterior insula are associated with difficulty making inferences about others' emotional states[23], and surgical resection of the insula impairs emotion recognition accuracy[24], reduces self-reported empathy[24], and diminishes responsiveness to others' pain[25]. Damage to right inferior frontal gyrus is linked to impaired ability to recognize and express emotions[21,26–28]. A large study including right and left hemisphere stroke patients found that damage to right anterior insula, right inferior frontal gyrus and right posterior superior temporal gyrus/sulcus (but no left hemisphere areas) was associated with impaired facial emotion recognition[5]. Recent reports also link impaired emotion recognition accuracy to reduced social activity participation[29,30] and lower marital satisfaction[31] following stroke. Poor social connectedness can have damaging effects on stroke outcomes related to functional independence, quality of life, morbidity, and mortality[32–42]. Thus, better understanding how stroke lesion location is associated with social decline is both empirically and clinically significant.

Adding to the complexity of understanding social decline following stroke, aphasia and other impairments in language functioning after left hemisphere stroke can also lead to social isolation[43,44]. Patients with aphasia frequently report losing friendships[41,43,45,46], and damage to left inferior frontal gyrus in particular is tied to poor psychosocial quality of life[47]. In addition, stroke severity or impaired motor function may explain as much or more variation in social connectedness outcomes as hemispheric damage. Stroke severity (e.g., NIHSS score[48]) and motor deficits are both associated with a wide range of outcomes following stroke[37,49–51]. Notably, social outcomes can be severely affected even without physical disability[1,14]. This suggests that some types of stroke

[1]Interdisciplinary Program in Neuroscience, Georgetown University, Washington, DC 20057, USA. [2]Department of Psychology, Georgetown University, Washington, DC 20057, USA. [3]Center for Brain Plasticity and Recovery, Georgetown University Medical Center, Washington, DC 20057, USA. ✉email: kmo52@georgetown.edu

may specifically alter social functioning, possibly due to damage of brain areas involved in empathy and emotion perception.

This investigation therefore assessed social activity and perceived social connectedness in a large, diverse sample of adults living with stroke who were included in the UK Biobank brain imaging sample. We hypothesized that damage to the right-lateralized network that underlies processes like empathic accuracy and emotion perception—including right posterior superior temporal gyrus/sulcus, inferior frontal gyrus, and anterior insula—would be associated with worse social outcomes since prior studies link impaired emotion recognition to both reduced social activity[29,30] and lower relationship satisfaction[31]. We also examined participants with impact to contralateral left hemisphere areas, which may be associated with aphasia-related social decline. Lastly, we considered the role of additional variables, including stroke lesion extent, fluid intelligence, stroke-related motor weakness, and the number of people in participants' households. Results indicate that right, but not left hemisphere damage, particularly in the anterior insula, is specifically associated with decreased reported social connectedness.

Results

ICD-10 records of a stroke were available for 141 participants; 105 with ischemic stroke (74%), 8 with hemorrhagic stroke (6%), 4 with subarachnoid hemorrhage (3%), 1 with ischemic and hemorrhagic strokes (< 1%), 1 with hemorrhagic and subarachnoid hemorrhagic strokes (< 1%) and 22 with unspecified strokes (16%). Stroke lesion volume was highly skewed (M = 14.50 cm^3, SD = 29.81 cm^3, median = 4.54 cm^3, IQR = 11.85 cm^3, skewness = 4.4, kurtosis = 26.1) as the majority of strokes were small. Therefore, voxel-wise lesion overlap among participants was minimal (Supplementary Fig. 1). This low degree of overlap prohibited voxel-based lesion symptom mapping (VLSM[52]) because VLSM results are often considered interpretable only in voxels in which at least 10 participants exhibit damage[53,54]. By this criterion, lesion symptom mapping would have been restricted to only 339 gray matter voxels (0.25%) across right and left cortical and subcortical regions and 2,229 white matter voxels (3.56%) according to overlap with Harvard-Oxford 25% tissue probability maps. Thus, we decided to use a region-of-interest (ROI) based approach instead, focusing on three regions of interest with known links to emotion recognition and empathy: the right inferior frontal gyrus, the right anterior insula, and the right posterior superior temporal sulcus, as well as their left hemisphere counterparts (Fig. 1).

Forty-two participants had a stroke affecting right hemisphere ROIs, and 45 participants had a stroke affecting left hemisphere ROIs. The number of subjects with a stroke affecting each ROI were comparable between right and left hemisphere (right inferior frontal gyrus = 30, left inferior frontal gyrus = 26, right anterior insula = 25, left anterior insula = 25, right posterior superior temporal gyrus/sulcus = 18, left posterior superior temporal gyrus/sulcus = 15).

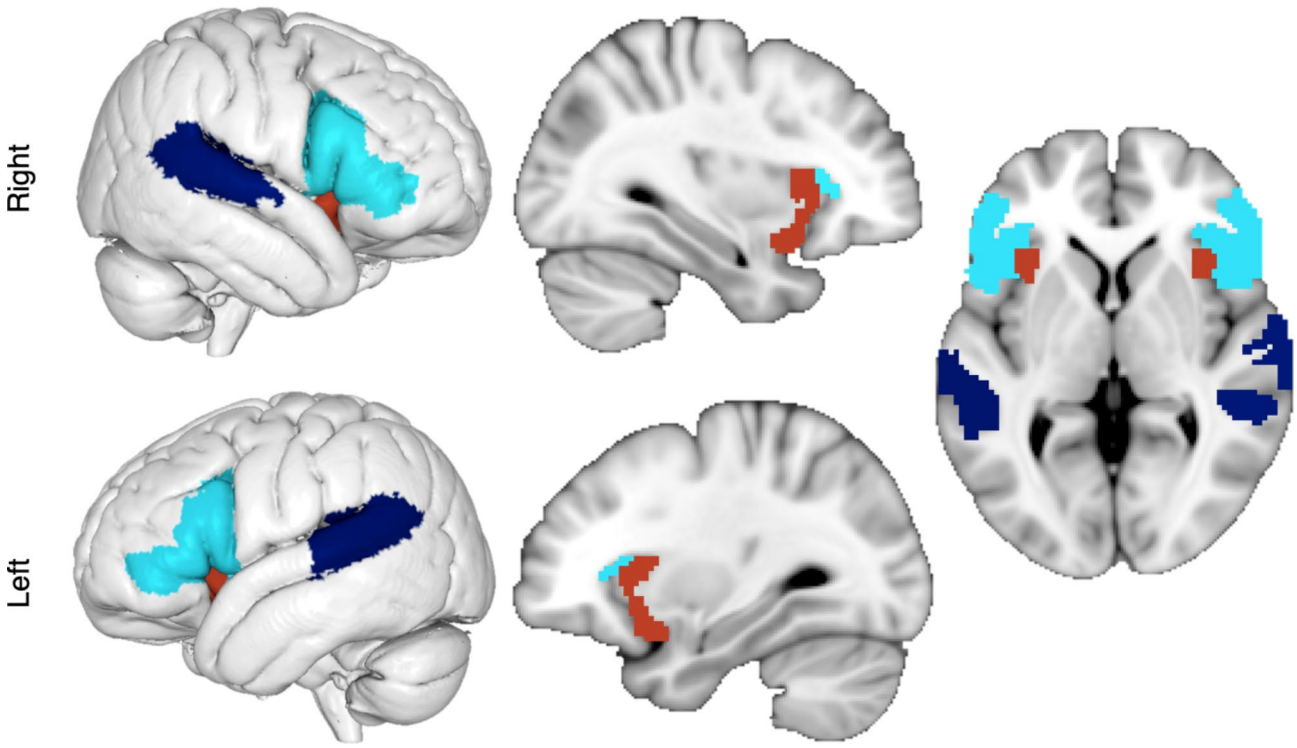

Fig. 1. Regions of interest. Posterior superior temporal gyrus/sulcus (navy blue), inferior frontal gyrus (light blue), and anterior insula (red) were separately defined in right and left hemisphere. Axial slice shows right hemisphere on the right.

Right hemisphere lesions are associated with lower perceived social connectedness

Relative to participants whose lesions spared the right hemisphere ROIs, participants who had a stroke affecting these ROIs exhibited lower perceived social connectedness (right ROI damage: M = − 0.39, SD = 0.23, $n = 42$, no right ROI damage M = 0.10, SD = 0.10, $n = 167$; t(207) = 2.05, $p = 0.041$), but no significant difference in social activity (right ROI damage: M = − 0.16, SD = 0.16, $n = 42$, no right ROI damage M = 0.04, SD = 0.09, $n = 167$; t(207) = 1.06, $p = 0.288$). Participants with strokes affecting any left hemisphere ROIs did not significantly differ from participants whose lesions spared these ROIs in terms of perceived social connectedness (left ROI damage: M = − 0.14, SD = 0.16, $n = 45$, no left ROI damage M = 0.04, SD = 0.11, $n = 164$; t(207) = 0.77, $p = 0.442$), or social activity (left ROI damage: M = 0.06, SD = 0.14, $n = 45$, no left ROI damage M = − 0.02, SD = 0.09, $n = 164$; t(207) = 0.39, $p = 0.697$).

Next, we set perceived social connectedness as the dependent variable in a multiple linear regression to examine whether age, sex, number of people in a participant's household, lesion size, stroke-related motor weakness, or fluid intelligence play a role in explaining the effect of right hemisphere damage. We first included age, sex (0 = female, 1 = male), number of individuals in the household, total lesion volume, and separately coded participants for having a stroke lesion that affected right or left ROIs (0 = no, 1 = yes). Due to skew, total lesion volume (cm^3) was log transformed. In subsequent steps, stroke-related motor weakness (estimated as the reduction in grip strength of the hand contralateral to the stroke relative to that of the ipsilateral—unaffected—hand) and fluid intelligence scores were entered, which reduced the sample size to 201 and 166, respectively, due to missing data. Age, number of individuals in the household, and fluid intelligence scores were mean centered.

Damage to right hemisphere ROIs remained significantly associated with lower perceived social connectedness after accounting for all covariates (Table 1). On average, damage to these ROIs was associated with a 0.58 standard deviation reduction in connectedness. No association was observed for damage to left hemisphere ROIs. Having fewer individuals in the household was associated with reduced connectedness, and a trending positive relationship emerged between fluid intelligence and connectedness. Repeating the regression while excluding 6 participants whose stroke had occurred within one year prior to assessment (and who might still have been adjusting to their post-stroke lives) did not meaningfully alter results. Using the same variables to predict social activity resulted in a model that was not significant and confirmed no relationship with damage to right or left ROIs (Supplementary Table S3).

We also tested these regression models using a continuous measure of lesion extent to the ROIs rather than the binary approach to damage described above. Results confirmed that the extent of damage to right hemisphere ROIs significantly predicted social connectedness (Supplementary Table S4, Supplementary Fig. S2).

In particular, lesions to the right anterior insula are associated with lower social connectedness

The regression model predicting perceived social connectedness was then repeated three times to evaluate the role of damage to each ROI separately. These analyses applied Bonferroni correction for six comparisons (three right and three left hemisphere ROIs). In the full models, results indicated that strokes affecting right anterior insula, but not left anterior insula, were associated with reduced perceived connectedness ($p_{uncorr} = 0.005$; $p_{corr} = 0.030$; Supplementary Table S5). No significant relationship was observed for left or right hemisphere damage to the other ROIs (Supplementary Tables S6 and S7).

Again, excluding participants whose stroke had occurred within one year prior to the assessment had no meaningful impact on results. In addition, using a continuous measure of anterior insula lesion extent also significantly predicted social connectedness (Supplementary Table S8 and Supplementary Fig. S3).

Lesion size and motor weakness are not correlated with perceived social connectedness

Surprisingly, total stroke lesion size exhibited no relationship with perceived social connectedness in the models. A non-parametric correlation test further confirmed that there was no relation between total lesion volume and perceived connectedness (rho = − 0.053, $p = 0.449$) or with social activity (rho = − 0.076, $p =$

	Step 1			Step 2			Step 3		
	b	95% CI	p	b	95% CI	p	b	95% CI	p
Constant	0.23	[− 0.13, 0.59]		0.23	[− 0.15, 0.60]		0.29	[− 0.10, 0.68]	
Age	0.02	[− 0.01, 0.05]	0.215	0.02	[− 0.01, 0.05]	0.245	0.02	[− 0.01, 0.05]	0.164
Sex	− 0.25	[− 0.64, 0.15]	0.224	− 0.26	[− 0.67, 0.15]	0.214	− 0.19	[− 0.62, 0.24]	0.385
N household	0.65	[0.36, 0.94]	< 0.001***	0.66	[0.36, 0.97]	< 0.001***	0.63	[0.32, 0.95]	< 0.001***
Lesion volume	0.07	[− 0.06, 0.21]	0.272	0.08	[− 0.06, 0.22]	0.241	0.03	[− 0.12, 0.18]	0.721
Left ROI damage	− 0.18	[− 0.66, 0.30]	0.453	− 0.24	[− 0.75, 0.28]	0.365	0.01	[− 0.55, 0.58]	0.960
Right ROI damage	− 0.71	[− 1.22, − 0.21]	0.005**	− 0.67	[− 1.19, − 0.14]	0.014*	− 0.81	[− 1.37, − 0.25]	0.005**
Motor weakness				− 0.08	[− 0.26, 0.09]	0.351	− 0.06	[− 0.24, 0.13]	0.538
Fluid intel.							0.09	[0.00, 0.18]	0.053
R^2			0.114***			0.116***			0.150**
ΔR^2						0.002			0.034

Table 1. Linear regression predicting perceived social connectedness. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

0.274). Additional pairwise correlations are reported in Supplementary Table S9. Of note, stroke-related motor weakness was modestly associated with reduced social activity (rho = − 0.16, p = 0.022), but not perceived connectedness (rho = 0.00, p = 0.971), suggesting that it captured variance in motor deficits relevant to social activity engagement.

Incident stroke to right anterior insula is associated with reductions in relationship satisfaction

Eighty-six participants suffered an incident stroke during the study and 11 of them had lesion damage affecting right anterior insula. Missing data in baseline (pre-stroke) assessments led us to investigate changes in individual social questionnaire items rather than composite measures of social connectedness and social activity. Change in family relationship satisfaction was more negative for participants with an incident stroke affecting right anterior insula (right anterior insula damage: Mdn = − 1, n = 3; no right anterior insula damage: Mdn = 0, n = 13; W = 33.5, p = 0.044). Similar results were observed for change in friendship satisfaction (right anterior insula damage: Mdn = − 1, n = 3; no right anterior insula damage: Mdn = 0, n = 13; W = 37.5, p = 0.009).

Changes in being able to confide in someone (right anterior insula damage: Mdn = 0, n = 11; no right anterior insula damage: Mdn = 0, n = 70; W = 403.5, p = 0.788) and loneliness (right anterior insula damage: Mdn = 0, n = 11; no right anterior insula damage: Mdn = 0, n = 74; W = 439.0, p = 0.527) were not significantly different. No differences emerged for change in weekly social activities (right anterior insula damage: Mdn = 0, n = 11; no right anterior insula damage: Mdn = 0, n = 75; W = 391.5, p = 0.770) or for frequency of friend/family visits (right anterior insula damage: Mdn = 0, n = 11; no right anterior insula damage: Mdn = 0, n = 72; W = 399.5, p = 0.967).

Discussion

In this sample of stroke survivors with diverse lesion locations and extents, we observed that damage to right hemisphere regions involved in empathy and emotion recognition (right inferior frontal gyrus, anterior insula, posterior superior temporal gyrus/sulcus) was associated with decreased perceived social connectedness. This effect was driven by lesions affecting the right anterior insula and persisted after adjusting for demographic, household, lesion extent, stroke-related motor weakness, and fluid intelligence variables. The relationship was specific to perceived social connectedness—which indexed participants' satisfaction with relationships, emotional support, and loneliness—and was not observed with reported amount of social activity. In a small, exploratory subsample of individuals who had reported social connectedness data prior to suffering a stroke that impacted right anterior insula, satisfaction with family relationships and friendships was reduced relative to individuals whose stroke did not impact right anterior insula. In combination, these observations point to a critical feature of right hemisphere stroke—its negative association with social connectedness. Gaining a better understanding of this decline is vital for future research, given the importance of staying socially connected during stroke recovery[37,41,55,56].

Despite prior evidence that left hemisphere stroke can lead to social isolation and psychosocial decline[41,43,45,47], we found no evidence that damage to left posterior superior temporal gyrus/sulcus, left inferior frontal gyrus, or left anterior insula was associated with altered social activity or connectedness. While communication is commonly difficult in patients with left hemisphere stroke, their impairments are often clearly stroke-related. It is possible that friends and family members of these individuals may even work harder to communicate and connect with them. On the contrary, empathic deficits after right hemisphere stroke are less evident in ordinary interactions and resulting poor social interactions may be misattributed to patients' lack of interest or effort, apathy, or callousness—possibly resulting in family and friends being less motivated to stay emotionally connected. Prior work consistently demonstrates more impaired empathy and emotion recognition after right relative to left hemisphere stroke[4–11], and even suggests that explicit emotion training can be helpful[57,58], but few studies investigate the real-world consequences of these impairments. The current research adds to this literature by revealing that strokes affecting right anterior insula, a primary hub for empathy and emotional awareness, are linked to social decline.

The anterior insula is highly connected to salience processing and executive control areas and is thought to support the integration of emotional experiences[59–62] including empathic experiences[25,63–65]. One consideration for our anterior insula results is this region's proximity to major white matter pathways, which, for example, connect frontal, temporal and subcortical areas. It is possible that participants exhibiting damage to right anterior insula also had white matter damage to these major tracts, and that lesions to those tracts, rather than the anterior insula itself, are responsible for the observed reductions in social connectedness. Even so, a key observation is that results were specific to right hemisphere. There was a trending relationship between damage to right inferior frontal gyrus and lower perceived social connectedness (which did not survive correction for multiple comparisons), but surprisingly no relationship with damage to right posterior superior temporal gyrus/sulcus. A recent review reported that strokes affecting right posterior superior temporal gyrus/sulcus are more often linked to emotion perception difficulties, whereas damage to right inferior frontal gyrus and anterior insula are more often associated with impaired emotional expression[21]. Therefore, one possible interpretation of the current results is that stroke survivors who are unable to appropriately respond to others using emotional cues of their own are most at risk for reduced perceived connectedness. Alternatively, because the anterior insula is also associated with the internal experience of emotion[61,62,66], its damage may moderate some stroke survivors' ability to feel emotionally responsive towards others, resulting in their lower perceived connectedness.

Twenty-four percent of participants in the sample reported living alone. Across participants, having fewer individuals in the household was strongly predictive of reduced perceived social connectedness. This relationship is similarly observed in non-stroke samples[67,68], and living alone is associated with increased mortality across older age[69]. A study of more than 10,000 stroke survivors showed that living alone is associated with worse

acute stroke treatment (e.g., increased latency to hospitalization[70]), which may also help explain the relationship between household composition and poor outcomes. Because the number of individuals living alone is increasing in many countries including the U.K. and U.S.[71], additional research is important to understand and ideally mitigate the adverse effects of living alone after stroke.

A few limitations and potential future directions should be noted. First, strokes affecting the cortex, although the focus of most stroke research including here, account for only about 30% of strokes, while the majority are small subcortical impacts[72,73]. Future work could more closely investigate the relationship between small subcortical impacts and social decline, for example, by examining damage to relevant white matter paths. Second, representation of racial minorities is low in the UK Biobank dataset. Similar to other reports[74,75], 98% of our sample identified as white. Thus, future research is needed to ascertain the generalizability of our findings to more diverse populations. Third, comprehensive stroke medical records were not always available, and more than 20% of ICD-10 coded strokes did not specify stroke type. Defining stroke lesions based on brain imaging 10 or more years after the impact is a challenge and may have resulted in the exclusion of participants with small strokes that were not clearly identifiable. We were unable to directly measure the socio-emotional deficits often linked to right hemisphere stroke, such as poor emotion recognition. Therefore, we cannot definitively link such deficits as underpinning the relationship between right hemisphere damage and worse social outcomes. Lastly, the social activity variable was composed of only two items—frequency of family/friend visits and total number of weekly social activities. The limited scope of this measure may explain why no association was observed with lesion location, especially considering that past research suggests a potential link[29,30]. This null result should thus be interpreted with caution, and improved measurements of social activity should be considered for inclusion in large, prospective cohort studies.

In conclusion, this study ties damage to right hemisphere brain areas involved in empathic processes such as empathic accuracy and emotion recognition to reduced perceived social connectedness after stroke. Specifically, we observed that strokes affecting right anterior insula drove this perceived social decline. Additional work could adapt recent optimizations in clinical stroke rehabilitation[76] to investigate the potential real-world social implications of ameliorating empathic deficits after right hemisphere stroke.

Methods

Study participants

The UK Biobank is an ongoing, longitudinal study including > 500,000 U.K.-dwelling adults over the age of 40. Details about the UK Biobank sample are described elsewhere[77]. We selected from the sample in a series of steps, restricting to participants who: (1) had a stroke either according to linked hospital records or self-report ($n = 13{,}134$), (2) completed the brain imaging session ($n = 562$), (3) had T1-weighted MP-RAGE data available for download as of April 2021 ($n = 471$), (4) were confirmed to have an identifiable stroke lesion on structural images ($n = 236$), (5) did not have other major neurological abnormalities (e.g., a tumor or foreign object) or a history of traumatic brain injury ($n = 233$), (6) had usable T1-weighted images without excessive motion artifact ($n = 231$), (7) completed all 6 social connectedness questions at the brain imaging session ($n = 212$), and (8) experienced their first stroke after the age of 25 ($n = 209$), which is the approximate age of brain maturation[78].

Participants completed the baseline UK Biobank assessment between 2006 and 2010, which included an extensive medical history evaluation and questionnaire completion among other testing. Brain imaging sessions were completed between 2014 and 2020, which similarly included medical history evaluation and questionnaire completion.

The final sample included 209 participants (140 male, 69 female) with an average age of 68.9 years (SD = 6.9, min = 49, max = 81) at the time of MRI scanning. Participants completed the baseline assessment an average of 8.9 years prior to the imaging session (SD = 1.8, min = 4.5, max = 12.4) and suffered their stroke an average of 10.7 years prior (SD = 7.4, min = 0.18, max = 42.1). Ninety participants (43%) had an incident stroke, meaning their stroke occurred between the baseline and brain imaging sessions. One participant did not report a stroke date, but was retained in the final sample. ICD-10 records indicated essential hypertension in 127 participants (61%), a diagnosis of aphasia in 13 participants (6%), and a diagnosis of hemiplegia in 29 participants (14%). Similar to other UK Biobank studies[74,75], the majority of participants identified as white (98%). Additional demographic data can be found in Supplementary Table S1.

The research was performed in accordance with the Declaration of Helsinki; the UK Biobank has research ethics approval from the North West Multi-centre Research Ethics Committee and all participants provided written informed consent at their baseline and imaging session.

Structural brain imaging data

T1-weighted MP-RAGE and T2-weighted FLAIR images were obtained with permission from UK Biobank. Details of brain imaging data collection and initial processing can be found elsewhere[79]. Trained researchers manually traced stroke lesions on T1 anatomical images and confirmed extent using FLAIR images when available (for 97.4% participants).

We performed custom normalization procedures to transform lesion maps to standard space. T1 images underwent field of view reduction and skull-stripping using FSL's robustfov and bet programs[80,81], respectively. Six participants had poor skull-stripping due to stroke lesion location, so their brain masks were manually edited. Images were then deobliqued and normalized to MNI152 T1 standard space using AFNI's @auto_tlrc affine registration program[82]. Visual inspection was completed for all subjects' normalized T1 images and each lesion tracing was overlaid on the MNI template and visually compared with the lesion tracing in native anatomical space to ensure appropriate normalization.

Regions of interest

Regions of interest (Fig. 1) were obtained using the Brainnetome atlas, which defines cortical parcels based on connectional architecture in healthy adults[83]. This atlas includes right and left hemisphere areas that are approximately homologous based on both structural and functional connections. Participants with any degree of stroke impact (i.e. lesion tracing overlap) with each region of interest were considered affected.

The posterior superior temporal gyrus/sulcus region of interest included posterior sulcul regions most commonly associated with emotion perception from visual cues such as facial expressions[5,16,17,84,85] and posterior-to-mid superior temporal gyrus, which is most commonly associated with vocal emotional prosody[19,22,86,87]. This region of interest included parcels labeled as BA41, BA42, caudal BA22 and posterior superior temporal sulcus (label IDs 72, 76, 122, and 124 for right posterior superior temporal gyrus/sulcus and 71, 75, 121, and 123 for left posterior superior temporal gyrus/sulcus). This region encompassed peak coordinates reported by meta-analyses of emotion perception[88,89].

Matching prior work assessing emotion recognition after stroke, inferior frontal gyrus damage was defined by any impact to BA44 or BA45[90], which span label IDs 30, 34, 36, 38, and 40 for right inferior frontal gyrus and 29, 33, 35, 37, and 39 for left inferior frontal gyrus.

Anterior insula is the cytoarchitecturally-defined region of the insula most closely linked to empathy in general and emotion recognition in particular[25,59,62]. This region is structurally and functionally distinct from middle and posterior insula, which are linked more to autonomic, gustatory, pain, and interoceptive processing[91]. The Brainnetome atlas includes two parcels defined as anterior insula (i.e., agranular insular cortex; label IDs 166 and 168 for right anterior insula and 165 and 167 for left anterior insula), which we collapsed into a single region of interest.

Principle component analysis (PCA) of social measures

Six measures that index social connectedness were collected at the UK Biobank brain imaging session via a touchscreen questionnaire: family relationship satisfaction (Data-Field 4559), friendship satisfaction (Data-Field 4570), being able to confide in someone (Data-Field 2110), loneliness (Data-Field 2020), frequency of friend/ family visits (Data-Field 1031), and weekly number of social/leisure activities (Data-Field 6160). Additional information about these items is available on the UK Biobank Data Showcase (https://biobank.ndph.ox.ac.uk/showcase/). To reduce the number of outcome variables for the lesion analyses, these items were entered into a principal components analysis (PCA) with varimax rotation, and we expected to find support for components that separately index perceived social connectedness and social activity. Prior to entry to PCA, scores were adjusted such that higher values indicated better functioning. A standard eigenvalue cutoff > 1 was used to determine the number of components extracted and factor scores were calculated for each participant. We chose PCA as a dimension reduction technique because the primary goal was to reduce the number of items to a smaller set for statistical purposes while retaining the most amount of information and variability.

The PCA generated two factors that explained 53.2% of the variance in the six social connectedness items. Use of PCA was validated by the Kaiser-Meyer-Olkin measure of sampling adequacy (KMO = 0.68) and Bartlett's test of sphericity ($\chi^2 = 147.263$, d.f. = 15, $p < 0.001$). Based on the item loadings (Supplementary Table S2) we interpret the first rotated component as perceived social connectedness (satisfaction with family relationships and friendships, emotional support, and low-loneliness), which explained 32.2% of the variance, and the second component as frequency of social activity, which explained 21.0% of the variance.

Regression modeling

Statistical analyses were performed in R 4.4.1[92]. Models described in the main text employed linear hierarchical regressions. Regressions included multiple covariates, two of which were selected to index two constructs reliably linked to social connectedness in older adults: household composition[67,93], and cognitive ability[94–97]. Household composition was indexed as the total number of individuals living in the participant's household, as reported by the participant at the brain imaging session (Data-Field 709). Cognitive ability was indexed using a 13-item multiple choice touchscreen measure of fluid intelligence, which assessed problem solving requiring logic and reasoning ability (Data-Field 20016). Each item had a 120 s timer, and correct items answered in time were summed resulting in a Fluid Intelligence score ranging from 0 to 13. Participants could opt out if they felt unable to try the test. Therefore, because fluid intelligence scores were missing non-randomly, the regression models use a step-wise method including the fluid intelligence variable last.

Since motor deficits following stroke could restrict a participant's ability to engage in social activity, we additionally included a measure of stroke-related motor weakness. Specifically, the difference between the maximal grip strength of the ipsilateral and the contralateral (stroke-affected) hand was computed and converted to Z-scores based on the distribution of grip strength difference between hands among participants with no record of having had a stroke. Higher values indicated greater motor weakness (lower relative grip strength) of the contralateral, affected hand. For participants with cerebellar strokes we assessed contralateral–ipsilateral grip strength instead and for participants with bilateral stroke, we assumed the hemisphere with larger stroke lesion volume would be most affected. One complication of adjusting for stroke-related motor weakness is that emotion perception involves motor and sensory simulation processes[98,99]. Patients with lesions affecting right somatosensory areas have emotion perception impairments that correlate with their somatosensory deficits[100]. Thus, adjusting for stroke-related motor impairment may reduce variance of interest in social outcomes, and including motor weakness as a variable makes for a particularly conservative test of our predictions.

Regression models that assessed lesion extent as a continuous measure instead of a binary measure included both linear and quadratic terms for extent of damage to right and left ROIs. We used this approach because we did not expect a linear relationship between lesion extent and social connectedness outcomes (e.g., we thought that damage to even a small area of anterior insula could have large consequences for functioning). Lesion extent

to each ROI was calculated by counting the voxels that overlapped between the lesion tracing and the ROI and dividing by the total number of voxels in the ROI. Otherwise, these models followed the same hierarchical procedures explained above.

Statistical analysis of incident strokes

We performed exploratory analyses on change scores for each of the six self-reported social outcome variables, comparing participants who had an incident stroke affecting right anterior insula versus participants who had an incident stroke not affecting right anterior insula. These analyses applied non-parametric Mann-Whitney U tests due to the small and unequal group sizes and report median values in each group. We unfortunately could not calculate change scores of the PCA components because baseline assessments were not available for all social variables for many participants.

Data availability

All statistical code is available on the Open Science Framework repository (https://osf.io/5qhju/). The data that support the findings of this study are available from the UK Biobank but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the UK Biobank. Manual lesion tracings and other individual-level variables created by this study are in process of being returned to the UK Biobank for use by other researchers.

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Author contributions

KMO: conceptualization, data acquisition, lesion tracing, formal analysis, writing – original draft, writing - review & editing.AAM: conceptualization, writing – review & editing.ASG: conceptualization, funding acquisition, lesion tracing, writing – review & editing.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to K.O.

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