Received: 27 December 2021 | Revised: 15 April 2022 | Accepted: 30 May 2022

DOI: 10.1002/da.23275

RESEARCH REPORT

ANXIETY AND DEPRESSION ASSOCIATION OF AMERICA WILEY

Structural brain features signaling trauma, PTSD, or resilience? A systematic exploration

Sigal Zilcha-Mano[1] | Xi Zhu[2,3] | Amit Lazarov[4,5] | Benjamin Suarez-Jimenez[3,6] | Liat Helpman[7,8] | Yoojean Kim[2,3] | Carly Maitlin[2,3] | Yuval Neria[2,3] | Bret R. Rutherford[9]

[1]Department of Psychology, University of Haifa, Mount Carmel, Haifa, Israel

[2]Department of Psychiatry, Columbia University, New York, New York, USA

[3]New York State Psychiatric Institute, Columbia University Medical Center, New York, New York, USA

[4]School of Psychological Sciences, Tel-Aviv University, Tel-Aviv, Israel

[5]Department of Psychiatry, Columbia University Medical Center, New York, New York, USA

[6]Department of Neuroscience, University of Rochester, Rochester, New York, USA

[7]Department of Counseling and Human Development, University of Haifa, Mount Carmel, Haifa, Israel

[8]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[9]Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, New York City, New York, USA

Correspondence
Sigal Zilcha-Mano, PhD, Department of Psychology, University of Haifa, Mt Carmel, Haifa 31905, Israel.
Email: sigalzil@gmail.com

Funding information
National Institute of Mental Health; United States - Israel Binational Science Foundation

Abstract

Background: Studies have searched for neurobiological markers of trauma exposure, posttraumatic stress disorder (PTSD) diagnosis, and resilience to trauma to identify therapeutic targets for PTSD. Despite some promising results, findings are inconsistent.

Aims: The present study adopted a data-driven approach to systematically explore whether structural brain markers of trauma, PTSD, or resilience emerge when all are explored.

Materials & Methods: Differences between clusters in the proportion of PTSD, healthy controls (HC), and trauma-exposed healthy controls (TEHC) served to indicate the presence of PTSD, trauma, and resilience markers, respectively. A total of 129 individuals, including 46 with PTSD, 49 TEHCs, and 34 HCs not exposed to trauma were scanned. Volumes, cortical thickness, and surface areas of interest were obtained from T1 structural MRI and used to identify data-driven clusters.

Results: Two clusters were identified, differing in the proportion of TEHCs but not of PTSDs or HCs. The cluster with the higher proportion of TEHCs, referred to as the resilience cluster, was characterized by higher volume in brain regions implicated in trauma exposure, especially the thalamus and rostral middle frontal gyrus. Cross-validation established the robustness and consistency of the identified clusters.

Discussion & Conclusion: Findings support the existence of structural brain markers of resilience.

KEYWORDS
posttraumatic stress disorder, resilience, structural MRI, trauma

1 | INTRODUCTION

Studies have searched for neurobiological markers of posttraumatic stress disorder (PTSD), trauma exposure, and resilience to trauma to better understand the pathophysiology of PTSD and possibly identify potential targets for treatment. Yet, the meaning of structural differences between individuals, the extent to which they correspond to clinical differences, and whether they signify abnormality have been the subject of growing debate. Such structural differences have been interpreted as marking the presence of PTSD, the traces of exposure to trauma (Ahmed et al., 2012), or the resilience of individuals who have been exposed to trauma but did not develop PTSD (Ohashi et al., 2019).

It has been speculated that PTSD is associated with regionally specific structural changes in the brain, so that the brain of individuals developing PTSD following a traumatic event is different from that of trauma-exposed healthy controls (TEHC) who experience trauma but do not develop PTSD, and of healthy controls (HC) who never experienced trauma (Wang et al., 2021). A meta-analysis comparing individuals with PTSD and controls (both TEHC and HC) identified PTSD markers characterized by smaller volumes of the insula, superior frontal gyrus, temporal gyri, anterior cingulate, rostral anterior cingulate, hippocampus, and amygdala (Bromis et al., 2018). Of these regions, the hippocampus and amygdala received most attention and are considered to play a central role in the pathophysiology of PTSD (Karl et al., 2006; Kitayama et al., 2005; Logue et al., 2018; O'Doherty et al., 2015; Smith, 2005). The hippocampus is implicated in the contextual modulation of behavior and in fear learning and suppression (Garfinkel et al., 2014; Maren et al., 2013), and is sensitive to the effects of elevated glucocorticoids (Sapolsky et al., 2000). The amygdala is interconnected with the hippocampus, especially in the modulation of emotional memory (Phelps, 2004), and is implicated in fear learning and expression (Etkin & Wager, 2007; Paré et al., 1995). Although there are some indications that alteration in the hippocampus and amygdala may serve as markers of PTSD, inconsistencies were found between studies: some reported smaller hippocampus volume in PTSD (Hedges et al., 2003; Morey et al., 2012; Pavić et al., 2007; Villarreal et al., 2002), whereas others did not (Fennema-Notestine et al., 2002; Golier et al., 2005; Jatzko et al., 2006; Pederson et al., 2004; Schuff et al., 2001). Similarly, several studies showed a smaller volume of the amygdala in PTSD (Morey et al., 2012), whereas others found a larger volume (Kuo et al., 2012). In searching for PTSD markers, some studies used longitudinal designs in which structural MRI features and PTSD symptoms were assessed immediately after a traumatic event and again at several follow-up points. These studies have presented some evidence of alteration of the rostral anterior cingulate cortices (Ben-Zion et al., 2020), but not of the hippocampal volume (Bonne et al., 2001), as potential PTSD markers. It has been suggested that an important reason for the inconsistencies across studies is the confounding effect of potential markers of trauma exposure (O'Doherty et al., 2015). If trauma exposure per se changes brain structure, differentiating TEHCs from HCs, different blends of these groups in a given control group may yield different results.

Previous studies exploring the effects of trauma exposure have documented smaller hippocampal (Bromis et al., 2018), insula, and cingulate gyrus (Ahmed et al., 2012) volume in individuals who were exposed to trauma (whether or not they developed PTSD) than in those who were not. Such findings may indicate that exposure to a traumatic event in itself, even if the exposed individual did not develop PTSD, may be associated with structural changes in the brain, specifically with volume reduction in the hippocampus. It has been suggested that at least some of the structural changes following trauma are caused by trauma exposure, rather than clinical-level PTSD (Kühn et al., 2021).

Complementing this line of research, the differences in brain structure between those who were exposed to trauma and developed PTSD and those who did not, have recently prompted studies to focus on markers of resilience in the face of exposure to trauma, comparing PTSD and TEHC participants (Rakesh et al., 2019). Resilience can be defined as the capacity to maintain adaptive functioning in the face of trauma and significant adversity (Charney, 2004; van der Werff et al., 2013). Identifying markers of resilience is of particular interest given that most individuals exposed to trauma do not develop PTSD (Bonanno, 2005). Several studies have found structural differences between those exposed to trauma who did and those who did not develop PTSD (Ohashi et al., 2019; Sun et al., 2018). The most prevalent findings in these studies are greater hippocampal (Gilbertson et al., 2002; Koch et al., 2021), anterior cingulate cortex (ACC) (Woodward et al., 2006), and medial prefrontal cortex (PFC) volume in resilient individuals (Bolsinger et al., 2018; Eckart et al., 2011; Morey et al., 2016). Amygdala (Kuo et al., 2012; Morey et al., 2012, 2016), with the insular cortex volume (Chen et al., 2006; Kasai et al., 2008) were also been identified as potentially signaling resilience (Bolsinger et al., 2018; Dedovic et al., 2009). Yet, results concerning these regions are mixed (Bolsinger et al., 2018).

To shed light on the mixed results of studies searching for structural brain markers of PTSD, trauma exposure, and resilience, it is critical to evaluate their presence while all three are given the opportunity to emerge simultaneously and competitively (Figure 1).

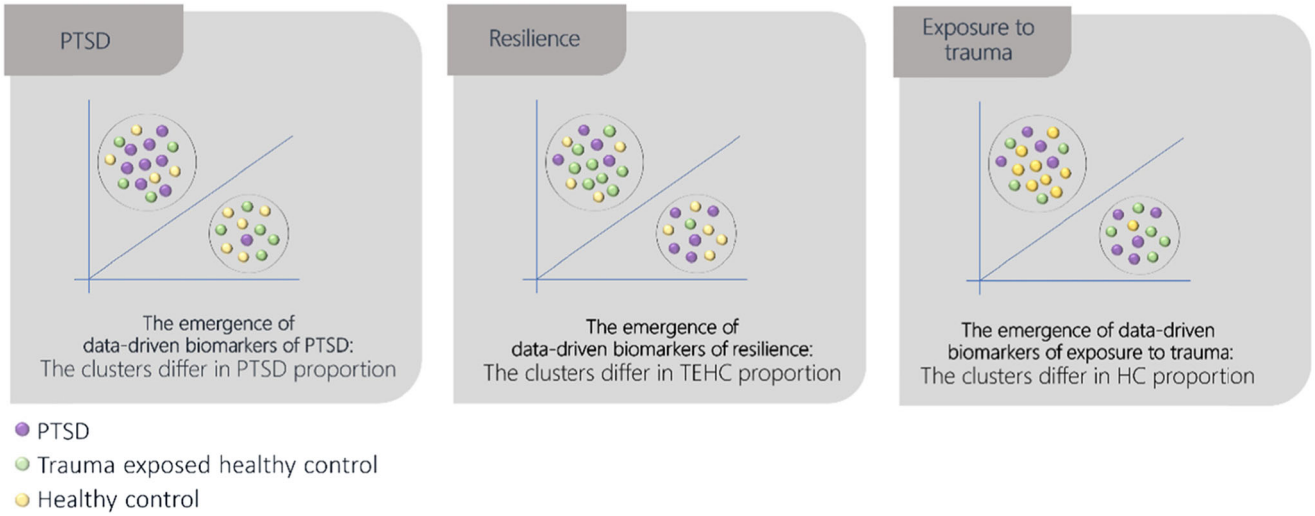

FIGURE 1 A data-driven approach to distinguishing between neurobiological markers of posttraumatic stress disorder (PTSD) versus trauma exposure versus resilience to traumatic events.

Most studies to date focused only on one of the three types of potential markers. For example, studies comparing individuals with PTSD and TEHC cannot detect neurobiological markers of trauma exposure. Similarly, studies comparing individuals with PTSD and HCs cannot disentangle trauma exposure from PTSD diagnosis to identify resilience markers. The fact that most studies compared only three out of the two groups makes it impossible to determine which of the three is most responsible for the variability between individuals that appears in structural MRI (Bolsinger et al., 2018). In addition, most studies that included all three groups performed comparisons between them rather than using data-driven methods to mine heterogeneity by identifying markers. Consequently, these studies produced mixed results, regarding structure abnormalities in the hippocampus (Bremner et al., 2003; H. J. Chen et al., 2020; Fennema-Notestine et al., 2002; Freeman et al., 2006; Golier et al., 2005; Gurvits et al., 1996; Pederson et al., 2004; Winter & Irle, 2004; Zhang et al., 2021), the amygdala (Gurvits et al., 1996; Morey et al., 2016), and the anterior cingulate cortex (Eckart et al., 2011). All three groups (PTSD, TEHC, and HC) need to be scanned and data-driven methods need to be used to allow the three markers to compete against one another.

The present study used a data-driven approach to identify clusters that differ in structural abnormalities in MRI data of PTSD, TEHC, and HC individuals. We focused a priori on regions considered to be implicated in trauma, PTSD, and resilience (Bolsinger et al., 2018): subcortical regions/the limbic system, including the cingulate cortex (posterior cingulate cortex, anterior cingulate cortex; Bremner et al., 2007; Etkin et al., 2011; Karl et al., 2006), accumbens, amygdala (Funayama et al., 2001), caudate, hippocampus (Lyons et al., 2007; Woon et al., 2010), pallidus, putamen, thalamus; cortical regions, including the frontal cortex (caudal middle frontal, lateral orbitofrontal, medial orbitofrontal, superior frontal, rostral middle frontal, pars orbitalis, pars opercularis, pars triangularis; Fonzo et al., 2017; Phelps, Delgado, et al., 2004), and the insula cortex (Manoliu et al., 2014). Based on the literature, we considered three main alternatives (Figure 1), expecting to find, in each case, two data-driven clusters that differ in the proportion of individuals with (a) PTSD, (b) HCs, or (c) THECs, depending on whether the markers most instrumental for understanding structural variability between individuals are those of (a) PTSD, (b) trauma exposure, or (c) resilience, respectively. This setup also allows identifying more than two data-driven clusters, signaling different markers based on the possibilities listed above. For example, both resilience and PTSD markers may emerge. Transdiagnostic clusters may also emerge, which cannot be differentiated by group membership (i.e., showing no differences in PTSD, TEHC, and HC membership)(Romer et al., 2021). Significant differences between the clusters in PTSD symptoms are expected only if a PTSD signature is identified, resulting in two clusters that differ on PTSD proportion, with the PTSD cluster showing more severe symptoms than the non-PTSD cluster. In the case of resilience or trauma exposure signatures, these differences in PTSD symptoms between the two clusters are not expected because different rates of HC or TEHC individuals are not expected to meaningfully affect symptoms level.

2 | METHODS

2.1 | Participants

We combined data from two studies conducted at the New York State Psychiatric Institute (NYSPI) and approved by the NYSPI Institutional Review Board, with all participants providing written informed consent after receiving an explanation of the procedures. After the exclusion of 10 participants who failed the imaging quality control check, the analyses were based on a total of 129 individuals who underwent MRI scanning: 46 with PTSD, 49 TEHC, and 34 HC.

Of those, 83 were scanned with a GE 750, and 47 with a GE Signa because of technical constraints (scanner upgrading) at the MRI center. Detailed inclusion and exclusion criteria for each study appear in Table S1. Briefly, all participants in the PTSD and TEHC, but not the HC, met DSM criterion A for adult traumatic events. Clinical evaluators administered the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1996) and the Clinician-Administered PTSD Scale (CAPS) (Weathers et al., 2001). Exclusion criteria for participants in the TEHC and HC groups consisted of current or past Axis I disorders, including substance use disorders and the use of any psychotropic medications. Exclusion criteria for all groups included any condition that would rule out MRI scanning.

2.2 | Neuroimaging

We obtained a structural T1 image (TE/TR = 3 ms/6.5 ms, TI = 450 ms, flip angle = 12°, voxel size=1 × 1 × 1 mm, 180 contiguous slices, total acquisition time =4 min) for all participants. We obtained subcortical volumetric and cortical surface measurements from T1 weighted scans using Freesurfer 6.0. Reconstructed images were visually inspected for quality control by a well-trained research assistant. The technical details of the freesurfer pipeline have been described extensively in previous publications (Fischl et al., 1999). Briefly, using the standard freesurfer processing pipeline (Reuter et al., 2010), we performed motion correction, skull stripping, Talairach transformation, segmentation of the subcortical white matter and gray matter volumetric structures (Fischl et al., 2002), correction of the topology of cortical surfaces, and intensity normalization. Region of interest (ROI)-specific cortical thickness, surface area, and volume measures were extracted from the automated anatomical parcellation, using the Desikan-Killiany Atlas (Desikan et al., 2006) for cortical ROIs and the aseg atlas for subcortical ROIs. This process created 68 ROIs, of which we a priori selected a set of 29 T1 features, based on the literature (see above) (Bolsinger et al., 2018). Consistent with the literature, for cortical regions, the measure of cortical volume was broken down into the separate and almost orthogonal components of cortical thickness and surface area. Thickness measures may provide indication of underlying neuronal loss, reduced size of neuronal cell bodies, or degradation; surface area measures may reflect underlying white matter fibers (Van Essen, 1997), where tension or shrinkage of these fibers leads to deeper sulci and extended area measures.

2.3 | Overview of statistical analyses

We conducted a set of multiple linear regressions to adjust all a priori selected 29 T1 features for age, sex, and estimated intracranial volume (eTIV). This procedure resulted in 29 residual scores (also referred to as adjusted features), to be used in further analysis. Positive values of adjusted features mean higher scores than what can be anticipated based on age, sex, and eTIV. To divide individuals into homogeneous clusters according to common neuroimaging-based characteristics, we used an unsupervised machine learning algorithm, based on the k-means clustering method, developed by Hartigan and Wong (1979). K-means clustering seeks to identify clusters in which the total within-cluster variation is minimized. Total within-cluster variation is defined as the sum of squared Euclidean distances between items and the corresponding centroid. Each observation is assigned to a given cluster in such a way that the sum of squared distances of the observation to their assigned cluster centers is minimized. The K-means clustering method was chosen because of its many advantages, including the fact that it is not model-based and applies optimization algorithms to define patient assignment to clusters (Wu, 2012; Yuan & Yang, 2019). We implemented the k-means clustering on the 29 adjusted features, and used the average silhouette method to determine the optimal number of clusters that best fit the data (Rousseeuw, 1987), which computes the average silhouette of observations for different values of k. The optimal number of clusters k is the one that maximizes the average silhouette over a range of possible values for k. We used the R function *kmeans* in package *stat* for clustering.

We used the following three steps to characterize the clusters and identify the features that best differentiate between them: (a) we conducted a two-sample *t*-test to compare the two clusters on demographic and clinical characteristics; (b) we performed importance analyses using the random forest R package (mean decrease GINI) (Archer & Kimes, 2008) to identify the top 10 T1 features that best differentiate between clusters; and (c) we built a classification tree using the party R package (Maechler et al., 2013) to predict cluster membership. We built a *machine learning classification tree analysis*, using random forest variable selection and Monte Carlo simulation for multiple testing adjustment (Strasser & Weber, 1999).

To assess robustness and consistency within this sample, we cross-validated the procedure described above using the validation set approach (Hastie et al., 2009). In this method, the data set is divided randomly into training and validation sets. The number of clusters is determined by the silhouette results. Next, we identified the determined number of k-means clusters for each training sample, and built classification trees for that number of clusters. The training sample is based on P = 20%, 30%, …, 90% of all participants. We used the data of the other individuals (P − 100%) as a validation sample to classify them to the new clusters based on the newly created classification tree.

3 | RESULTS

3.1 | Demographic and clinical characteristics

As shown in Table S2, the three groups did not differ in age, race, and sex. The PTSD and the TEHC groups did not differ in age at trauma (exact age or childhood vs. adult trauma), time since trauma, or severity. As expected, the three groups differed in PTSD and depression symptom severity.

3.2 | Cluster identification

The average silhouette method suggested that two clusters best fit the data (Figure S1). Two clusters were identified using the k-means clustering method: Cluster 1 ($N = 51$) and Cluster 2 ($N = 78$). Two-sample *t*-test analyses suggested that the two clusters did not differ in the proportion of PTSD (Table 1), providing no support for PTSD markers. Similarly, the two clusters did not differ in the proportion of HC, providing no support for trauma exposure markers. By contrast, the two clusters significantly differed in the proportion of TEHC, with Cluster 2 having a higher proportion of TEHCs, suggesting markers of resilience in the face of trauma.

3.3 | Cluster robustness and consistency

For each percentage $P = (20\%, 30\% \ldots 90\%)$ of all participants to be used as a training sample, the other $(100 - P)\%$ of individuals were used as a validation sample, and were classified as the new clusters based on the newly created classification tree. Table S3 presents the mean percentage (and 95% confidence interval [CI]) of individuals classified by the smaller trees (of the validation set) into the original clusters built from the full data. For example, when the algorithm was applied to a training set of 40% of the individuals, 87% of the validation sample was classified as the original clusters (on average). Table S3 suggests that the clusters are robust and consistent within the sample.

3.4 | Cluster characteristics

The clusters differed significantly in the volume of 21 of the selected 29 T1 features (Figures 2 and 3 and Table S4) so that for the vast majority of the features, Cluster 2 (high resilience) had a higher volume than Cluster 1 (low resilience). In Cluster 2 (high resilience), the scores had a positive value, suggesting that they were higher than what can be anticipated based on eTIV, sex, and age. Next, we examined the importance of the 29 residual features that were used

TABLE 1 Proportion of TEHC, PTSD, and HC in Cluster 1 (low resilience) and Cluster 2 (high resilience)

	Cluster 1 (low resilience; $N = 51$)	Cluster 2 (high resilience; $N = 78$)	Z	Effect size h	Significance (p value)
TEHC	13 (25.5%)	36 (46.2%)	−2.36	0.44	.018
PTSD	20 (39.2%)	26 (33.3%)	0.83	0.12	.40
HC	18 (35.3%)	16 (20.5%)	1.99	0.33	.05

Note: Z = Z-score test for proportion comparison between two groups. Effect size h = Cohen's h effect size, 0.2-small; 0.5-medium, 0.8-large.
Abbreviations: HC, healthy controls; PTSD, posttraumatic stress disorder TEHC, trauma-exposed healthy controls.

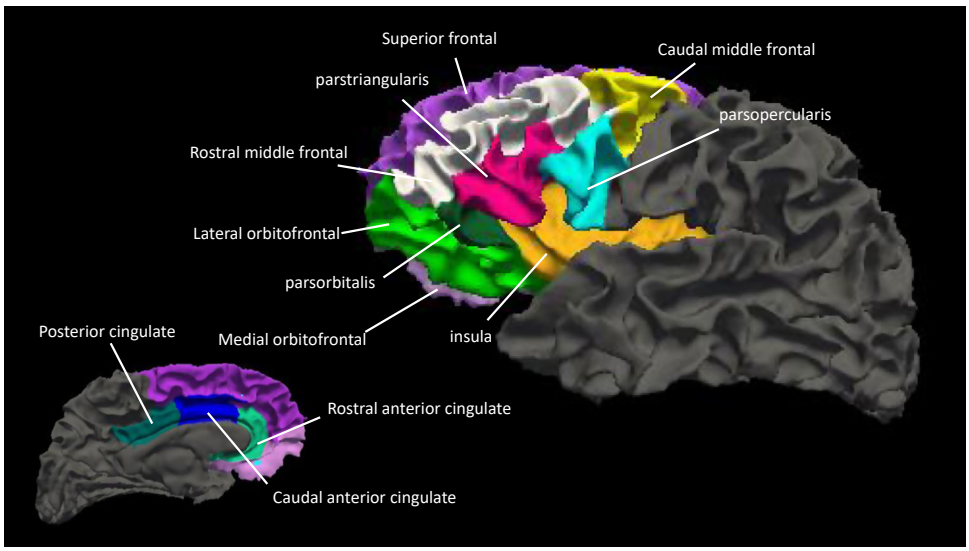

FIGURE 2 Brain maps of the structural differences between the two clusters. Posterior cingulate (blue green), rostral anterior cingulate (light green), and caudal anterior cingulate (blue) are shown at the bottom left figure. Superior frontal (violet), pars triangularis (red), rostral middle frontal (white), lateral orbitofrontal (light green), pars orbitalis (green), medial orbitofrontal (mauve), insula (orange), caudal middle frontal (yellow), and pars opercularis (light blue) are shown in the figure to the right.

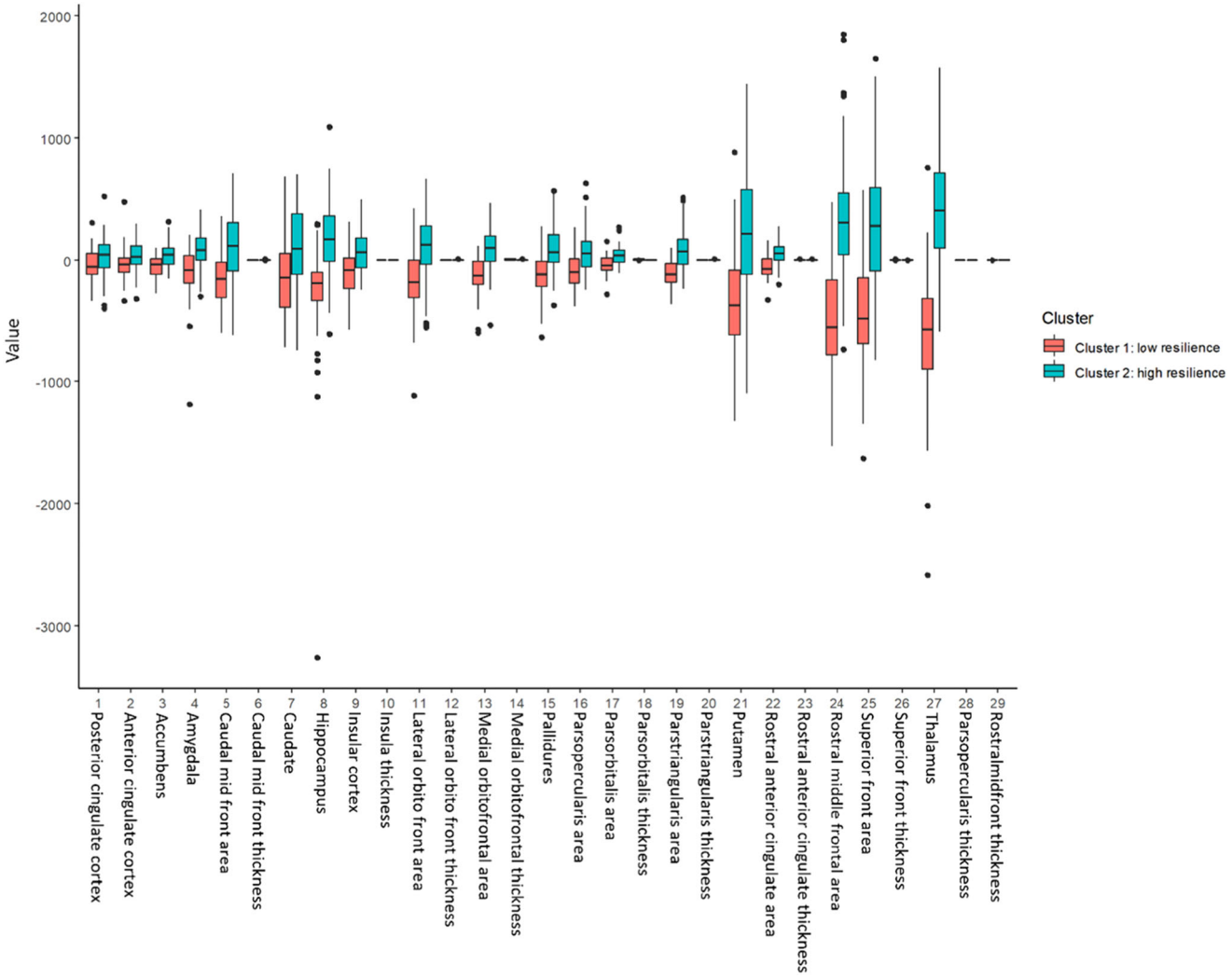

FIGURE 3 A box plot of the structural differences between the two clusters.

for building the clusters, employing a mean decrease importance index (GINI). The 10 most significant features differentiating between the clusters appear in Figure S2, and the top five include the thalamus (importance = 12.96), the rostral middle frontal gyrus area (importance = 6.51), the hippocampus (importance = 5.21), the superior frontal gyrus area (importance = 4.70), and the pars triangularis area (importance = 3.60).

To further crystalize the features contributing most to differentiating between the two clusters, we conducted a classification tree analysis. The results of the classification tree indicate a significant split in the thalamus, with individuals scoring −232.7 or less showing a higher tendency to be in Cluster 1. By contrast, individuals with a score greater than −232.7 and a rostral middle frontal gyrus area > −490 showed a higher tendency to be in Cluster 2 (Figure S3).

Table 2 presents the sample demographic and clinical characteristics by clusters, showing that the clusters cannot be discriminated based on trauma characteristics (age, time since trauma, and severity of trauma) or by clinical characteristics (CAPS, HAM-D). Clusters cannot be differentiated either by most of the demographic characteristics (sex, education), with the exception of proportion of White race. These findings support the unique contribution of the structural markers differentiating those with high versus low resilience in the face of trauma.

3.5 | Sensitivity analyses

Repeating our analysis with the latent class analysis (LCA) approach resulted in similar findings. The optimal LCA solution yielded two clusters. To investigate the extent to which these clusters are similar to those obtained using the k-means, we compared the patient groupings derived independently by the two methods to investigate patterns of commonality and dissimilarity. Next, we checked the overlap between grouping methods. We found that 85% of patients defined as Cluster 2 in LCA were also defined as high resilience by k-means. In Cluster 1, there was 83% agreement between the two methods. The two clusters obtained by the LCA also showed a significantly different proportion of TEHC, with 13 individuals in the low-resilience and 36 in the high-resilience cluster.

TABLE 2 Demographics by clusters

	N	Cluster 1 (low resilience; N = 51)	Cluster 2 (high resilience; N = 78)	T(df)/χ(df)	Effect size	Significance (p value)
Race	129			8.9(3)	0.24	.028
	Asian	1 (1.96%)	5 (6.41%)			
	Black	27 (52.9%)	32 (41.0%)			
	Other	13 (25.5%)	10 (12.8%)			
	White	10 (19.6%)	31 (39.7%)			
Education	117	14.9 (2.79)	14.7 (2.43)	0.4 (89)	0.07	.71
Childhood versus adult trauma	77			4.1 (2)	0.19	.337
	Adult	17 (65.4%)	40 (78.4%)			
	Childhood	9 (34.6%)	11 (21.6%)			
Sex	129			0.0 (1)	0.00	1
	F	23 (45.1%)	35 (44.9%)			
	M	28 (54.9%)	43 (55.1%)			
Age	129	37.9 (13.6)	38.5 (11.1)	−0.3 (92)	0.05	.769
Scanner	129			0.9 (3)	0.08	.436
Trauma age	60	17.5 (4.93)	20.8 (22.0)	−0.9 (57)	0.20	.342
Trauma duration	43	8.38 (20.9)	26.5 (73.6)	−1.3(39	0.33	.218
Trauma severity	64	1.13 (0.35)	1.29 (0.54)	−1.3 (36)	0.35	.209
CAPS	108	18.7 (16.6)	17.0 (16.9)	0.5(77)	0.10	.61
HAM-D	128	6.60 (8.84)	6.88 (7.83)	−0.2(95)	−0.04	.853

Note: Categorical variables were compared using the χ^2 test. Continuous variables were compared using two sample *t*-tests. Two sample *t*-test effect sizes: Cohen's *d* effect size, 0.1-small; 0.5-medium, 0.8-large. χ^2 test effect size: Cohen's *w* effect size, 0.1-small; 0.3-medium, 0.5-large.
Abbreviation: CAPS, Clinician-Administered PTSD Scale.

4 | DISCUSSION

The present study used a data-driven approach to unravel the effect of trauma exposure, PTSD, and resilience, and explore which markers receive the most support in a sample that includes PTSD, TEHC, and HC groups. This enabled the different neurobiological markers to compete with one another. The findings support the presence of neurobiological markers of resilience, distinguishing between two clusters that differed in the proportion of individuals who were exposed to trauma but did not develop PTSD. Specifically, one cluster, the high-resilience cluster, had 1.8 times more trauma-exposed healthy controls than did the low-resilience cluster.

The two emerging clusters were found to be robust, consistent within the sample and across two distinct clustering approaches, and to differ significantly in the volume of critical features previously identified as implicated in PTSD and trauma exposure. Specifically, the high-resilience cluster was characterized by larger volumes in the thalamus, the hippocampus, and the PFC than was the low-resilience cluster. Critically, demographic, clinical, and other characteristics were not sufficient to distinguish between the two clusters. The only exception was race, for which, consistent with the literature, the high-resilience cluster showed a high proportion of white race (Shonkoff et al., 2021). Trauma characteristics (age, duration, and severity) failed to differentiate between the two clusters. These findings attest to the importance of structural differences in distinguishing those showing high versus low resilience in the face of trauma. The findings are partially consistent with another study identifying data-driven subgroups in recent trauma survivors using structural measures, which stressed the importance of the rostral anterior cingulate cortices (Ben-Zion et al., 2020). Conversely, the findings diverge from those of studies that focused on task-based activation rather than on structural measures (Kundu et al., 2021; Sellnow et al., 2020).

The five most significant features differentiating between the clusters are consistent with accumulating literature, being implicated in confronting trauma (Bromis et al., 2018; Karl et al., 2006; Kitayama et al., 2005; O'Doherty et al., 2015; Ohashi et al., 2019; Smith, 2005; Woon et al., 2010): the thalamus, the rostral middle frontal gyrus area, the hippocampus, the superior frontal gyrus area, and the pars triangularis area. For example, reduced volume of the hippocampus is

commonly perceived as a generalized marker of mental health disorders and is associated with chronic hypercortisolemia (Axelson et al., 1993; Bremner et al., 1995) and with neurocognitive deficits, such as poor memory performance (Scott et al., 2015; Stricker et al., 2017). Furthermore, reduced volume in the thalamus, the hippocampus, and the PFC, all involved in relaying sensory information, memory (Halassa & Kastner, 2017), and executive functions (Ouhaz et al., 2018; Tanji & Hoshi, 2008), has been associated with PTSD (O'Doherty et al., 2017). This pattern suggests that the neurobiological markers of resilience may involve efficacious cognitive control and sensory and memory processing, allowing for spontaneous recovery following trauma. Future studies should investigate the association between sensory processing and resilience. More efficacious sensory processing may promote resilience through heightened glucose metabolism in the anterior insula regions (Jeong et al., 2019), and less resilience may be associated with an increased risk of sensory processing deficits (Yochman & Pat-Horenczyk, 2020).

Whereas the vast majority of areas showed a larger volume in the high–than in the low-resilience cluster, two of the 21 areas showing significant differences between the two clusters indicated a smaller volume in the high-resilience cluster: the medial-orbito frontal and the rostral anterior cingulate. This finding is consistent with previous reports of decreased cortical thickness and volume in rostral anterior cingulate cortex in remitters following prolonged exposure treatment (Helpman, Papini, et al., 2016) and decreased post-treatment activation in these regions, compared with pretreatment, during a fear extinction recall task (Helpman, Marin, et al., 2016).

The findings demonstrate the potential of data-driven approaches to contribute new insights about the alterations associated with the neurobiology of resilience (Neria, 2021). The main limitation of the present study lies in its small sample size. Therefore, we cannot exclude the possibility that additional types of neurobiological markers may be identified in larger samples, where significant differences may emerge in HC proportion as well. If future longitudinal studies support the existence of two clusters that meaningfully differ in both HC and TEHC proportion, two potential explanations can be offered. First, if resilience develops as a result of exposure to trauma, it may suggest that in the face of trauma both a trauma signature and a potential signature of growth may be apparent. Second, if resilience to trauma exists irrespective of trauma exposure, several HC individuals may not be resilient and could develop PTSD following exposure to future traumatic events. Furthermore, it is not clear whether the resilience cluster represents general resilience against stressors (a genetic predisposition), so that the same characteristics may protect individuals from other mental health disorders, such as depressive ones (Bromis et al., 2018), or specific protective qualities against traumatic events. Third, although some studies sought to demonstrate causality (Gilbertson et al., 2002; Kasai et al., 2008; Kremen et al., 2012; Kühn et al., 2021), in the present study it is not possible to determine whether the volumetric differences between the clusters preceded the trauma exposure or were acquired as the result of confronting trauma without developing PTSD. The differences between the clusters in race may reflect the way in which social determinants of mental health may shape health inequalities, for example by causing added risk, then leading to lower resilience (Alegría et al., 2018; Bailey, 2015). This is consistent with the concept of the "social gradient," according to which individuals from certain groups in society face greater health risks and lower life expectancy than those from other groups. Finally, future studies should explore which neuroimaging markers emerge when using multimodal neuroimaging features (Kundu et al., 2021).

5 | CONCLUSION

The findings suggest the existence of resilience neurobiological markers, defined as high levels of TEHC in the face of trauma, characterized by a higher volume in structural features previously shown to be implicated in PTSD. Distinguishing between the brains of those developing PTSD following trauma and those showing resilience can shed light on the neurobiology of resilience and indicate which populations are less at risk when determining profiles of individuals for serving in special units to be deployed in a war zone.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Sigal Zilcha-Mano http://orcid.org/0000-0002-5645-4429
Amit Lazarov http://orcid.org/0000-0002-2811-2739
Bret R. Rutherford https://orcid.org/0000-0002-4660-119X

REFERENCES

Ahmed, F., Spottiswoode, B. S., Carey, P. D., Stein, D. J., & Seedat, S. (2012). Relationship between neurocognition and regional brain volumes in traumatized adolescents with and without posttraumatic stress disorder. *Neuropsychobiology*, *66*(3), 174–184.

Alegría, M., NeMoyer, A., Falgàs Bagué, I., Wang, Y., & Alvarez, K. (2018). Social determinants of mental health: Where we are and where we need to go. *Current Psychiatry Reports*, *20*(11), 1–13.

Archer, K. J., & Kimes, R. v (2008). Empirical characterization of random forest variable importance measures. *Computational Statistics & Data Analysis*, *52*(4), 2249–2260.

Axelson, D. A., Doraiswamy, P. M., McDonald, W. M., Boyko, O. B., Tupler, L. A., Patterson, L. J., Nemeroff, C. B., Ellinwood, Jr., E. H., & Krishnan, K. R. R. (1993). Hypercortisolemia and hippocampal changes in depression. *Psychiatry Research*, *47*(2), 163–173.

Bailey, R. K. (2015). The Social Determinants of Mental Health. *American Journal of Psychiatry*, *172*, 913–914.

Ben-Zion, Z., Zeevi, Y., Keynan, N. J., Admon, R., Kozlovski, T., Sharon, H., Halpern, P., Liberzon, I., Shalev, A. Y., & Benjamini, Y. (2020). Multi-domain potential biomarkers for post-traumatic stress disorder (PTSD) severity in recent trauma survivors. *Translational Psychiatry*, *10*(1), 1–11.

Bolsinger, J., Seifritz, E., Kleim, B., & Manoliu, A. (2018). Neuroimaging correlates of resilience to traumatic events—A comprehensive review. *Frontiers in Psychiatry*, *9*, 693.

Bonanno, G. A. (2005). Resilience in the face of potential trauma. *Current Directions in Psychological Science*, *14*(3), 135–138.

Bonne, O., Brandes, D., Gilboa, A., Gomori, J. M., Shenton, M. E., Pitman, R. K., & Shalev, A. Y. (2001). Longitudinal MRI study of

hippocampal volume in trauma survivors with PTSD. *American Journal of Psychiatry*, *158*(8), 1248–1251.

Bremner, J. D., Elzinga, B., Schmahl, C., & Vermetten, E. (2007). Structural and functional plasticity of the human brain in posttraumatic stress disorder. *Progress in Brain Research*, *167*, 171–186.

Bremner, J. D., Randall, P., Scott, T. M., Bronen, R. A., Seibyl, J. P., Southwick, S. M., Delaney, R. C., McCarthy, G., Charney, D. S., & Innis, R. B. (1995). MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *The American Journal of Psychiatry*, *152*(7), 973–981.

Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Nazeer, A., Khan, S., Vaccarino, L. V., Soufer, R., & Garg, P. K. (2003). MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *American Journal of Psychiatry*, *160*(5), 924–932.

Bromis, K., Calem, M., Reinders, A. A. T. S., Williams, S. C. R., & Kempton, M. J. (2018). Meta-analysis of 89 structural MRI studies in posttraumatic stress disorder and comparison with major depressive disorder. *American Journal of Psychiatry*, *175*(10), 989–998.

Charney, D. S. (2004). Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *American Journal of Psychiatry*, *161*(2), 195–216.

Chen, H. J., Qi, R., Ke, J., Qiu, J., Xu, Q., Zhong, Y., Lu, G. M., & Chen, F. (2020). Evaluation of gray matter reduction in patients with typhoon-related posttraumatic stress disorder using causal network analysis of structural MRI. Psychological Medicine, 1–10.

Chen, S., Xia, W., Li, L., Liu, J., He, Z., Zhang, Z., Yan, L., Zhang, J., & Hu, D. (2006). Gray matter density reduction in the insula in fire survivors with posttraumatic stress disorder: A voxel-based morphometric study. *Psychiatry Research: Neuroimaging*, *146*(1), 65–72.

Dedovic, K., D'Aguiar, C., & Pruessner, J. C. (2009). What stress does to your brain: A review of neuroimaging studies. *The Canadian Journal of Psychiatry*, *54*(1), 6–15.

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., & Hyman, B. T. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980.

Eckart, C., Stoppel, C., Kaufmann, J., Tempelmann, C., Hinrichs, H., Elbert, T., Heinze, H.-J., & Kolassa, I.-T. (2011). Structural alterations in lateral prefrontal, parietal and posterior midline regions of men with chronic posttraumatic stress disorder. *Journal of Psychiatry & Neuroscience: JPN*, *36*(3), 176–186.

Essen, D. C. V. (1997). A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature*, *385*(6614), 313–318.

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, *15*(2), 85–93.

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry*, *164*(10), 1476–1488.

Fennema-Notestine, C., Stein, M. B., Kennedy, C. M., Archibald, S. L., & Jernigan, T. L. (2002). Brain morphometry in female victims of intimate partner violence with and without posttraumatic stress disorder. *Biological Psychiatry*, *52*(11), 1089–1101.

First, M. B., Spitzer, R., Gibbon, M., & Williams, J. (1996). *Structured clinical interview for DSM-IV axis I disorders research version (SCID-I). Biometrics Research, New York State Psychiatric Institute*. SCID-I/P

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., & Klaveness, S. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355.

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis: II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage*, *9*(2), 195–207.

Fonzo, G. A., Goodkind, M. S., Oathes, D. J., Zaiko, Y. v, Harvey, M., Peng, K. K., Weiss, M. E., Thompson, A. L., Zack, S. E., & Lindley, S. E. (2017). PTSD psychotherapy outcome predicted by brain activation during emotional reactivity and regulation. *American Journal of Psychiatry*, *174*(12), 1163–1174.

Freeman, T., Kimbrell, T., Booe, L., Myers, M., Cardwell, D., Lindquist, D. M., Hart, J., & Komoroski, R. A. (2006). Evidence of resilience: neuroimaging in former prisoners of war. *Psychiatry Research: Neuroimaging*, *146*(1), 59–64.

Funayama, E. S., Grillon, C., Davis, M., & Phelps, E. A. (2001). A double dissociation in the affective modulation of startle in humans: Effects of unilateral temporal lobectomy. *Journal of Cognitive Neuroscience*, *13*(6), 721–729.

Garfinkel, S. N., Abelson, J. L., King, A. P., Sripada, R. K., Wang, X., Gaines, L. M., & Liberzon, I. (2014). Impaired contextual modulation of memories in PTSD: An fMRI and psychophysiological study of extinction retention and fear renewal. *Journal of Neuroscience*, *34*(40), 13435–13443.

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., & Pitman, R. K. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience*, *5*(11), 1242–1247.

Golier, J. A., Yehuda, R., de Santi, S., Segal, S., Dolan, S., & de Leon, M. J. (2005). Absence of hippocampal volume differences in survivors of the Nazi holocaust with and without posttraumatic stress disorder. *Psychiatry Research: Neuroimaging*, *139*(1), 53–64.

Gurvits, T. v, Shenton, M. E., Hokama, H., Ohta, H., Lasko, N. B., Gilbertson, M. W., Orr, S. P., Kikinis, R., Jolesz, F. A., & McCarley, R. W. (1996). Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biological Psychiatry*, *40*(11), 1091–1099.

Halassa, M. M., & Kastner, S. (2017). Thalamic functions in distributed cognitive control. *Nature Neuroscience*, *20*(12), 1669–1679.

Hartigan, J. A., & Wong, M. A. (1979). Algorithm AS 136: A k-means clustering algorithm. *Journal of the Royal Statistical Society. Series c (Applied Statistics)*, *28*(1), 100–108.

Hastie, T., Tibshirani, R., & Friedman, J. (2009). *The elements of statistical learning* (p. 33). Springer.

Hedges, D. W., Allen, S., Tate, D. F., Thatcher, G. W., Miller, M. J., Rice, S. A., Cleavinger, H. B., Sood, S., & Bigler, E. D. (2003). Reduced hippocampal volume in alcohol and substance naive Vietnam combat veterans with posttraumatic stress disorder. *Cognitive and Behavioral Neurology*, *16*(4), 219–224.

Helpman, L., Marin, M.-F., Papini, S., Zhu, X. I., Sullivan, G. M., Schneier, F., Neria, M., Shvil, E., Aragon, M. J. M., & Markowitz, J. C. (2016). Neural changes in extinction recall following prolonged exposure treatment for PTSD: A longitudinal fMRI study. *NeuroImage: Clinical*, *12*, 715–723.

Helpman, L., Papini, S., Chhetry, B. T., Shvil, E., Rubin, M., Sullivan, G. M., Markowitz, J. C., Mann, J. J., & Neria, Y. (2016). PTSD remission after prolonged exposure treatment is associated with anterior cingulate cortex thinning and volume reduction. *Depression and Anxiety*, *33*(5), 384–391.

Jatzko, A., Rothenhöfer, S., Schmitt, A., Gaser, C., Demirakca, T., Weber-Fahr, W., Wessa, M., Magnotta, V., & Braus, D. F. (2006). Hippocampal volume in chronic posttraumatic stress disorder (PTSD): MRI study using two different evaluation methods. *Journal of Affective Disorders*, *94*(1–3), 121–126.

Jeong, H., Chung, Y.-A., Ma, J., Kim, J., Hong, G., Oh, J. K., Kim, M., Ha, E., Hong, H., & Yoon, S. (2019). Diverging roles of the anterior insula in trauma-exposed individuals vulnerable or resilient to posttraumatic stress disorder. *Scientific Reports*, *9*(1), 1–8.

Karl, A., Schaefer, M., Malta, L. S., Dörfel, D., Rohleder, N., & Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience & Biobehavioral Reviews*, *30*(7), 1004–1031.

Kasai, K., Yamasue, H., Gilbertson, M. W., Shenton, M. E., Rauch, S. L., & Pitman, R. K. (2008). Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. *Biological Psychiatry*, *63*(6), 550–556.

Kitayama, N., Vaccarino, V., Kutner, M., Weiss, P., & Bremner, J. D. (2005). Magnetic resonance imaging (MRI) measurement of hippocampal volume in posttraumatic stress disorder: A meta-analysis. *Journal of Affective Disorders*, *88*(1), 79–86.

Koch, S. B. J., van Ast, V. A., Kaldewaij, R., Hashemi, M. M., Zhang, W., Klumpers, F., & Roelofs, K. (2021). Larger dentate gyrus volume as predisposing resilience factor for the development of trauma-related symptoms. *Neuropsychopharmacology*, *46*(7), 1283–1292.

Kremen, W. S., Koenen, K. C., Afari, N., & Lyons, M. J. (2012). Twin studies of posttraumatic stress disorder: Differentiating vulnerability factors from sequelae. *Neuropharmacology*, *62*(2), 647–653.

Kühn, S., Butler, O., Willmund, G., Wesemann, U., Zimmermann, P., & Gallinat, J. (2021). The brain at war: Effects of stress on brain structure in soldiers deployed to a war zone. *Translational Psychiatry*, *11*(1), 1–9.

Kundu, S., Ming, J., & Stevens, J. (2021). Developing multimodal dynamic functional connectivity as a neuroimaging biomarker. *Brain Connectivity*, *11*, 529–542.

Kuo, J. R., Kaloupek, D. G., & Woodward, S. H. (2012). Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: A cross-sectional study. *Archives of General Psychiatry*, *69*(10), 1080–1086.

Logue, M. W., van Rooij, S. J. H., Dennis, E. L., Davis, S. L., Hayes, J. P., Stevens, J. S., Densmore, M., Haswell, C. C., Ipser, J., & Koch, S. B. J. (2018). Smaller hippocampal volume in posttraumatic stress disorder: A multisite ENIGMA-PGC study: subcortical volumetry results from posttraumatic stress disorder consortia. *Biological Psychiatry*, *83*(3), 244–253.

Lyons, D. M., Parker, K. J., Zeitzer, J. M., Buckmaster, C. L., & Schatzberg, A. F. (2007). Preliminary evidence that hippocampal volumes in monkeys predict stress levels of adrenocorticotropic hormone. *Biological Psychiatry*, *62*(10), 1171–1174.

Maechler, M., Rousseeuw, P., Struyf, A., Hubert, M., & Hornik, K. (2013). *Cluster Analysis Basics and Extensions. R package version 1.14. 4. CRAN*.

Manoliu, A., Meng, C., Brandl, F., Doll, A., Tahmasian, M., Scherr, M., Schwerthöffer, D., Zimmer, C., Förstl, H., & Bäuml, J. (2014). Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. *Frontiers in Human Neuroscience*, *7*, 930.

Maren, S., Phan, K. L., & Liberzon, I. (2013). The contextual brain: implications for fear conditioning, extinction and psychopathology. *Nature Reviews Neuroscience*, *14*(6), 417–428.

Morey, R. A., Gold, A. L., LaBar, K. S., Beall, S. K., Brown, V. M., Haswell, C. C., Nasser, J. D., Wagner, H. R., & McCarthy, G. (2012). Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. *Archives of General Psychiatry*, *69*(11), 1169–1178.

Morey, R. A., Haswell, C. C., Hooper, S. R., & de Bellis, M. D. (2016). Amygdala, hippocampus, and ventral medial prefrontal cortex volumes differ in maltreated youth with and without chronic posttraumatic stress disorder. *Neuropsychopharmacology*, *41*(3), 791–801.

Neria, Y. (2021). Functional neuroimaging in PTSD: from discovery of underlying mechanisms to addressing diagnostic heterogeneity. *American Journal of Psychiatry*, *178*(2), 128–135.

O'Doherty, D. C. M., Chitty, K. M., Saddiqui, S., Bennett, M. R., & Lagopoulos, J. (2015). A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. *Psychiatry Research: Neuroimaging*, *232*(1), 1–33.

O'Doherty, D. C. M., Tickell, A., Ryder, W., Chan, C., Hermens, D. F., Bennett, M. R., & Lagopoulos, J. (2017). Frontal and subcortical grey matter reductions in PTSD. *Psychiatry Research: Neuroimaging*, *266*, 1–9.

Ohashi, K., Anderson, C. M., Bolger, E. A., Khan, A., McGreenery, C. E., & Teicher, M. H. (2019). Susceptibility or resilience to maltreatment can be explained by specific differences in brain network architecture. *Biological Psychiatry*, *85*(8), 690–702.

Ouhaz, Z., Fleming, H., & Mitchell, A. S. (2018). Cognitive functions and neurodevelopmental disorders involving the prefrontal cortex and mediodorsal thalamus. *Frontiers in Neuroscience*, *12*, 33.

Paré, D., Smith, Y., & Paré, J.-F. (1995). Intra-amygdaloid projections of the basolateral and basomedial nuclei in the cat: *Phaseolus vulgaris*-leucoagglutinin anterograde tracing at the light and electron microscopic level. *Neuroscience*, *69*(2), 567–583.

Pavić, L., Gregurek, R., Radoš, M., Brkljačić, B., Brajković, L., Šimetin-Pavić, I., Ivanac, G., Pavliša, G., & Kalousek, V. (2007). Smaller right hippocampus in war veterans with posttraumatic stress disorder. *Psychiatry Research: Neuroimaging*, *154*(2), 191–198.

Pederson, C. L., Maurer, S. H., Kaminski, P. L., Zander, K. A., Peters, C. M., Stokes-Crowe, L. A., & Osborn, R. E. (2004). Hippocampal volume and memory performance in a community-based sample of women with posttraumatic stress disorder secondary to child abuse. *Journal of Traumatic Stress: Official Publication of The International Society for Traumatic Stress Studies*, *17*(1), 37–40.

Phelps, E. A. (2004). Human emotion and memory: Interactions of the amygdala and hippocampal complex. *Current Opinion in Neurobiology*, *14*(2), 198–202.

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, *43*(6), 897–905.

Rakesh, G., Morey, R. A., Zannas, A. S., Malik, Z., Marx, C. E., Clausen, A. N., Kritzer, M. D., & Szabo, S. T. (2019). Resilience as a translational endpoint in the treatment of PTSD. *Molecular Psychiatry*, *24*(9), 1268–1283.

Reuter, M., Rosas, H. D., & Fischl, B. (2010). Highly accurate inverse consistent registration: A robust approach. *NeuroImage*, *53*(4), 1181–1196.

Romer, A. L., Elliott, M. L., Knodt, A. R., Sison, M. L., Ireland, D., Houts, R., Ramrakha, S., Poulton, R., Keenan, R., & Melzer, T. R. (2021). Pervasively thinner neocortex as a transdiagnostic feature of general psychopathology. *American Journal of Psychiatry*, *178*(2), 174–182.

Rousseeuw, P. J. (1987). Silhouettes: A graphical aid to the interpretation and validation of cluster analysis. *Journal of Computational and Applied Mathematics*, *20*, 53–65.

Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, *21*(1), 55–89.

Schuff, N., Neylan, T. C., Lenoci, M. A., Du, A.-T., Weiss, D. S., Marmar, C. R., & Weiner, M. W. (2001). Decreased hippocampal N-acetylaspartate in the absence of atrophy in posttraumatic stress disorder. *Biological Psychiatry*, *50*(12), 952–959.

Scott, J. C., Matt, G. E., Wrocklage, K. M., Crnich, C., Jordan, J., Southwick, S. M., Krystal, J. H., & Schweinsburg, B. C. (2015). A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychological Bulletin*, *141*(1), 105–140.

Sellnow, K., Sartin-Tarm, A., Ross, M. C., Weaver, S., & Cisler, J. M. (2020). Biotypes of functional brain engagement during emotion processing differentiate heterogeneity in internalizing symptoms and interpersonal violence histories among adolescent girls. *Journal of Psychiatric Research*, *121*, 197–206.

Shonkoff, J. P., Slopen, N., & Williams, D. R. (2021). Early childhood adversity, toxic stress, and the impacts of racism on the foundations of health. *Annual Review of Public Health*, *42*, 115–134.

Smith, M. E. (2005). Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: A meta-analysis of structural MRI studies. *Hippocampus*, *15*(6), 798–807.

Strasser, H., & Weber, C. (1999). On the asymptotic theory of permutation statistics.

Stricker, N. H., Lippa, S. M., Green, D. L., McGlynn, S. M., Grande, L. J., Milberg, W. P., & McGlinchey, R. E. (2017). Elevated rates of memory impairment in military service-members and veterans with posttraumatic stress disorder. *Journal of Clinical and Experimental Neuropsychology*, *39*(8), 768–785.

Sun, D., Davis, S. L., Haswell, C. C., Swanson, C. A., Mid-Atlantic MIRECC Workgroup, LaBar, K. S., & Yoash-Gantz, R. E. (2018). Brain structural covariance network topology in remitted posttraumatic stress disorder. *Frontiers in Psychiatry*, *9*, 90.

Tanji, J., & Hoshi, E. (2008). Role of the lateral prefrontal cortex in executive behavioral control. *Physiological Reviews*, *88*(1), 37–57.

Villarreal, G., Hamilton, D. A., Petropoulos, H., Driscoll, I., Rowland, L. M., Griego, J. A., Kodituwakku, P. W., Hart, B. L., Escalona, R., & Brooks, W. M. (2002). Reduced hippocampal volume and total White matter volume in posttraumatic stress disorder. *Biological Psychiatry*, *52*(2), 119–125.

Wang, X., Xie, H., Chen, T., Cotton, A. S., Salminen, L. E., Logue, M. W., Clarke-Rubright, E. K., Wall, J., Dennis, E. L., & O'Leary, B. M. (2021). Cortical volume abnormalities in posttraumatic stress disorder: An ENIGMA-psychiatric genomics consortium PTSD workgroup mega-analysis. *Molecular Psychiatry*, *26*(8), 4331–4343.

Weathers, F. W., Keane, T. M., & Davidson, J. R. T. (2001). Clinician-Administered PTSD scale: A review of the first ten years of research. *Depression and Anxiety*, *13*(3), 132–156.

van der Werff, S. J. A., van den Berg, S. M., Pannekoek, J. N., Elzinga, B. M., & van der Wee, N. J. A. (2013). Neuroimaging resilience to stress: A review. *Frontiers in Behavioral Neuroscience*, *7*, 39.

Winter, H., & Irle, E. (2004). Hippocampal volume in adult burn patients with and without posttraumatic stress disorder. *American Journal of Psychiatry*, *161*(12), 2194–2200.

Woodward, S. H., Kaloupek, D. G., Streeter, C. C., Martinez, C., Schaer, M., & Eliez, S. (2006). Decreased anterior cingulate volume in combat-related PTSD. *Biological Psychiatry*, *59*(7), 582–587.

Woon, F. L., Sood, S., & Hedges, D. W. (2010). Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: A meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(7), 1181–1188.

Wu, J. (2012). Cluster analysis and K-means clustering: an introduction, *Advances in K-means Clustering* (pp. 1–16). Springer

Yochman, A., & Pat-Horenczyk, R. (2020). Sensory modulation in children exposed to continuous traumatic stress. *Journal of Child & Adolescent Trauma*, *13*(1), 93–102.

Yuan, C., & Yang, H. (2019). Research on k-value selection method of k-means clustering algorithm. *J*, *2*(2), 226–235.

Zhang, L., Lu, L., Bu, X., Li, H., Tang, S., Gao, Y., Liang, K., Zhang, S., Hu, X., & Wang, Y. (2021). Alterations in hippocampal subfield and amygdala subregion volumes in posttraumatic subjects with and without posttraumatic stress disorder. *Human Brain Mapping*, *42*(7), 2147–2158.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zilcha-Mano, S., Zhu, X., Lazarov, A., Suarez-Jimenez, B., Helpman, L., Kim, Y., Maitlin, C., Neria, Y., & Rutherford, B. R. (2022). Structural brain features signaling trauma, PTSD, or resilience? A systematic exploration. *Depression and Anxiety*, 39, 695–705. https://doi.org/10.1002/da.23275