Large-scale lesion symptom mapping of depression identifies brain regions for risk and resilience

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Understanding neural circuits that support mood is a central goal of affective neuroscience, and improved understanding of the anatomy could inform more targeted interventions in mood disorders. Lesion studies provide a method of inferring the anatomical sites causally related to specific functions, including mood. Here, we performed a large-scale study evaluating the location of acquired, focal brain lesions in relation to symptoms of depression. Five hundred and twenty-six individuals participated in the study across two sites (356 male, average age 52.4 ± 14.5 years). Each subject had a focal brain lesion identified on structural imaging and an assessment of depression using the Beck Depression Inventory-II, both obtained in the chronic period post-lesion (>3 months). Multivariate lesion–symptom mapping was performed to identify lesion sites associated with higher or lower depression symptom burden, which we refer to as ‘risk’ versus ‘resilience’ regions. The brain networks and white matter tracts associated with peak regional findings were identified using functional and structural lesion network mapping, respectively. Lesion–symptom mapping identified brain regions significantly associated with both higher and lower depression severity (r = 0.11; P = 0.01). Peak ‘risk’ regions include the bilateral anterior insula, bilateral dorsolateral prefrontal cortex and left dorsomedial prefrontal cortex. Functional lesion network mapping demonstrated that these ‘risk’ regions localized to nodes of the salience network. Peak ‘resilience’ regions include the right orbitofrontal cortex, right medial prefrontal cortex and right inferolateral temporal cortex, nodes of the default mode network. Structural lesion network mapping implicated dorsal prefrontal white matter tracts as ‘risk’ tracts and ventral prefrontal white matter tracts as ‘resilience’ tracts, although the structural lesion network mapping findings did not survive correction for multiple comparisons. Taken together, these results demonstrate that lesions to specific nodes of the salience network and default mode network are associated with greater risk versus resiliency for depression symptoms in the setting of focal brain lesions.

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Introduction

Depression is the leading cause of disability worldwide and the leading cause of disease burden in the US. A central goal of translational research on depression is to understand the anatomy of neural networks that contribute to symptoms of depression. With recent advances in therapeutic neuromodulation there is a very direct path for translating advances in understanding the neuroanatomical substrates of depression to improved treatments. Yet, our current understanding of which anatomical regions and networks target to alleviate specific symptoms of depression is incomplete. One of the challenges with this line of research is that work in humans relies heavily on correlational data from functional imaging, which limits causal inferences. Thus, there is a critical need to revisit these questions on the functional neuroanatomy of mood and depression using methods that facilitate causal inferences and have the potential to improve upon existing models.

Human lesion studies provide a strong method for drawing causal inferences relating brain anatomy to function. Lesion studies have provided important insights upon which current models of human brain function have been built, with seminal contributions in domains of memory, language, motor, and attention. This approach, termed lesion–symptom mapping, has also been successfully utilized for symptoms relevant to psychiatric disorders, including executive dysfunction, hallucinations, and emotion regulation. Yet, there is a relative paucity of large-scale systematic efforts to leverage modern methods for mapping the anatomy of depressed mood following focal brain lesions. Prior studies have examined whether lesion location relates to one’s risk for developing or resistance to depression. Some studies implicate lesions of the left frontal lobe closer to the frontal pole as increasing risk for post-stroke depression, whereas lesions of the ventromedial prefrontal cortex have been associated with lower depression ratings. However, these findings have not been reliably replicated, matching the overall trend in the literature. Potential reasons for this include the complexity of depressive symptoms themselves, combined with heterogeneity of behavioural rating scales across studies, small sample sizes or crude lesion location information. Another limitation relates to the challenge of ‘localizing’ a constellation of symptoms that may map onto spatially distributed networks as opposed to a single anatomical location; this can result in a lack of lesion localization due to insufficient power.

Symptoms associated with focal brain lesions can also be considered in relation to their role in disrupting anatomically distributed brain networks. Newer imaging tools have been utilized to investigate the network effects of focal lesions in relation to depressed mood. This includes studies that have performed functional imaging of individuals with lesions as well as studies that have used connectivity information from healthy cohorts to infer the network effects of focal lesions, termed lesion–network mapping (LNM). One recent study of depressed mood, which had a null result for lesion–symptom mapping of depression ratings, used LNM to demonstrate that lesions functionally connected to the left prefrontal cortex (PFC) were associated with higher levels of depression than lesions not connected to this site. This brain-wide network spanned multiple regions beyond the left PFC, and while this is an important advance, it has the same limitations of functional MRI in that it is unclear which regions within the brain-wide functional network are the most critical for depression.

Our study was designed such that it may overcome some of the challenges of prior lesion studies of depression. We utilize a larger sample size than prior studies and employ a widely used and validated depression rating scale across all participants, the Beck Depression Inventory-II (BDI-II). This study also uses multivariate lesion–symptom mapping for depression, a statistical approach for linking lesion location and outcomes that has advantages over a mass univariate approach when multiple nodes of a network may be critical for the expression of symptoms, as is likely the case for depression. Leveraging a combination of large sample size, uniform assessment method and multivariate statistical approach, we investigate whether there are brain regions that, when damaged, are significantly associated with higher levels of depression—here referred to as depression ‘risk’—and whether there are brain regions that, when damaged, are associated with a relative lack of depression, or ‘resilience’. In addition, we perform LNM of brain regions having the strongest association with depression ratings from the lesion–symptom mapping analysis. Structural and functional networks are derived from these regions using normative data to identify the networks most associated with depressed mood following acquired brain lesions.

Materials and methods

Subjects

Participants included 526 individuals who met study criteria, selected from the Patient Registry of the Division of Behavioral Neurology and Cognitive Neuroscience at the University of Iowa Department of Neurology (Iowa cohort; n = 330) and the Vietnam Head Injury Study (VHIS cohort; n = 196). For the University of Iowa Registry, inclusion criteria were presence of a stable, acquired focal brain lesion and depression assessment using the BDI-II, performed as part of a neuropsychological testing battery. Each participant was enrolled approximately 3 months or greater after the lesion onset. Exclusion criteria for the Patient Registry included a history of significant alcohol or substance abuse, psychiatric disorder prior to the brain lesion, medically intractable epilepsy, or other neurologic disorder unrelated to the lesion. For the VHIS cohort, all subjects were drawn from the W.F. Caveness Vietnam Head Injury Study registry, which consists of military veterans who suffered penetrating head trauma while in combat during the Vietnam War era (1967–1970). Subjects were included if they had neuroimaging of their lesion and had completed a BDI-II in the chronic phase post-injury, defined as >3 months later. All VHIS combat veterans had been declared fit for duty at the time of their enlistment in the military prior to their head injury. In accordance with federal and institutional guidelines, all procedures including informed consent were approved by the Institutional Review Boards of the participating institutions and are in accordance with the Declaration of Helsinki.

Mood assessment

The BDI-II is a 21-item self-reported questionnaire that evaluates characteristic attitudes and symptoms of depression experienced...
over the preceding 2 weeks. The items correspond to affective, cognitive, somatic and vegetative symptoms of depression that align with the criteria used to diagnose major depression in the fourth edition of the Diagnostic and Statistical Manual (DSM-IV). Test-retest reliability is high at 0.93, which suggests a robustness against daily mood variations; the validity is further supported by high correlations with Hamilton Depression Rating Scale ($r = 0.71$) and Minnesota Multiphasic Personality Inventory—Depression Subscale ($r = 0.77$). For the current study, if participants had repeated assessments, the highest score was selected.

Lesion segmentation

Each participant included in the analysis had a focal brain lesion with visible boundaries evident from research-quality structural imaging from $T_1$ and $T_2$ sequences on MRI. CT scans were used in the VHIS and in rare cases in the Iowa Registry when MRI was contraindicated ($n = 35$ of 330 Iowa subjects). All imaging was performed in the chronic epoch (>3 months since onset) to ensure relative stability of the lesion. Lesions were manually segmented in three dimensions by a rater blind to mood ratings, and anatomical accuracy of each tracing was reviewed by a neurologist (A.D.B.) in both native space and upon transformation to Montreal Neurologic Institute Structural MNI Template (MN1152) 1-mm template brain using a combination of linear and non-linear registration techniques. Additional details of lesion segmentation are provided in Supplementary material, Appendix 1.

Multivariate lesion–symptom mapping

Lesion–symptom mapping analyses were performed on the BDI-II mood rating results using sparse canonical correlation analysis (SCCAN) as implemented in LESYMAP, a package available in R (https://github.com/dorianps/LESYMAP). The SCCAN method involves an optimization procedure that finds voxel weights that maximize the multivariate correlation between voxel values and BDI-II depression scores. The predictive value and sparseness of the model is derived empirically using a 4-fold, within-sample correlation between model-predicted and actual BDI-II scores. LESYMAP deems a map ‘valid’ if it is associated with a statistically significant predictive correlation. Briefly, SCCAN builds a model using 75% of the sample, applies it to the remaining 25% of the sample in order to predict the BDI-II scores from lesion location and correlates these predictions with actual BDI-II scores. This approach tests the statistical significance of the entire map at once and avoids the pitfalls associated with voxel-wise (i.e. mass univariate) methods, such as inflated rates of false-positive errors. This previously validated method has been demonstrated as more accurate than mass univariate methods and is better able to identify when multiple brain regions are associated with a behavioural variable.

Functional lesion network mapping

Functional lesion network mapping was performed similarly to prior work, in which networks were derived from regional peak brain–behaviour associations identified from the lesion–symptom map. This differs from the approach of using each lesion mask to ‘seed’ the network analysis to avoid some of the problems associated with signal averaging from large lesions. To identify peak regions of interest with the strongest association with BDI-II ratings from the lesion–symptom map, a cluster tool in FSL was used. Peaks were identified for ‘risk’ and ‘resilience’ maps and assigned to grey or white matter using brain masks for each tissue class.

Four-millimetre spherical regions of interest were placed at each of the peak grey matter coordinates and used to seed separate functional connectivity analyses. Resting state functional connectivity MRI (rs-fcMRI) data from a normative database ($n = 98$) were used, as in previous work. The rs-fcMRI data were processed in accordance with previously described methods and are described in detail in Supplementary material, Appendix 1. Global signal regression was included in the primary analysis. For all datasets the time course of the average blood oxygen level-dependent (BOLD) signal within each spherical region of interest was compared with the BOLD signal time course of other brain voxels to identify regions with positive and negative correlations. Pearson correlation coefficients were converted to normally distributed $Z$-scores using the Fisher transformation.

A group mean $t$-test was performed separately for the positive and negative maps of $Z$-scores using FSL flameo using ordinary least-squares, and then clustered for significance at an alpha level of 0.05, $t > 3.1$. These maps of significant positive and negative rs-fcMRI correlations were combined to generate a single positive and a single negative rs-fcMRI map for each individual in the normative dataset derived from the spherical regions of interest. Next, the individual positive and negative rs-fcMRI maps were entered into separate weighted principal components analyses (PCA) using MATLAB (2012b, Natick, MA, USA) in order to identify the principal component networks that explain the most variance in network maps derived from ‘risk’ and ‘resilience’ regions. These network maps were compared to the Yeo et al. canonical resting state functional MRI 7-network parcellation using spatial correlation analysis to relate our findings to previously described rs-fcMRI networks. Additional details of LNM methods are provided in Supplementary material, Appendix 1. To ensure the results were not unique to the specific methodological approach to lesion network mapping, two secondary analyses were conducted: one using ‘each lesion mask as a seed’ and another using the first principal component of the rs-fcMRI signal computed from within the lesioned area as the seed. The resulting relationship between the rs-fcMRI and BDI scores was evaluated with a voxel-wise permutation analysis of linear models (FSL PALM), as performed previously and described in more detail in Supplementary material, Appendix 1.

Structural lesion network mapping

To evaluate structural networks associated with lesion location, each lesion mask was used to seed an individual deterministic tractography analysis using Lead-DBS software as performed previously. This method employs a normative dataset of neurologically healthy individuals with high-quality diffusion tensor imaging data included in the Human Connectome Project’s MGH 32-fold group connectome (https://ida.loni.usc.edu/login.jsp). For structural lesion–network mapping the challenges of signal averaging within a large lesion mask that occur with BOLD do not apply, and thus individual lesion masks were used to seed networks rather than regional peaks derived from the lesion–symptom maps. The direction of streamlines was not constrained to any other region of interest beyond the starting ‘seed’ region of interest. The 526 unthresholded individual lesion-derived tractography maps were evaluated in FSL using a voxel-wise permutation analysis of linear models (PALM, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/UserGuide). The BDI rating was the behavioural variable in the general linear model, with lesion volume entered as a
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covariate and statistical significance evaluated with threshold free cluster enhancement, 2-tailed significance and 2000 permutations. Regional findings for the ‘risk’ and ‘resilience’ peaks were compared to the HCP-842 and JHU white matter tractography atlases using spatial correlation analysis to relate our findings to common white matter tracts. A visual outline of the lesion–symptom mapping and lesion–network mapping methods is provided in Fig. 1.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request. The data are not publicly available, and some data cannot be made available due to containing information that could compromise the privacy of research participants.

Results

Demographics

Across the two datasets, 526 lesion subjects were included in the primary analysis (67.7% male, average age 52.4 years at time of assessment). The Iowa cohort (n = 330) was 48.5% male, average age 48.9 years. In contrast, the VHIS cohort was entirely male (100%), average age 58.3 years. Both populations were predominantly right-handed (88.2 and 83.7%, respectively) and predominantly White (97.6 and 90.8%, respectively). The Iowa cohort consisted of various lesion aetiologies, with ischaemic stroke representing the largest proportion (43.0%); the VHIS cohort consisted entirely of lesions due to penetrating head injury. Additional demographic details can be found in Table 1.

Lesion coverage

Lesion overlap maps show greatest lesion coverage in the medial PFC (mPFC), with slightly greater coverage on the right hemisphere in both cohorts of patients (maximum overlap 60; Fig. 2). Areas with the least coverage include the brainstem, cerebellum and thalamus.

Beck Depression Inventory

Figure 3 shows the distribution of BDI-II scores across the two samples. Individual BDI-II scores ranged from 0 to 48 (scale maximum is 63) across the two samples, with fair representation across all depression severities. Three hundred and forty-seven patients qualified as having ‘minimal depression’ by BDI-II standards (score < 14), 84 patients had ‘mild depression’ (BDI-II score 14–19) and 95 patients met criteria for ‘moderate to severe depression’ (BDI-II score > 19).

Lesion–symptom mapping results

Multivariate lesion–symptom mapping results demonstrated several brain regions that were significantly associated with higher and lower levels of depression severity (r = 0.11, P = 0.013; Fig. 4A). The most robust ‘risk’ regional findings were in the bilateral mid-to anterior insula and the left prefrontal deep white matter. Many regions of the left and right dorsolateral PFC and underlying white matter were included, as well as the left dorsomedial PFC. The most robust ‘resilience’ peaks were in the R > L orbitofrontal cortex (OFC) and medial PFC (mPFC) and the right inferolateral temporal cortex. In total, the clustering analysis identified 24 ‘risk’ peak regions of interest (15 grey matter peaks, 9 white matter peaks) and 20 ‘resilience’ peak regions of interest (13 grey matter peaks, 7 white matter peaks), shown in Fig. 4B and Supplementary Fig. 1. The cross-validated correlation value, a measure of the strength of the correlation, for this dataset is modest (r = 0.11), and running each dataset individually fails to reach statistical significance (Iowa r = 0.09, P = 0.12; VHIS r = 0.13, P = 0.06).

A post hoc analysis of the lesion–symptom mapping findings was undertaken to evaluate whether ‘resilience’ regions in fact reflected distinctly ‘sub-normal’ depression levels, as opposed to representing an artefact associated with ‘lack of risk’. We assessed the
percentage of patients with clinically significant depression (defined as a BDI-II score >13)²⁶ based on the proportion of the ‘risk’ or ‘resilience’ map that was lesioned. As shown in Fig. 5, patients with lesions that involve an increasing proportion of the ‘risk’ map had a higher rate of clinically significant depression; the opposite is true for ‘resilience’ regions, where patients with lesions overlapping with a greater proportion of the ‘resilience’ map had a lower rate of clinically significant depression. The average BDI-II scores from patients that overlap with >10% of the ‘risk’ or ‘resilience’ maps were significantly higher (BDI-II 17.7 ± 9.0) than the scores from patients that overlap with <10% of the ‘risk’ or ‘resilience’ maps (BDI-II 9.0 ± 5.9, n = 135, BDI-II 10.8 ± 9.0). The disparity between the BDI-II scores in the ‘risk’ and ‘resilience’ groups and a lesion comparison group suggest that the lesions associated with ‘risk’ and ‘resilience’ are each uniquely associated with higher and lower levels of depression than average, respectively. This supports the notion that lesions involving ‘resilience’ regions are associated with significantly lower overall depression symptoms, rather than simply being regions not associated with higher depression severity. Further support comes by way of a large normative community-dwelling sample²⁶ having average BDI-II scores of 8.6 ± 7.7 (n = 356), which is significantly greater than 5.7 ± 5.9 (P = 0.011).

In evaluating potential confounding relationships that may impact our results, we evaluated the roles of lesion size, education level (as an available correlate for socioeconomic status) and post-lesion IQ (as a correlate for overall cognitive function). We first evaluated the potential role of lesion size. Lesion volume was not correlated with BDI-II scores (r = 0.02, P = 0.64). Controlling for lesion size in the analysis had minimal bearing on the statistical map (spatial correlation with the primary map = 0.98). We next evaluated the effect of education level and found this to have a weak but statistically significant correlation with BDI-II scores in the patients for whom education level was recorded (n = 522, r = 0.14, P = 0.001). When SCCAN was performed while controlling for lesion volume and education level, the cross-validation correlation value improved from 0.11 in the primary finding to 0.13 (n = 522, P = 0.002), and the map looked largely similar to the primary lesion–symptom map (spatial correlation = 0.92). We also evaluated the relationship of our findings to cognitive function as estimated with full scale IQ post-lesion. We again observed a weak but significant correlation between IQ and BDI-II scores in a subset of subjects with available IQ scores (n = 248, r =−0.18, P = 0.005). However, a lesion symptom mapping analysis of full-scale IQ using SCCAN was not statistically significant and localized to different brain regions than BDI-II (spatial correlation <0.01), suggesting that lesion localization of depressed mood was unlikely to be associated with lesion-associated differences in cognition. Unfortunately, additional measures of post-lesion cognitive status and functional status were not systematically available or readily accessible for the majority of subjects at parallel time points to allow for more extensive evaluation of the relationship between post-lesion functional status and depressive symptom burden.

### Table 1 Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Iowa cohort (n = 330)</th>
<th>VHIS cohort (n = 196)</th>
<th>Combined cohort (n = 526)</th>
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<tr>
<td><strong>Population</strong></td>
<td>Civilian</td>
<td>Military</td>
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<tr>
<td>Age at assessment, years (SD)</td>
<td>48.9 (17.2)</td>
<td>58.3 (3.1)</td>
<td>52.4 (14.5)</td>
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<td>Gender</td>
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<td>196 M (100%)</td>
<td>356 M (67.7%)</td>
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<tr>
<td>Time from lesion to scan, years (SD)</td>
<td>4.0 (8.1)±</td>
<td>&gt;30</td>
<td>–</td>
</tr>
<tr>
<td>Time from lesion to BDI-II assessment, years (SD)</td>
<td>4.9 (8.8)±</td>
<td>&gt;30</td>
<td>–</td>
</tr>
<tr>
<td>BDI-II total score, average (SD)</td>
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<td>9.3 (9.1)</td>
<td>11.5 (9.4)</td>
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<td>Handedness</td>
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<td>164 R (83.7%)</td>
<td>455 R (86.5%)</td>
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<tr>
<td></td>
<td>32 L</td>
<td>27 L</td>
<td>59 L (11.2%)</td>
</tr>
<tr>
<td></td>
<td>7 ambidextrous</td>
<td>5 ambidextrous</td>
<td>12 ambidextrous</td>
</tr>
<tr>
<td></td>
<td>322 White (97.6%)</td>
<td>178 White (90.8%)</td>
<td>500 White (95.0%)</td>
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<td>Race</td>
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<td>17 Black (3.2%)</td>
</tr>
<tr>
<td></td>
<td>3 American Indian</td>
<td>2 Asian American</td>
<td>9 Other (1.7%)</td>
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<td>1 American Indian</td>
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<tr>
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<td>1 unidentified</td>
<td>1 other</td>
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<tr>
<td>Ethnicity</td>
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<td>187 Non-Hispanic</td>
<td>516 Non-Hispanic</td>
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<tr>
<td></td>
<td>(99.7%)</td>
<td>(95.4%)</td>
<td>(98.1%)</td>
</tr>
<tr>
<td>Years of education (SD)</td>
<td>13.8 (2.4)</td>
<td>14.8 (2.5)±</td>
<td>14.2 (2.5)</td>
</tr>
<tr>
<td>Lesion aetiology (% of sample)</td>
<td>43.0%</td>
<td>0%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Stroke, ischaemic</td>
<td>19.7%</td>
<td>0%</td>
<td>12.4%</td>
</tr>
<tr>
<td>Stroke, haemorrhagic</td>
<td>18.8%</td>
<td>0%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Tumour resection (primarily benign meningiomas)</td>
<td>6.1%</td>
<td>0%</td>
<td>3.8%</td>
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<tr>
<td>Subarachnoid haemorrhage</td>
<td>3.9%</td>
<td>100%</td>
<td>39.7%</td>
</tr>
<tr>
<td>Head trauma</td>
<td>8.5%</td>
<td>0%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Other (AVM, cavernoma resection, encephalitis, cyst ± resection, abscess resection, developmental)</td>
<td></td>
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</table>
Lesion–network mapping results

Functional LNM

The first principal components derived from the 15 ‘risk’ grey matter peaks and the 13 ‘resilience’ peaks are shown in Fig. 6B. They accounted for 43 and 39% of the variance of individual maps, respectively. The ‘risk’ PCA network was most similar to the salience/ventral attention network ($r = 0.805$) and the ‘resilience’ PCA network was most similar to the default mode network (DMN, $r = 0.914$; Fig. 6B and C). The results of the other components and their relation to canonical networks are shown in Supplementary Figs 2–4. The topography of ‘risk’ and ‘resilience’ networks was similar when employing alternate approaches, such as using each lesion mask to ‘seed’ the rs-fcMRI network (secondary analysis 1, $r = 0.742$ and $-0.762$ for ‘risk’ and ‘resilience’, respectively, Supplementary Fig. 5) or using the first principal component of the rs-fcMRI signal within the lesion as the seed (secondary analysis 2, $r = 0.747$ and $-0.752$ for ‘risk’ and ‘resilience’, respectively, Supplementary Fig. 5). These alternate methods generated almost identical maps to one another ($r = 0.996$) and also highlight the salience/ventral attention network and default mode networks as the most strongly correlated and anticorrelated networks within the Yeo 7-network parcellation ($r = 0.749$ and $-0.832$ for salience/ventral attention, $-0.832$ and $-0.836$ for default mode, respectively). To assess whether our findings were being driven by one cohort of subjects over another (Iowa cohort versus VHIS cohort), the above analyses were re-run for each individual cohort. The uncorrected lesion network mapping results were highly correlated between the Iowa and VHIS cohorts (Supplementary Fig. 6) using both the results of secondary analysis 1 ($r = 0.368$) and secondary analysis 2 ($r = 0.423$), and each demonstrated similar regions of significance which were relevant to the peak findings in our primary lesion symptom mapping result. No findings in either individual cohort survived multiple comparisons correction.
Structural LNM

White matter tracts maximally associated with ‘risk’ for depression included dorsal frontal white matter pathways on the left more so than the right, including frontopontine fibre tracts, frontal aslant tracts and association fibre tracts ($r = 0.354, 0.335, 0.334$, respectively). ‘Resilience’ tracts included cerebellar outflow tracts as well as ventral frontal white matter tracts, primarily forceps minor and the uncinate fasciculus, with all findings stronger in the right hemisphere ($r = 0.139, 0.128$, and $0.111$, respectively; Fig. 7). These findings were each significant at $P$ values $<0.000001$, but no findings survived a whole-brain voxel-wise correction for multiple comparisons using family-wise error correction. Additional details and images are provided in Supplementary Fig. 7.
Discussion

Our results demonstrate that specific brain regions, when lesioned, have an association with higher depressive symptoms. The most prominent of these ‘risk’ regions are the bilateral anterior insula and dorsolateral PFC, including grey and white matter. We also identified regions that, when lesioned, were associated with lower depressive symptoms. These ‘resilience’ regions are the right OFC, right mPFC and right inferolateral temporal lobe. Moreover, our functional LNM results suggest that these regions are not randomly distributed, but fall primarily within two functional networks, with lesions of the salience network associated with increased depressive symptoms (24 positive ‘risk’ regions of interest and 20 negative ‘resilience’ regions of interest). Activity patterns in these networks are negatively correlated with each other at rest (Fig. 6B and Supplementary Fig. 4) and our results support an inverse relationship with mood when lesioned. This may help to inform the robust literature that exists on the role of these two networks in depression, as discussed below.

Our results also highlight why lesion studies of depression have been challenging. The strength of association in the brain–behaviour relationship is weak compared to other neurological functions, with an r value of 0.11. By comparison, we obtained an r-value of 0.62 for naming, using the same lesion–symptom mapping approach in a similarly large sample. Prior work with conflicting or null findings could potentially be explained by insufficient power, which is underscored by the fact that dividing our two samples into individual cohorts fails to detect a significant relationship, despite similar correlation values to the combined sample (0.09 and 0.13). Moreover, the regional findings were distributed across several brain areas spanning the cerebral cortex, white matter and subcortical sites. As such, the multivariate approach used here was likely important for identifying the distributed regional patterns. For example, another large-scale lesion symptom mapping study employing a multivariate analysis with a similar sample size identified some similar regions of interest (e.g. right basal ganglia and right mesial temporal lobe structures; see Supplementary Fig. 1B for reference) as associated with greater post-lesion depression symptoms. However, this study was limited to include only subjects with ischaemic stroke and lacked lesion coverage of medial prefrontal regions, likely limiting its ability to detect some of the ‘resilience’ regions identified here. In the next paragraphs we discuss our strongest individual findings and relate them to other literature on depression.

The anterior to mid-insula is the ‘risk’ region with the strongest findings in both hemispheres. Interestingly, few lesion–symptom mapping studies implicate the insula as a cortical region associated with depression.
with depression when lesioned, despite its known role in emotion processing. This brain region is associated with prediction, 77 emotion regulation after stroke, 78 autonomic functioning, interoception and integration of emotional valence with our physiological state. Furthermore, the anterior insula demonstrates altered grey matter volume and abnormal functional connectivity in studies of depression 99,100 and has been implicated in other forms of psychopathology, 73,81,82 as well as in the generation of ecstatic or blissful experiences with stimulation. 83

Interestingly, the anterior insula also serves as a hub for the salience/ventral attention network of the brain, 84-87 which has nodes in other `risk` regions identified in this study including the dorsolateral PFC, dorsomedial PFC and dorsal anterior cingulate cortex. 88 Additionally, one of the key white matter tracts connecting cortical regions of the salience network is the frontal aslant tract, also a primary tract associated with white matter `risk` regions in the structural LNM results. 89 This relationship between `risk` regions and the salience network is especially informative from a treatment perspective—studies suggest salience network connectivity abnormalities correlate with depressive symptoms 90 and are predictive of antidepressant response in patients undergoing transcranial magnetic stimulation (TMS). 91 The dorsolateral PFC was included as a `risk` region, as implicated by others in lesion studies. 13,14,16 The dorsolateral FPC includes a node of the salience network 92 with connectivity to the anterior insula; this salience node of the PFC is in the region of the TMS target for treating depression. 93-95 Finally, the dorsomedial PFC and dorsal anterior cingulate, both `risk` regions, have also been implicated as potential targets for neuromodulation of mood, with stimulation inducing antidepressant responses, laughter, and the will to persevere. 98-100 The dorsolateral PFC, dorsomedial PFC and dorsal cingulate cortex regions have all been associated with increases in activity in depression remitters following antidepressant medication administration. 101

The `resilience` regions—those locations where a lesion was associated with less depressive symptom burden—were the OFC, mPFC (right > left) and the right inferolateral anterior temporal lobe. These brain regions are involved in impulse control, decision making, reward and emotion processing (OFC, mPFC) 103,104 and higher-order visual processing (inferolateral anterior temporal lobe). 105 They are also notably hubs of the DMN, a network involved in self-referential thinking. 106 In depressed patients, research suggests hyperconnectivity within the DMN is associated with negative rumination and depressive symptoms, 71,109-112 and excessive connectivity between the DMN and attentional, externally focused brain networks also correlates with depression, possibly related to patients struggling to `disengage` from their internally focused state. Some studies suggest that stimulating brain networks anticorrelated with the DMN can have an antidepressant effect, 52,97,113-117 and lesioning or `virtually lesioning` DMN structures such as the mPFC and nearby white matter tracts has been hypothesized to have antidepressant effects in prior studies. 14 Indeed, the `resilience` findings from the structural LNM results here implicate two of the three mPFC white matter tracts targeted with deep brain stimulation for treatment-refractory depression in some studies, a technique thought to induce a virtual lesion or disruption of pathological information processing. 118

The purported functional contributions of the salience and DMN to mood and depression offer a potentially parsimonious explanation for our findings. The salience network, here found to be the primary `risk` network for post-lesion depression, is considered important for task-switching to reallocate neural processing resources towards meaningful stimuli. In fact, the strongest

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**Figure 7 Structural lesion network mapping results.** t-Stat map highlighting the significant white matter findings from the voxel-wise permutational analysis of linear models for both `risk` (red-yellow) and `resilience` (blue-green) and how they align with common white matter tracts (white outlined in black). The three white matter tracts with the highest spatial correlation for both the `risk` and `resilience` stat maps are shown with representative brain slices. `Risk` findings tended to align with dorsal prefrontal pathways and `resilience` findings tended to overlap with ventral prefrontal tracts and cerebellar outflow tracts.
In doing so, the salience network may have a role in coordinating transitions in attention between internally mediated thought processes supported by the DMN and externally focused processes supported by other ‘task positive’ brain networks.75 Damage to the integrity of the salience network (such as via an insula lesion) theoretically would result in impairments disengaging from internally focused processing in favour of orienting one’s attention to the environment, as is observed in association with depressive symptoms. Indeed, one study identified emotional processing deficits as the most commonly reported symptom category after salience network disturbance.120 In contrast, the DMN supports self-referential thinking, including negative rumination and depressive symptoms.71,109–112 Prior work from our lab demonstrated that lesions of the DMN reduce mind wandering,121 and one could postulate that a lesion to this network may similarly reduce negative rumination in a way that is protective against depressed mood.

This study is not without limitations. First, although the sample size was large, we did not have sufficient coverage of some brain areas, particularly subcortical sites like the brainstem, thalamus and cerebellum; as sample size can influence the results of lesion symptom mapping of depression. Meanwhile, the OFC, mPFC and inferolateral anterior temporal lobe; these regions are nodes of the salience network. Equally intriguing, another study has shown that OFC, mPFC and inferolateral anterior temporal lobe can be associated with regional ‘risk’ findings of anywhere in the brain correspond closely with overlapping datasets.14,16 For example, Koenigs et al.14 conducted seminal work identifying ventral mPFC lesions as associated with lower depression scores, and this dataset included n = 18 subjects that are in our Iowa (n = 7) and VHIS (n = 11) patient samples. To ensure our findings were not being unduly influenced by this cohort, we also conducted our lesion symptom mapping analysis excluding these 18 subjects (n = 508 remaining). Our findings in this unique cohort showed statistically significant findings (r = 0.09, P = 0.037) largely similar to our primary analysis results, with a spatial correlation of 0.93.

Next, although the Iowa cohort incorporated patients with no known psychiatric disorders, the pre-lesion psychiatric history of patients in the VHIS cohort is unknown; however, all VHIS subjects were deemed fit for combat in Vietnam. Thus, interindividual differences in mood, personality/temperament, psychosocial circumstance (combat exposure, other trauma history, family history) or structural and functional connectivity that preceded the onset of the lesion may reduce the strength of the brain–behaviour relationship24–26, this could be addressed in future studies by assessing these pre-lesion factors at the time of the injury or studying a population with pre-lesion clinical and neuroimaging data available.

The studies had a variable degree of time from the lesion occurrence to the depression assessment and imaging. Assessments were obtained in the chronic phase (>3 months post-injury), which attempts to minimize the confounds of acute functional or psychosocial effects of the lesion on depressive symptom reporting, but simultaneously also limits any inferences that can be made about direct causality of the lesion on depressive symptoms. The timing of assessments was not standardized beyond this and thus cannot control for chronic effects of brain network reorganization or other post-lesion psychosocial or biological changes affecting depression ratings. For example, damage to the OFC, mPFC or DMN could influence one’s emotional reasoning,14,127 moral judgement105 and associated self-referential introspection. This could alter one’s appraisal and self-report on his or her internal state, although family reports tend to confirm self-reports in some studies.128 Similarly, clinical depressive disorders are often episodic in nature. Although some studies suggest that depressive symptoms persisting 6 months post-lesion frequently develop a chronic course,29,129 the natural history of post-lesion depression can be variable.30 Thus, the severity of symptoms captured by a depression inventory provides only a snapshot of active symptoms that cannot characterize the longitudinal nature of symptoms or the effect of ongoing treatments. Although we were unable to thoroughly evaluate the relationship between post-lesion depression and post-lesion functional impairment in our sample, our evaluation of confounding cognitive status was reassuring. In general, the relationship between post-lesion cognitive or functional impairment and post-lesion depressive symptoms is mixed in prior literature,17,21,131,132 and our lack of depression ‘risk’ findings in regions classically associated with the most obvious functional impairments (e.g. Broca’s area, primary motor cortices) provides further reassurance that the findings in this study are not confounded by functional impairment. Furthermore, despite the identification of mood-relevant brain regions and networks in our analyses, the findings and conclusions are restricted to depression manifested following focal brain lesions; we cannot generalize or extrapolate to make conclusions about primary mood disorders such as major depressive disorder, which likely have unique pathophysiology.

Due to the variety of lesion aetiologies included in this study, there is a chance that the underlying pathology leading to the lesion may have an influence on the development of depression (i.e. subjects with cardiovascular disease may be at higher risk for both ischaemic stroke with a specific regional distribution and depression, which could present a confound).

Finally, this study was conducted on a cohort of subjects that was predominantly White and predominantly male. Further study of gender, racial and ethnic differences is prudent, as these findings require validation in other demographic groups before they can be generalized.

In conclusion, we present findings from one of the largest lesion–symptom mapping studies of depressive symptoms to date. Our results suggest that lesions to certain brain regions are associated with a higher post-lesion depression symptom burden, including the anterior insula, dorsolateral PFC and left dorsomedial PFC—regions that are nodes of the salience network. Equally intriguing, certain brain lesion locations are associated with lower than expected post-lesion depressive symptoms, including lesions to the OFC, mPFC and inferolateral anterior temporal lobe; these best correspond with regions of the DMN. Future studies will focus on lesion–symptom mapping of specific depression subtypes or symptom categories as well as longitudinal evaluation of the relationship between salience network or DMN connectivity and development of depressive symptoms after lesion onset.

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**Competing interests**
The authors report no competing interests.

**Supplementary material**
Supplementary material is available at Brain online.

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