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CLINICAL RESEARCH

Structural and Functional Brain Changes in Acute Takotsubo Syndrome

Hilal Khan, MB BCH, BAO,[a] David T. Gamble, MBCHB,[a] Amelia Rudd, RDCS, BSE,[a] Alice M. Mezincescu, MD, PHD,[a] Hassan Abbas, MBCHB, BSC,[a] Awsan Noman, MBCHB, MD,[a] Andrew Stewart, MBCHB, PHD,[a] Graham Horgan, BSC, PHD,[a] Rajeev Krishnadas, MBBS, DNB, MD, PHD,[b] Christopher Williams, MBCHB, BSC, MMEDSC, MD,[b,c] Gordon D. Waiter, PHD,[a] Dana K. Dawson, MD, DPHIL[a]

ABSTRACT

BACKGROUND Takotsubo syndrome mimics an acute myocardial infarction, typically in the aftermath of mental or physical stress.

OBJECTIVES The mechanism by which emotional processing in the context of stress leads to significant cardiac injury is poorly understood, so a full exploration of brain structure and function in takotsubo syndrome patients merits investigation.

METHODS Twenty-five acute (<5 days) takotsubo patients and 25 control subjects were recruited into this observational cross-sectional study. Surface-based morphometry was carried out on magnetic resonance imaging (MRI) brain scans to extract cortical morphology based on volume, thickness, and surface area with the use of Freesurfer. Cortical morphology general linear models were corrected for age, sex, photoperiod, and total brain volume. Resting-state functional MRI and diffusion tensor tractography images were preprocessed and analyzed with the use of the Functional Magnetic Resonance Imaging of the Brain Diffusion Toolbox and Functional Connectivity Toolbox.

RESULTS There was significantly smaller total white matter and subcortical gray matter volumes in takotsubo ($P < 0.001$), with smaller total brain surface area but increased total cortical thickness (both $P < 0.001$). Individual gray matter regions (hippocampus and others) were significantly smaller in takotsubo ($P < 0.001$); only thalamus and insula were larger ($P < 0.001$). There was significant hyperfunctional and hypofunctional connectivity in multiple areas, including thalamus-amygdala-insula and basal ganglia ($P < 0.05$). All structural tractography connections were increased in takotsubo ($P < 0.05$).

CONCLUSIONS The authors showed smaller gray and white matter volumes driven by smaller cortical surface area, but increased cortical thickness and structural tractography connections with bidirectional changes in functional connectivity linked to emotion, language, reasoning, perception, and autonomic control. These are interventional targets in takotsubo patients' rehabilitation. (J Am Coll Cardiol HF 2023;11:307–317) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]University of Aberdeen, Aberdeen, United Kingdom; [b]University of Glasgow, Glasgow, United Kingdom; and [c]Five Areas, Glasgow, United Kingdom.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

FLAIR = fluid attenuation inversion recovery

fMRI = functional magnetic resonance imaging

LGA = lesion growth algorithm

MRI = magnetic resonance imaging

Takotsubo syndrome is an acute heart failure cardiomyopathy mimicking an acute myocardial infarction in its presentation.[1] Typically, it occurs in the aftermath of intense psychologic or physical stress, affecting women in more than 90% of cases. The mechanism by which emotional processing in the context of stress leads to significant cardiac injury and acute left ventricular dysfunction has yet to be elucidated. Therefore, a full exploration of the brain structure and function in takotsubo syndrome merits investigation.

A recent retrospective analysis using ^{18}F-fluorodeoxyglucose positron emission tomographic-computed tomographic examination of a patient cohort investigated for cancer showed higher amygdala activity (an area involved in the experiencing of emotions) in subjects who subsequently developed takotsubo syndrome after 2 years,[2] suggesting the possibility of a premorbid state affecting the brains of patients with takotsubo syndrome. Several reports have shown structural and functional differences of the brain limbic system and areas involved in regulating the autonomic nervous system in patients with takotsubo syndrome, suggesting impaired interaction between centers responsible for processing emotional inputs and the autonomic nervous system.[3-5] All of these studies, except one,[5] included patients at variable later stages after the acute presentation, possibly masking phasic variations that occur thereafter that may be important markers of recovery or sustained predisposing risk. Furthermore, a large international registry reported a significant stroke outcome in takotsubo patients,[6] and recently white matter hyperintensities (which reflect small vessel disease) have been linked to an increased risk of developing future stroke.[7]

In the present study, we explored a whole-brain magnetic resonance imaging (MRI) investigation of acute changes in takotsubo presenters. Specifically, we examined the cortical surface areas, cortical thickness, and white matter hyperintensity volumes as well as gray matter volumes, the structural connectivity network of gray matter centers (tractography) by means of diffusion tensor imaging, and their resting state connectivity with the use of functional magnetic resonance imaging (fMRI), compared with a matched control population.

METHODS

STUDY POPULATIONS. From October 2020 to July 2021, we recruited 25 patients with acute takotsubo syndrome who underwent brain MRI and validated psychology questionnaire assessment during the first 5 days after diagnosis (23 of these patients were recruited consecutively from a single center and 2 were referred from external collaborating centers). Exclusion criteria included patients too frail to participate, those with significant neurologic diseases or dementia, and contraindications or intolerance to MRI. Patients were identified by the attending cardiologist based on history, electrocardiography, biomarkers, echocardiography, coronary angiography, and cardiac MRI findings. All patients were screened by cardiac MRI to ensure that the patient had not had a myocardial infarction or other cardiomyopathy. In addition, all patients had follow-up cardiac imaging to ensure resolution of wall motion abnormalities. All patients met the European Society of Cardiology criteria for diagnosis of takotsubo syndrome. We selected a group of control subjects matched for age, sex, and medical and mental health comorbidity from participants who had identical neurologic investigations as part of the STRADL (Stratifying Resilience and Depression Longitudinally) study.[8] That study recruited participants with and without depression who completed the same psychology questionnaires and had MRI brain scans performed with the exact same sequences as in the takotsubo syndrome patients. The same MRI equipment was used to acquire the imaging data, and the same software version was used for data analysis of both patient cohorts. All patients gave written informed consent. The study was approved by the local research ethics committee (20/SC/0305).

PSYCHOLOGY QUESTIONNAIRES. All patients were given the Hospital Anxiety and Depression Scale[9] and the Eysenck Personality Questionnaire–Revised[10] to complete on the day of MRI scanning.

ENVIRONMENTAL VARIABLE—PHOTOPERIOD. To adjust for seasonal changes in brain volumes, all brain volumes were corrected for photoperiod.[11] The photoperiod of the scanning center was determined by using the United States Naval Observatory online data repository and calculated by subtracting the time of sunset from the time of sunrise on the day of scanning for each participant.[12]

BRAIN MRI PROTOCOL. Brain MRI was performed on a 3-T Philips Achieva TX-series MRI system (Philips Healthcare) based in the biomedical imaging center at Aberdeen Royal Infirmary with a 32-channel phased-array head coil. T1-weighted fast gradient echo images (160 sagittal slices, repetition time [TR] 8.2 ms, echo time [TE] 3.8 ms, inversion time [TI] 1,031 ms, fractional anisotropy [FA] 8°, field of view [FOV]

240 mm, matrix size 240 × 240 mm, voxel size 1.0 × 1.0 × 1.0 mm), diffusion tensor images (60 axial slices, TR 7,010 ms, TE 90 ms, FA 90°, FOV 220 mm, matrix size 96 × 94 mm, voxel size 2.3 × 2.3 × 2.3 mm, 64 noncollinear gradient directions [b = 1,200 s/mm^2], 8 unweighted [b = 0]), resting-state fMRI (32 axial slices, TR 1,560 ms, TE 26 ms, FA 70°, FOV 217 mm, matrix size 64 × 64 mm, voxel size 3.4 × 3.4 × 4.5 mm), and fluid attenuation inversion recovery (FLAIR) (160 sagittal slices, TR 8,000 ms, TE 349 ms, TI 2,400 ms, FA 8°, FOV 240 mm, matrix size 240 × 238 mm, voxel size 1.0 × 1.0 × 1.0 mm) were acquired in a 25-minute protocol.

WHITE MATTER HYPERINTENSITIES. Automated lesion segmentation was performed using the lesion growth algorithm (LGA) provided by the lesion segmentation tool. LGA requires T1 and FLAIR images and outputs lesion probability maps and total lesion volume and number. An initial binary lesion map obtained by imposing a predetermined initial threshold (0.5) on the independent maps is then grown along hyperintense voxels in the FLAIR image. Total lesion volume was calculated from the lesion probability maps with a threshold of 0.5.

VOLUMETRIC, SURFACE AREA, AND CORTICAL THICKNESS ANALYSIS FOR TOTAL AND INDIVIDUAL BRAIN CENTER AREAS. Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite v7.1.1, which is freely available online.[13] This involves several post-processing steps to output volume measurements that are well validated in the published reports. Once the cortical models were complete, several deformable procedures were performed for further data processing and analysis and creation of a variety of surface-based data, including surface area measurements. Cortical thickness was calculated from both intensity and continuity information from the entire 3-dimensional MRI volume in segmentation and deformation to produce representations of cortical thickness. Procedures for the measurement of cortical thickness have been validated against histologic analysis and manual measurements.[14]

FUNCTIONAL CONNECTIVITY. Resting state fMRI was analyzed using the CONN (Functional Connectivity Toolbox), which allowed takotsubo patients to be compared with matched control subjects for differences in functional connectivity with a bandpass filter of 0.008-0.090 Hz. Six motion-corrected parameters were included in the generalized linear model. An region of interest-region of interest based analysis was performed on all brain regions included in CONN. All results were corrected for age and sex. Pearson's correlation between clusters was calculated across all regions. The r value acquired for the Pearson correlation between every 2 regions was z transformed and group differences were calculated on the z-transformed values with a 2-sample Student's t-test. False discovery rate correction was used to correct for multiple comparisons at the cluster level, and corrected $P < 0.05$ was considered to be significant.

STRUCTURAL CONNECTIVITY (TRACTOGRAPHY). Diffusion tensor images were preprocessed using the FMRIB (Functional Magnetic Resonance Imaging of the Brain) Diffusion Toolbox. We corrected for motion and geometric distortion caused by eddy currents with the eddy correct tool in FMRIB Diffusion Toolbox, taking the average of the 8 b0 volumes as the reference image. Nonbrain tissue from the average b0 image was removed with the use of the FMRIB Diffusion Toolbox. False discovery rate correction was used to correct for multiple comparisons with the use of CONN at the cluster level, and corrected $P < 0.05$ was considered to be significant.

STATISTICAL ANALYSIS OF BRAIN VOLUME, SURFACE AREA, AND CORTICAL THICKNESS. SPSS v27 was used to analyze the differences in volumetric data with the use of the general linear model, and multivariate analyses of the brain volumes were corrected for total brain volume, age, sex, and photoperiod. Surface area was corrected for age, sex, and total brain volume. Cortical thickness was corrected for age, sex, and whole-brain cortical thickness. Multiple correction testing was performed for brain volume, surface area, and cortical thickness using the Bonferroni correction. A value of $P < 0.05$ after Bonferroni adjustment was considered to be statistically significant.

RESULTS

Baseline demographics and the validated questionnaire scores of the 50 participants recruited for the study are presented in **Table 1**. The median age was 65 years in the control group and 68 years in the takotsubo syndrome group ($P = 0.809$). There were 24 women and 1 man in each group ($P = 1.00$) There was no significant difference in comorbidities, including psychiatric illnesses, apart from a small number of patients with chronic obstructive pulmonary disease in the takotsubo group (n = 5; $P = 0.018$). There were 40% of takotsubo patients with an emotional trigger, 28% with a physical trigger, and 32% with no obvious identifiable trigger. The median time to MRI scanning was 5 days in the takotsubo syndrome group. The mean left ventricular ejection fraction in the takotsubo syndrome group was 45.0% ± 8.3%. The

TABLE 1 Baseline Characteristic In Patients With Takotsubo Syndrome and Matched Control Subjects

	Takotsubo Patients (n = 25)	Matched Control Subjects (n = 25)	*P* Value
Age, y	68 (47-83)	65 (64-69)	0.809
Female	24 (96)	24 (96)	1.0
Medical history			
Hypertension	8 (32)	6 (24)	0.538
Diabetes	2 (8)	3 (12)	0.646
Stroke	1 (4)	1 (4)	1.0
Thyroid disease	2 (8)	2 (8)	1.0
Psychiatric disease	6 (24)	4 (16)	0.490
Atrial fibrillation	2 (8)	0 (0)	0.155
COPD	5 (20)	0 (0)	0.018
Takotsubo trigger type			
Emotional	10 (40)		
Physical	7 (28)		
None	8 (32)		
Days from symptom onset to MRI	5 (2-8)		
LVEF on admission, %	45 ± 8.34		
Medications			
Beta-blocker	17 (68)	2 (8)	<0.001
ACE inhibitor	16 (64)	1 (4)	<0.001
Angiotensin receptor blocker	2 (8)	2 (8)	1.0
Mineralocorticoid antagonist	4 (16)	0 (0)	0.038
Calcium channel blocker	3 (12)	2 (8)	0.646
Antiplatelets	15 (60)	2 (8)	<0.001
Anticoagulants	4 (16)	0 (0)	0.038
Diuretic	4 (16)	3 (12)	0.691
Statin	17 (68)	2 (8)	<0.001
Hypoglycemic drugs	3 (12)	1 (4)	0.561
Nitrates	3 (12)	1 (4)	0.307
Antidepressants	4 (16)	2 (8)	0.394
Antipsychotics	0 (0)	0 (0)	1.0
Validated questionnaire scores			
HADS	13.20 ± 10.30	3.68 ± 2.43	<0.001
Eysenck Extraversion	10.72 ± 5.09	13.34 ± 7.18	0.143
Eysenck Introversion	12.28 ± 5.09	9.66 ± 7.18	0.143
Eysenck Neuroticism	9.52 ± 5.5	7.28 ± 6.45	0.191
Eysenck Stability	14.48 ± 5.5	16.72 ± 6.45	0.191

Values are median (IQR), n (%), or mean ± SD.

ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; HADS = Hospital Anxiety and Depression Scale; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging.

Hospital Anxiety and Depression Scale score was significantly higher in the patient group compared with control subjects ($P < 0.001$). See Supplemental Table 1 for detailed case description of patients.

WHITE MATTER HYPERINTENSITIES. There was no difference in either number or total volume of white matter hyperintensity lesions between acute takotsubo syndrome patients and matched control subjects (Supplemental Table 2).

SURFACE AREA OF INDIVIDUAL BRAIN REGIONS. As seen in **Table 2** and Supplemental Table 3, acute takotsubo patients had significantly smaller surface areas of several brain regions, such as the left rostral anterior cingulate and the right and left insula. Overall, acute takotsubo patients had significantly smaller total and right and left hemisphere surface areas.

CORTICAL THICKNESS OF INDIVIDUAL BRAIN REGIONS. **Table 2** and Supplemental Table 4 show that patients with acute takotsubo have significantly larger cortical thickness in brain regions such as the right insula. In addition, they demonstrate significantly larger total right and left hemisphere cortical thickness.

TOTAL AND INDIVIDUAL BRAIN CENTER VOLUMES. As seen in **Table 2** and Supplemental Table 5, acute takotsubo patients had significantly smaller white matter and subcortical gray matter volumes, whereas their cortical gray matter was larger. In addition, there were numerous significant differences in many of the limbic center brain volumes between acute takotsubo syndrome patients and matched control subjects, notably, left, right, and total hippocampus and the brainstem were all significantly smaller in acute takotsubo patients. Conversely, left, right, and total thalamus and insula were larger in patients with takotsubo syndrome compared with matched control subjects ($P < 0.001$).

FUNCTIONAL CONNECTIVITY. As shown in **Figure 1**, there were multiple significantly increased (red lines) and decreased (blue lines) functional connectivity networks in takotsubo patients vs matched control subjects (all $P < 0.05$). Specifically, there was increased connectivity between either the right thalamus or the left thalamus and the left caudate and left nucleus accumbens, between the anterior cingulate cortex and the right cerebral cortex, or between the left thalamus and the posterior cerebellum. Conversely, there was significantly decreased functional connectivity between the right thalamus and the right inferior frontal gyrus, between the entire thalamus and the left amygdala, left insula, visual lateral and visual medial lobes, orbitofrontal cortex, and inferior frontal gyrus, or between the left insula and the left caudate and thalamus.

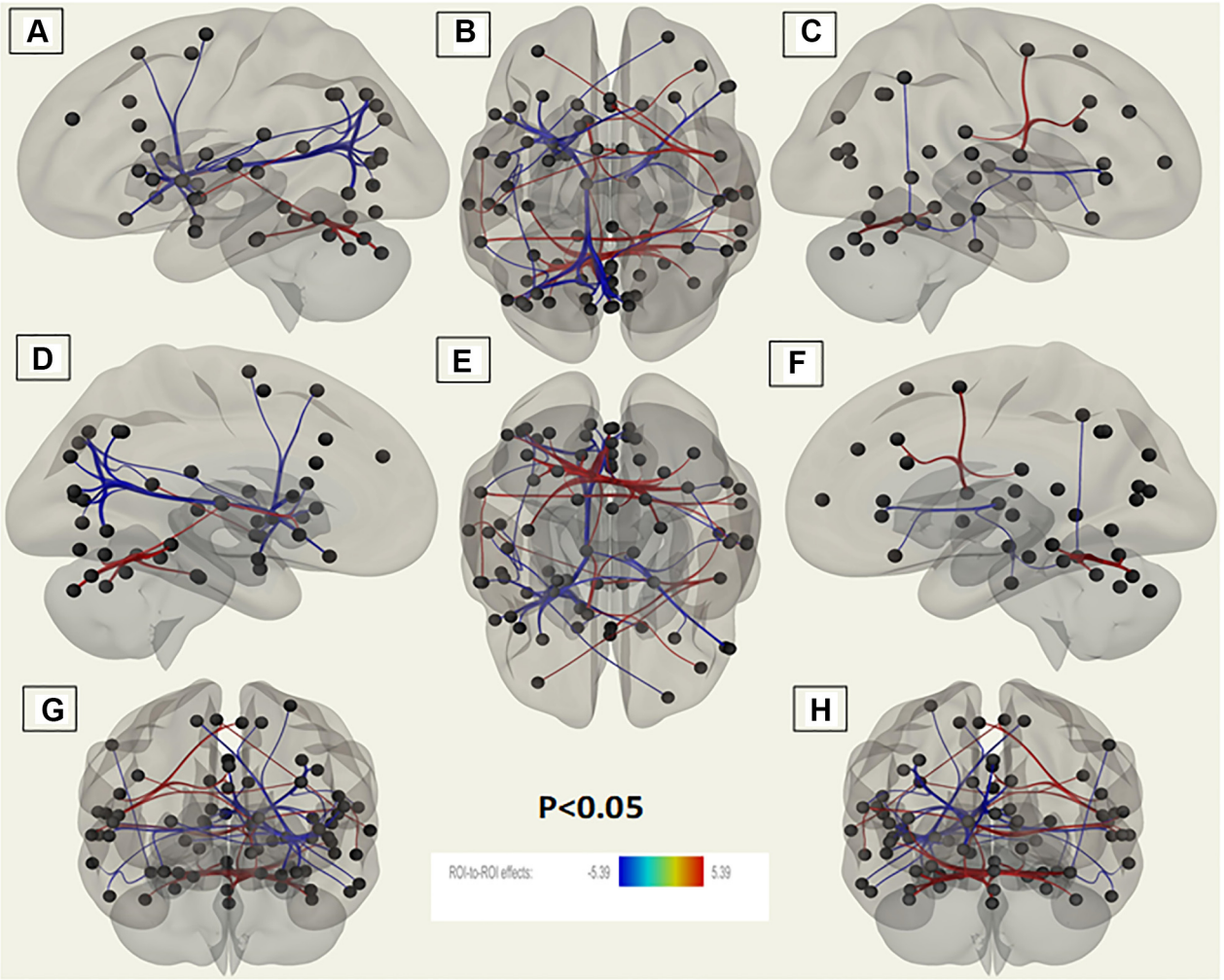
STRUCTURAL CONNECTIVITY (TRACTOGRAPHY). As shown in **Figure 2**, there was a significant increase in all structural connectivity connections in takotsubo syndrome compared with matched control subjects, notably with absence of any reduced structural connections in takotsubo patients. Specifically, the right and left thalamus showed significantly increased structural connectivity to the temporal regions. The left insula had significantly increased structural

TABLE 2 Brain Parameters

	Acute Takotsubo	Matched Control	*P* Value	*P* Value, Corrected
White matter hyperintensities, mm				
Total volume, mL	6.52 ± 10.25	5.91 ± 13.40	0.857	0.857
Number of lesions	11.52 ± 6.28	14.92 ± 17.01	0.353	0.353
Surface area of individual brain regions, mm^2				
Right isthmus cingulate	865 ± 89	829 ± 99	0.012	0.81
Left isthmus cingulate	924 ± 146	932 ± 131	0.045	NS
Right parahippocampal	556 ± 56	562 ± 53	0.001	0.07
Left parahippocampal	587 ± 76	581 ± 64	0.374	NS
Right rostral anterior cingulate	500 ± 93	540 ± 85	0.043	NS
Left rostral anterior cingulate	738 ± 159	755 ± 171	<0.001	0.007
Right insula	2,064 ± 239	2,132 ± 269	<0.001	<0.001
Left insula	2,206 ± 262	2,278 ± 310	<0.001	<0.001
Total right white surface area	75,441 ± 5,173	76,689 ± 5,795	<0.001	<0.001
Total left white surface area	75,379 ± 5,099	76,321 ± 5,721	<0.001	<0.001
Cortical thickness of individual brain regions, cm				
Right caudal anterior cingulate	2.38 ± 0.21	2.27 ± 0.18	0.016	NS
Left caudal anterior cingulate	2.45 ± 0.22	2.41 ± 0.23	0.814	NS
Right rostral anterior cingulate	2.78 ± 0.22	2.63 ± 0.18	0.030	NS
Left rostral anterior cingulate	2.63 ± 0.23	2.59 ± 0.18	0.043	NS
Right insula	2.89 ± 0.19	2.79 ± 0.11	<0.001	<0.001
Left insula	2.87 ± 0.16	2.77 ± 0.23	0.007	0.476
Total right mean thickness	2.37 ± 0.10	2.35 ± 0.09	<0.001	<0.001
Total left mean thickness	2.38 ± 0.10	2.35 ± 0.08	<0.001	<0.001
Brain volume (hemispheric/regional), mm^3				
Total cerebral white matter	411,342 ± 41,051	424,934 ± 41,984	<0.001	<0.001
Total gray matter	540,388 ± 41,158	539,419 ± 35,543	<0.001	<0.001
Subcortical gray matter	49,679 ± 4,087	50,154 ± 2,784	<0.001	<0.001
Left thalamus	6,235 ± 680	6,135 ± 437	<0.001	<0.001
Right thalamus	6,020 ± 660	5,958 ± 430	<0.001	<0.001
Total thalamus	12,256 ± 1,297	12,092 ± 827	<0.001	<0.001
Left hippocampus	3,656 ± 358	3,768 ± 273	<0.001	<0.001
Right hippocampus	3,731 ± 361	3,840 ± 308	<0.001	<0.001
Total hippocampus	7,387 ± 702	7,608 ± 556	<0.001	<0.001
Left amygdala	1,374 ± 233	1,417 ± 153	0.002	0.078
Right amygdala	1,560 ± 170	1,562 ± 190	0.007	0.273
Total amygdala	2,935 ± 384	2,979 ± 318	0.002	0.078
Left caudate	2,994 ± 341	3,055 ± 343	0.004	0.156
Right caudate	3,110 ± 403	3,236 ± 360	<0.001	0.037
Total caudate	6,104 ± 723	6,291 ± 683	0.001	0.039
Left accumbens	393 ± 106	457 ± 79	0.008	0.312
Right accumbens	476 ± 92	497 ± 79	0.027	NS
Total accumbens	869 ± 188	955 ± 140	0.008	0.312
Left isthmus cingulate volume	2,244 ± 377	2,286 ± 295	0.012	0.468
Right isthmus cingulate volume	2,157 ± 216	2,117 ± 253	0.01	0.39
Total isthmus cingulate volume	4,401 ± 515	4,402 ± 474	0.003	0.117
Left parahippocampus	1,828 ± 263	1,895 ± 280	0.006	0.234
Right parahippocampus	1,676 ± 244	1,778 ± 202	<0.001	<0.001
Total parahippocampus	3,504 ± 472	3,674 ± 458	<0.001	0.007
Left insula	6,342 ± 841	6,139 ± 773	<0.001	<0.001
Right insula	6,047 ± 754	5,902 ± 703	<0.001	<0.001
Total insula	12,389 ± 1,574	12,042 ± 1,415	<0.001	<0.001
Brainstem	18,782 ± 1,966	19,394 ± 1,956	<0.001	<0.001

Values are mean ± SD. *P* values were obtained after correction for total brain volume, age, sex, and photoperiod. Corrected *P* values are after Bonferroni correction.
NS = not significant.

FIGURE 1 Altered Functional Connectivity in Takotsubo Syndrome



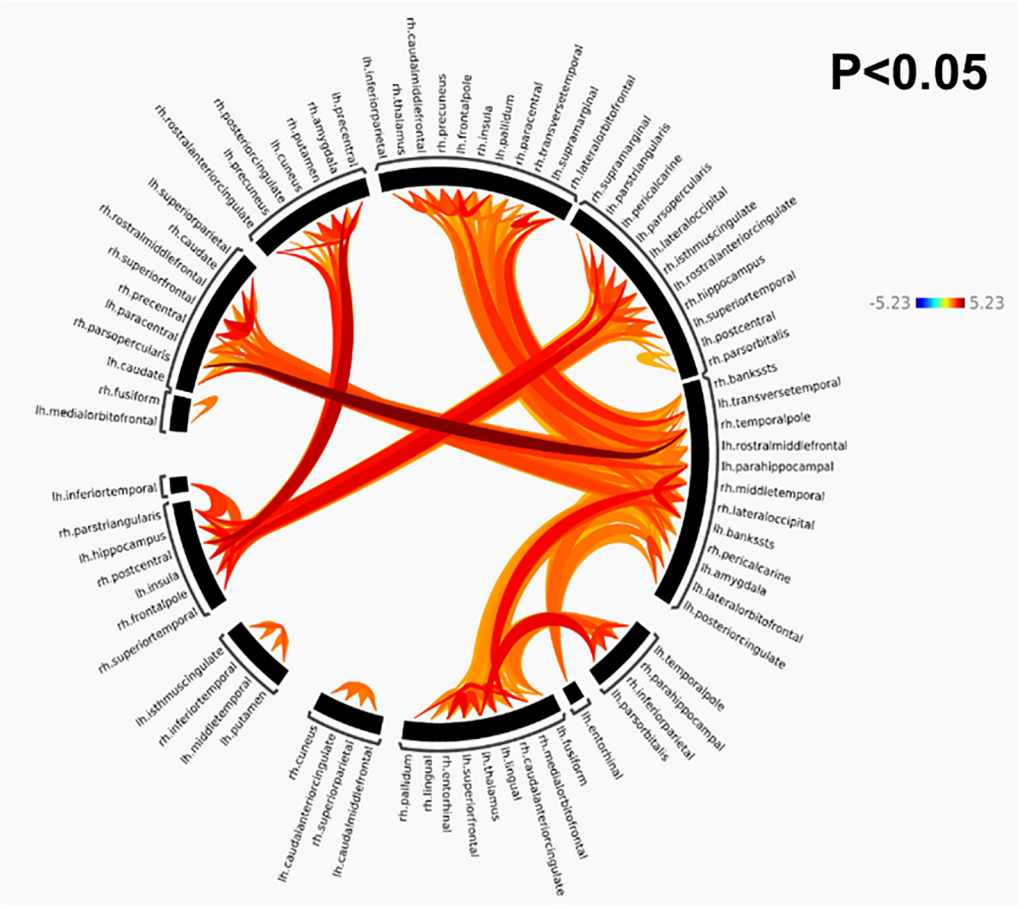
(A to H) Multiple areas of functional hypoconnectivity associated with regulation of the autonomic nervous systems and regions of hyperconnectivity involving the anterior cingulate gyrus and the salience networks (all $P < 0.05$). Color bars represent the set *t*-value of the connections between which the 2 groups differ in connectivity strength (**red** = hyperconnectivity; **blue** = hypoconnectivity). ROI = region of interest.

connectivity to the right amygdala, right putamen, right posterior cingulate gyrus, and right rostral anterior cingulate gyrus.

DISCUSSION

This is the largest cohort of takotsubo syndrome patients whose acute brain phenotype has been investigated. All cases were examined during the acute phase (within 5 days of presentation) to allow benchmarking of any changes that may have occurred before or during the subsequent convalescent phase because of medications or other interventions. We found no evidence of cerebral small vessel disease, as evidenced by similar number and volume of white matter hyperintensities compared with control subjects. In this study, takotsubo patients had greater cortical thickness but smaller cortical surface areas and smaller total white matter, total subcortical gray matter volume, and all individual gray matter brain centers except for the thalamus and insula, which were larger, in either hemisphere or combined. Distinct bidirectional changes in functional connectivity were seen compared with matched control subjects, and this occurred in the context of all structural tractography connections being significantly increased in takotsubo patients.

FIGURE 2 **Structural Connectivity of Regions of Interest Based on Diffusion Tensor Imaging Differences Between Acute Takotsubo Syndrome and Matched Control Subjects**



Only enhanced structural connections were seen in takotsubo patients (all $P < 0.05$).

ANATOMIC CHANGES IN TAKOTSUBO SYNDROME. It is well understood that there are different genes responsible for the development of cortical surface area vs cortical thickness.[15] The radial hypothesis suggests that during early development, the brain develops along columns, with each column being associated with a certain function. The surface area is determined by the number of columns, whereas cortical thickness is influenced by the number of cells within a column. Later in life, cortical thickness appears to be influenced by environmental factors such as alcohol consumption and smoking, whereas cortical surface area appears to be regulated by unique developmental factors.[16,17] Therefore, both a genetic difference as well as an adaptive cortical reorganization could be responsible for the findings seen in the brain of takotsubo patients compared with control subjects.

Smaller cortical surface area and greater cortical thickness as noticed in takotsubo patients in the present study is also seen in patients with major psychiatric disease, such as major depression.[18] In addition, smaller brain gray matter volumes, especially hippocampal volumes, that we observed in patients with takotsubo syndrome are also seen in patients with elevated levels of inflammation[19] and have been previously reported in the amygdala by Hiestand et al,[20] albeit at a later time after the index presentation. The reduction in gray matter volumes was also shown by Dichtl et al,[5] confirming the involvement of the gray matter in patients who develop takotsubo syndrome. Hiestand et al[20] showed reduced cortical thickness in a cohort of takotsubo patients 1 year after the acute event, which is contrary to our results and may be explained by the timeframe when scanning was performed in that

study. Both depression and anxiety disorders are associated with elevated levels of inflammation.[21] Systemic and myocardial inflammation is a well-recognized feature of takotsubo syndrome,[22,23] which raises the possibility that the changes we observed in the brain of takotsubo syndrome patients are potentially adaptive and related to inflammation.

White matter hyperintensity findings in this cohort would suggest that takotsubo patients have a similar risk of cognitive impairment, dementia and stroke as a matched control population.[24] If the increased risk of stroke suggested by the international takotsubo registry[6] was assigned to the significant premorbid incidence of neurologic disease of the patients included in this registry, it could mean that in the absence of preexistent neurologic disease, the risk of subsequent stroke for takotsubo patients may not be as high as suggested by registries.

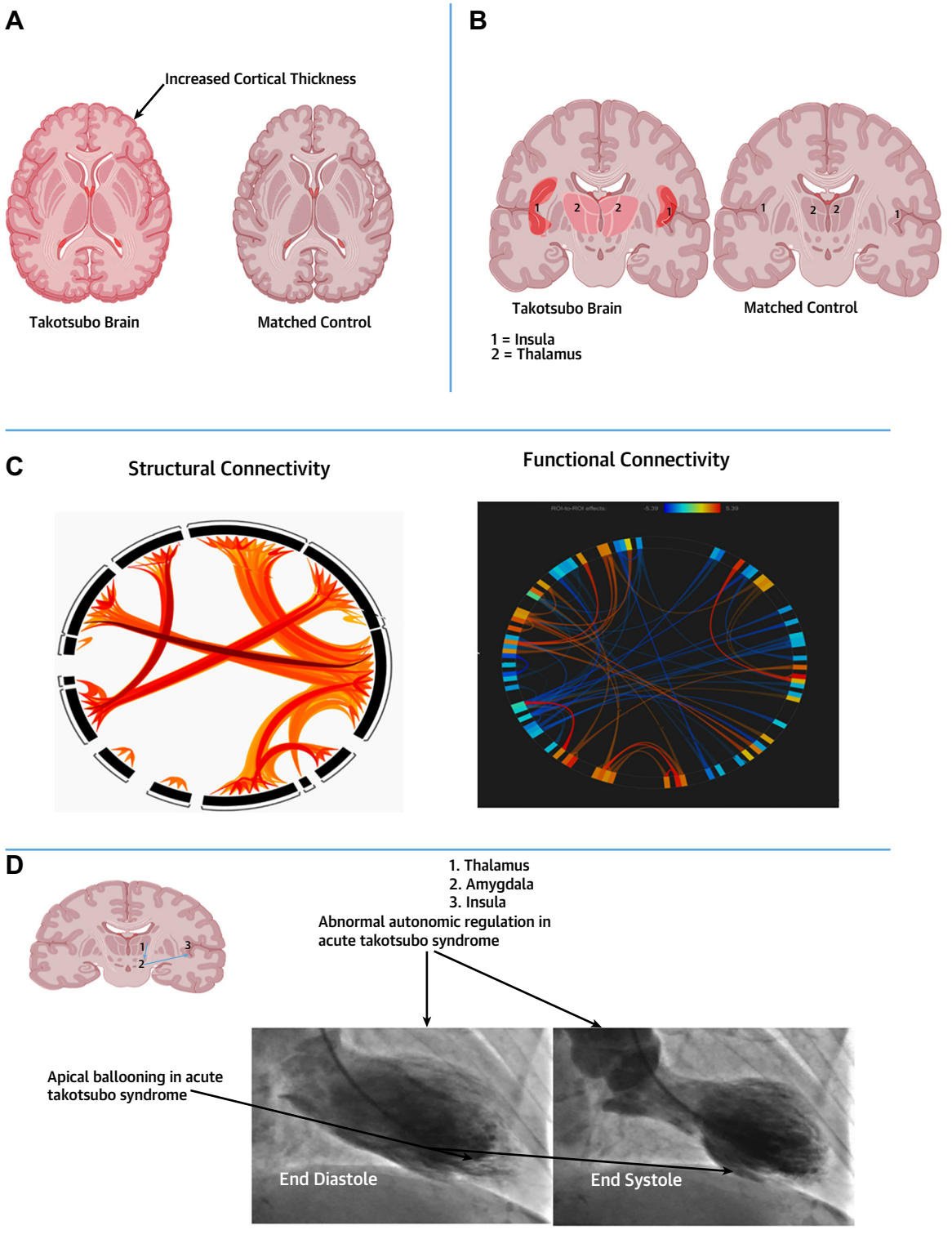
FUNCTIONAL AND STRUCTURAL CONNECTIVITY CHANGES IN TAKOTSUBO SYNDROME. Brain activity and functional connectivity networks are intricately linked to their structural connectivity patterns, such that brain regions with high structural connectivity normally exhibit high functional connectivity, whereas the converse is not necessarily true.[25] In this study, we showed that both thalamic and insulae nuclei were greater in size and had increased structural connections. Some of these findings overlap with those seen in other conditions, such as greater thalamic volumes seen in patients with major depression and suicidal ideation[26] or increased functional connectivity between thalamus and nucleus accumbens linked to emotional processing regulating the pain response[27] as well as involved in attenuating cardiac injury during ischemic damage.[28] We have previously noted that there are increased proinflammatory cytokines and inflammatory markers, such C-reactive protein, in patients with takotsubo syndrome.[29] Again, increased inflammation has been associated with reduced functional activation of the thalamus and insular cortex,[30] such as we observed here.

It is therefore intriguing to see a reduction in functional connectivity in the context of enhanced structural connections, which implies that the reduction in functional connectivity is not caused by abnormal structural connections. An inflammatory substrate hypothesis makes it easier to reconcile observations such as reduced functional connectivity from the right thalamus to the right inferior frontal gyrus (language center) or to the visual lateral cortex in takotsubo patients in this study. The first is also observed in schizophrenia and linked to aberrant encoding of semantic memory (abnormal processing of auditory stimuli, fixity of thinking with low flexibility, and high emotional distress),[31] and the latter is also seen in patients with anorexia nervosa and linked to abnormal processing of visual stimuli and overvalued ideation.[32]

A noteworthy finding in the present study is the reduced functional connectivity between the left thalamus and the left insular cortex. Lesions in the left amygdala or left insular cortex are associated with a 5-fold increased risk of sudden cardiac death in patients with schizophrenia.[33] In patients with left insular lesions, there is loss of parasympathetic control and sympathetic overactivity with an increased risk of cardiac injury and arrythmia.[34] Stroke patients with left insular lesions had poorer cardiac outcomes and were more likely to have cardiac wall motion abnormalities on echocardiography in the absence of obstructive coronary artery disease.[35] Left insular lesions induced in mice resulted in cardiac injury and elevated serum levels of noradrenaline. The extent of the insular injury corresponded with the degree of cardiac injury.[36] A previous study of patients with takotsubo syndrome 2 years after the acute event, however, noticed increased functional connectivity in the left insular cortex. A biphasic response with initial reduced insular functional connectivity leading to loss of parasympathetic control followed by increased insular connectivity thereafter is a plausible explanation of maladaptive autonomic response in these patients.[37] Dichtl et al[5] showed similar findings, with reduced functional connectivity of the insula during the acute period, in keeping with the results seen in our study. Templin et al[3] showed similar findings with reduced functional connectivity in the insular region. This recurring finding of abnormal insular function strongly suggests a role for this region in the pathogenesis of takotsubo syndrome.

Another interesting finding in takotsubo patients in this study is the reduced functional connectivity in the caudate, putamen, and pallidum with increased functional connectivity in the nucleus accumbens. These together form key parts of the basal ganglia. Abnormalities in the basal ganglia have been associated with altered vagal nerve function and an increased risk of both bradyarrhythmias and atrial fibrillation.[38,39] Altered functioning in this area may contribute to arrhythmic presentations seen in acute takotsubo syndrome or in the development of subsequent atrial fibrillation.[40]

CENTRAL ILLUSTRATION Brain-Heart Axis in Takotsubo Syndrome



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(A) Increased cortical thickness and reduced surface area in takotsubo syndrome. **(B)** Larger volume thalamus and insula in takotsubo syndrome compared with control. **(C)** Structural and functional connectivity changes in takotsubo syndrome. **(D)** Functional hypoconnectivity in key pathways involved in autonomic control of cardiac function in takotsubo syndrome.

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We also observed reduced functional connectivity in the amygdala of patients with acute takotsubo similarly to patients with a tendency to catastrophize events.[41] Previous observations showed reduction in functional connectivity in the amygdala years after the acute event. Together these findings would imply that this area of emotional processing is abnormal during both the acute phase and long term.[3]

These findings would support the nitrosative stress theory of takotsubo syndrome whereby maladaptive brain responses to stress involving the thalamus-amygdala-insular pathways lead to loss of autonomic control over the nervous system, leading to sympathetic overactivity, nitrosative stress, and cardiac injury, which contributes to the acute and chronic heart failure phenotype seen in takotsubo syndrome (**Central Illustration**).[22,29,42,43] The overlap of many of the anatomic and functional brain findings in takotsubo patients with those seen in psychiatric conditions is intriguing, particularly because patients with depression or schizophrenia also have decreased survival because of excess cardiac mortality.

STUDY LIMITATIONS. Because this was an observational study, it was not possible to apportion causality of the observations, which are merely hypothesis generating. Follow-up of the natural history of changes in the brain of takotsubo syndrome patients could provide further insight.

CONCLUSIONS

In the largest structural and functional brain study of acute takotsubo syndrome patients compared with matched control subjects we demonstrate smaller cortical surface area and greater cortical thickness, no increase in white matter hyperintensities, smaller gray matter centers except for the thalamus and insula, which were larger (in either hemisphere or combined), and enhanced structural tractography connections with distinct bidirectional changes in functional connectivity linked to emotion, mood, language, visual and auditory perception, and autonomic control.

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ADDRESS FOR CORRESPONDENCE: Dr Hilal Khan, Aberdeen Cardiovascular and Diabetes Centre, Room 1:03 Ashgrove House, Foresterhill, University of Aberdeen, King's College, Aberdeen AB24 3FX, United Kingdom. E-mail: hilal.khan@abdn.ac.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In the acute phase of illness, takotsubo syndrome patients demonstrate overall increased cortical thickness but smaller cortical surface areas, smaller white and gray matter volumes, and smaller individual brain center volumes, except thalamus and insula. Patients with takotsubo syndrome: 1) have no significant difference in white matter hyperintensities compared with control subjects, implying absence of small vessel disease; 2) show areas of functional hypoconnectivity in key brain regions involving the thalamus-amygdala-insula axis and basal ganglia, which are responsible for higher-level functions (emotion, reasoning, language, perception) as well as autonomic regulation of the brain-heart axis; and 3) have increased structural tractography connections compared with control subjects, suggesting that the abnormalities in functional connectivity are not caused by abnormalities in structural connections.

TRANSLATIONAL OUTLOOK: The abnormalities in the thalamus-amygdala-insula and basal ganglia support the concept of involvement of higher-level function centers in takotsubo syndrome, and interventions aimed at modulating these may be of benefit.

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KEY WORDS brain, cardiomyopathy, imaging, takotsubo

APPENDIX For supplemental tables, please see the online version of this paper.