Adaptive Identification of Cortical and Subcortical Imaging Markers of Early Life Stress and Posttraumatic Stress Disorder

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ABSTRACT

Background and Purpose: Posttraumatic stress disorder (PTSD) is a heterogeneous condition associated with a wide range of brain imaging abnormalities. Early life stress (ELS) contributes to this heterogeneity, but we do not know how a history of ELS influences traditionally defined brain signatures of PTSD. Here we used a data-driven method to identify shared and unique neuroimaging markers of ELS and PTSD in 97 military veterans. We hypothesized that clustering standard regions of interest would improve classification accuracy of PTSD and ELS, relative to using individual atlas-defined brain regions, with moderate overlap in the patterns associated with each condition.

Methods: We used a novel machine learning method - evolving partitions to improve classification (EPIC) - to determine how combinations of cortical thickness, surface area, and subcortical brain volumes, could contribute to classification of veterans with PTSD (n=40) relative to trauma-exposed controls (n=57), and classification of ELS within the PTSD (ELS^+ n=16; ELS^- n=24) and control groups (ELS^+ n=16; ELS^- n=41). Additional inputs included intracranial volume, age, sex, and self-reported depression.

Results: EPIC improved classification of PTSD, with 71% accuracy, on average. Within groups, EPIC classified ELS with 70% accuracy in controls on average, and 67% accuracy in PTSD; accuracy ranged from 75-84% for the best run of each analysis. For each binary analysis, EPIC identified unique predictors and combinations of neuroimaging variables that contributed to improve group classification from the classifier that modeled input features individually. Self-reported depression was a stronger predictor of PTSD and ELS than any combination of neuroimaging variables, along with adult trauma exposure in controls. Temporoparietal metrics were the strongest neuroimaging predictors of PTSD after depression, whereas regions of the cingulate cortex were strong markers of ELS in both subgroups.

Conclusions: Combinatorial machine learning methods such as EPIC may boost power to delineate underlying structural signatures of stress-related neuropathology.

Introduction

PTSD is a serious mental health condition in which patients often show brain abnormalities in regions involved in memory, fear, and emotional processing - namely the hippocampus and amygdala - and regions of the prefrontal and cingulate cortex[1]. However, the etiology of PTSD is complicated by individual differences in predisposing factors that may also affect brain structure and symptoms [2-3]. There is interest in identifying disease mechanisms and risk factors that influence brain outcomes among individuals with PTSD ($PTSD^+$), and early life stress (ELS) is one key predisposing factor that affects brain abnormalities in this population[4-5].

ELS affects cortical and subcortical brain structures implicated in PTSD[6], but studies show that ELS and PTSD do not impact brain structure identically[7-8]. In a study of military veterans[9], PTSD symptom severity was related to cortical thickness (CT) in the posterior cingulate (PCC)/paracentral area, but the direction of this association depended on ELS. Specifically, CT in these regions was positively associated with PTSD symptom severity in ELS-exposed (ELS^+) veterans, but negatively associated with symptom severity in ELS-unexposed (ELS^-) veterans. Further, associations of symptom severity with amygdala and hippocampal volumes were significant only in the ELS^+ group. ELS may therefore have a regionally selective influence on the brain that leads to different profiles of abnormalities in trauma exposed veterans with and without PTSD. We do not fully understand how PTSD affects cortical surface area (SA), but lower SA has been reported in maltreated children[10] and may have implications for $PTSD^+$ patients with a history of ELS.

We recently developed a new supervised machine learning tool, evolving partitions to improve classification (EPIC[*]), that adaptively selects and merges sets of brain measures to improve group

[*] EPIC was initially used to denote "evolving partitions to improve connectomics" - [11] it was used to cluster and simplify connectivity matrices to achieve better classification. In general, the adaptive merging process can be applied to improve classification based on clusters of any type of spatial data, including the structural data used here, so here we use the term to refer to "evolving partitions to improve classification".

classification[11]. EPIC is based on the idea that certain features may not relate to a grouping variable when examined independently, but when integrated with others, may better discriminate subjects from different classes. This top-down approach reduces the dimension of a set of imaging predictors by re-partitioning the cortex into regions and "super-regions" (the result of merging 2 or more regions) to boost group classification. Our group previously showed that EPIC improves the accuracy of disease classification in Alzheimer's disease[11], mild cognitive impairment[12], and traumatic brain injury[13]. Here we used EPIC to determine if unique combinations of SA, CT, and subcortical volumes (VL) could discriminate PTSD patients from trauma-exposed military veterans. We also used EPIC to identify preliminary neuroimaging predictors of ELS in veterans with and without PTSD.

Method

Participants

Data were collected from 97 combat-exposed Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) veterans (PTSD n=40, controls n=57) who took part in the military conflicts in Iraq and Afghanistan following the September 11th 2001 terrorist attacks. Participants were aged 18-65 (male, n=80; female, n=17) and recruited from the Durham VA and Duke University Medical Centers. Exclusion criteria consisted of any Axis I diagnosis other than PTSD or major depressive disorder, substance dependence (other than nicotine), high risk for suicide, history of learning disability or developmental delay, history of head injury with loss of consciousness > 5 min, neurological disorders, major medical conditions, and contraindications for MRI (e.g., claustrophobia). The same exclusion criteria applied to controls, except that control subjects could not meet criteria for any Axis I diagnosis. We did not exclude individuals who were taking medication for depression, anxiety, and/or sleep disturbances as these

conditions are prevalent in this population. All participants provided informed consent; procedures were approved by the local IRBs.

Clinical Assessment

A diagnosis of PTSD was determined using the Clinician Administered PTSD scale for DSM-IV. Adult trauma and ELS exposure were evaluated using the Traumatic Life Events Questionnaire (TLEQ)[14]. Adult trauma was quantified as a continuous variable reflecting exposure severity (i.e., total number of exposures). Participants indicating exposure to any traumatic event before age 18 were identified as ELS^+, whereas participants with no trauma exposure before age 18 were identified as ELS^- (unexposed)[15]. Current depression was measured using the Beck Depression Inventory-II (BDI)[16].

Neuroimaging Acquisition and Processing

MRI scanning was completed at two sites using a 3T GE MR750 (93% of sample) and 3T GE Signa EXCITE (7% of sample) scanner, each equipped with an 8-channel head coil. Chi-squared analyses revealed no significant differences between sites and target groups (PTSD by site, $x^2(1)=0.79$, p=0.375; ELS by site, $x^2(1)=0.33$, p=0.564). Independent of the target groups, we did not observe site differences in the distribution of sex ($x^2(1)=1.6$, p=0.205), age (t(95)= -0.86, p=0.393), BDI scores (t(95)= -1.24, p=0.216), or adult trauma exposure (t(95)= -0.33, p=0.743). T1-weighted axial brain images were obtained with 1-mm isotropic voxels using the following parameters: GE Signa EXCITE: TR/TE/flip=8.208-ms/3.22-ms/12°, GE MR750: TR/TE/flip=7.484-ms/2.984-ms/12°; all images were captured with FOV=256x256mm, 1-mm slice thickness. T1-weighted images were processed using FreeSurfer version 5.3. Cortical and subcortical extractions were performed and checked for quality control using standardized protocols from the ENIGMA consortium, yielding CT and SA for 34 bilateral cortical regions of interest (ROIs), and bilateral VL for 8 subcortical structures.

Design

Primary analyses were completed to determine if EPIC could distinguish $PTSD^+$ veterans from

trauma-exposed controls using 152 neuroimaging inputs (68 CT, 68 SA, and 16 VL). EPIC was also used to determine the role of ELS within each group (PTSD: N=40, ELS^+ (n=16) /ELS^- (n=24); Controls: N=57, ELS^+ (n=16) /ELS^- (n=41)). All analyses included age, sex, and intracranial volume (ICV) as input variables. Preliminary analyses revealed no significant differences in age, sex, BDI scores, TLEQ scores, PTSD, and ELS by site, therefore we did not include site as an input feature. Total score on the BDI was included as an input feature when depression differed significantly between the target groups in order to model depression symptoms as an important feature of PTSD and ELS. We further tested whether EPIC or the original FreeSurfer segmentation could distinguish target groups with good accuracy (>70%) after regressing out the effects of depression on the input features when BDI scores differed significantly between groups. We hypothesized that both classifiers would perform worse when the BDI was removed as input feature for analyses where depression differed between groups.

Classification with EPIC

The workflow of EPIC is shown in Figure 1. Here input variables included CT, SA, and VL measurements, and the respective covariates for each analysis. Structural MRI inputs were used to generate merged composite cortical partitions through iterative ROI sampling over the space of possible ROI groupings. We applied a 70/30 (training/testing) split of the data, in which a linear support vector machine (SVM) learned the optimal partitions for group classification in the training data, and then evaluated the partitions in the test data using stratified *k*-fold cross-validation (CV). After splitting the data, 67 participants were used for *k*-fold CV and 30 participants were held out for testing. We maintained 40% cases and 60% controls for each analysis, resulting in 12 cases/18 controls for hold-out, and 27 cases/40 controls for training. For the primary analysis of PTSD vs. controls, we applied 5-fold CV to the training data, resulting in approximately 5 PTSD cases and 8 controls per fold. For secondary analyses of ELS within the PTSD and control groups, we used 2-fold CV to account for lower cell sizes in the target subgroups. We then re-based the stratified CV rates according to 40% of ELS^+ participants and 60% of

ELS$^-$ participants within each subgroup. For the analysis of ELS in PTSD patients, the re-based CV rate provided a total test set of 6 ELS$^+$ and 14 ELS$^-$ PTSD patients, divided by 2 (folds), equaling 3 ELS$^+$ and 7 ELS$^-$ patients per fold. For the analysis of ELS in controls, the re-based cross-validation rate provided a total test set of 6 ELS$^+$ and 25 ELS$^-$ controls, divided by 2 (folds), equaling 3 ELS$^+$ and 13 ELS$^-$ controls per fold. *K*-fold cross validation was repeated 10 times for all analyses. Simulated annealing was used to better identify optimal partitions[11].

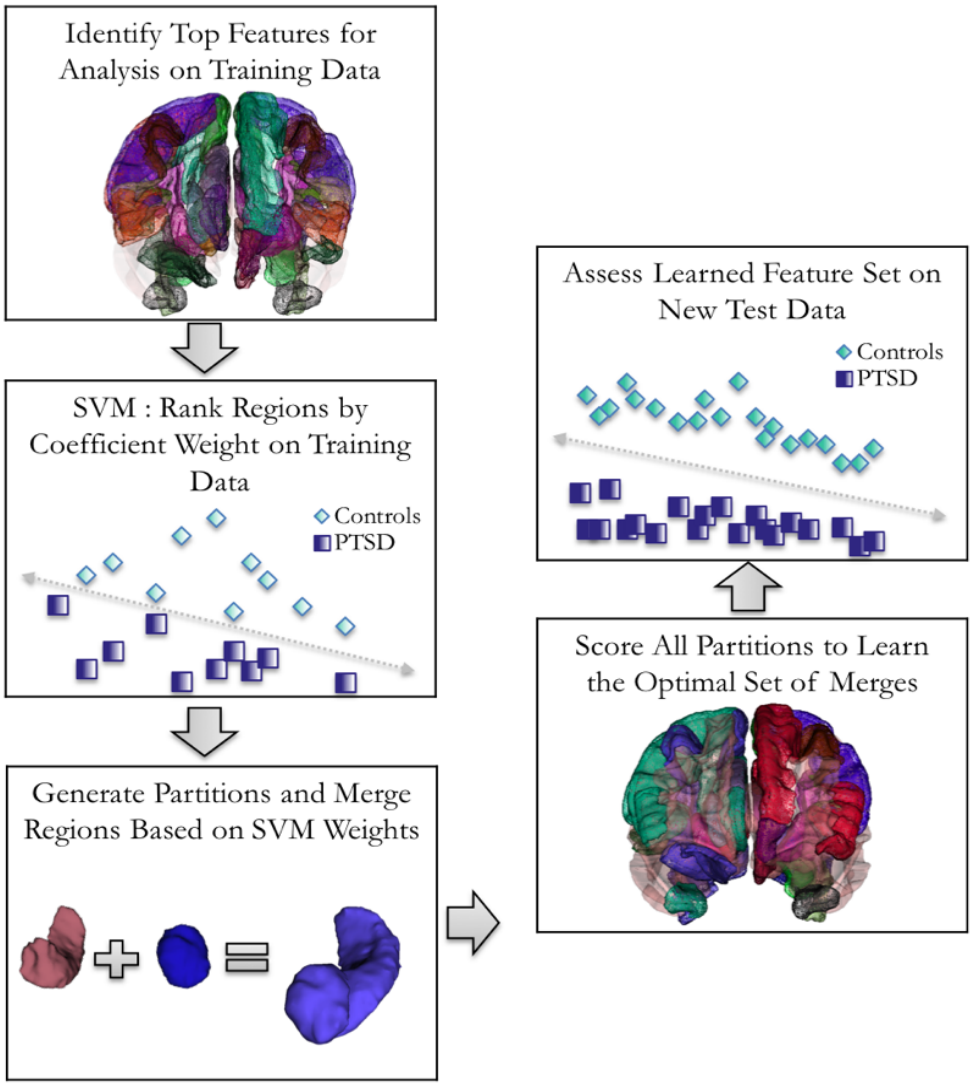

Figure 1. Workflow of EPIC applied to the target variables of the main analysis

We evaluated EPIC's performance using Accuracy (true positive (TP)+true negative (TN)/TP+TN+false positive (FP)+false negative (FN), sensitivity, and specificity averaged across the 10 repeats. We also report performance metrics for the best repeat of EPIC to facilitate future hypothesis generation. Accuracy (Acc) was used as our primary index of classifier performance because cell sizes in the minority class (i.e., PTSD) were up-sampled in our study compared to the true base rate in OEF/OIF veterans military populations [17]. Conversely, the proportion of the sample with ELS is slightly lower than current base rates in the general U.S. population, and significantly lower than the base rate in military samples [18]. Thus, we report the generalized index of balanced accuracy (IBA[19-20]) in conjunction with Acc to account for modest imbalances between the target groups. This metric is defined formulaically as $IBA\alpha(M) = (1+\alpha \cdot Dominance)*M$, where M equals the metric of classifier performance (here we use Acc), α equals the prospective alpha level, and Dominance = TP-TN; weighting dominance by $\alpha \geq 0$ (set here at 0.05) reduces the influence of the selected performance metric [20]. In the supplement we report 8 additional indices of classifier performance for comparison to the existing literature. We also report classifier performance measures for the SVM that used the original FreeSurfer brain measures and covariates modeled individually, to determine whether EPIC's combinatorial approach improved classification accuracy. Using a thresholding feature elimination procedure, individual regions and super-regions with absolute SVM coefficient weights (w) <0.05 on training data were considered noise and removed from the primary analysis to enhance power. We set a threshold of 0.003 for the secondary analyses, which was determined from the final accuracy outputs from the test data.

Results

PTSD vs. trauma-exposed controls

PTSD$^+$ veterans scored higher (M=15.9, SD= 11.2) on the BDI compared to controls (M=4.2, SD=5.4, p<0.001), so total BDI score was included as a covariate. Compared to average performance using the individual input features, EPIC improved classification accuracy from 68% to 71% (IBA=70%),

on average. Sensitivity and specificity improved from 56% to 58%, and 77% to 81%, respectively. Across repeats, the best performance with EPIC resulted in 79% classification accuracy (IBA=78%), 63% sensitivity, and 91% specificity, though this did not differ from the best performance using the individual measures. The SVM revealed 15 independent brain metrics that contributed to classification, but the BDI was the strongest predictor (*w*=0.25) compared to all imaging variables (*w*'s <0.15). Super-regions were identified across the 10 repeats but did not contribute to accuracy for the best individual repeat with EPIC (Figure 2).

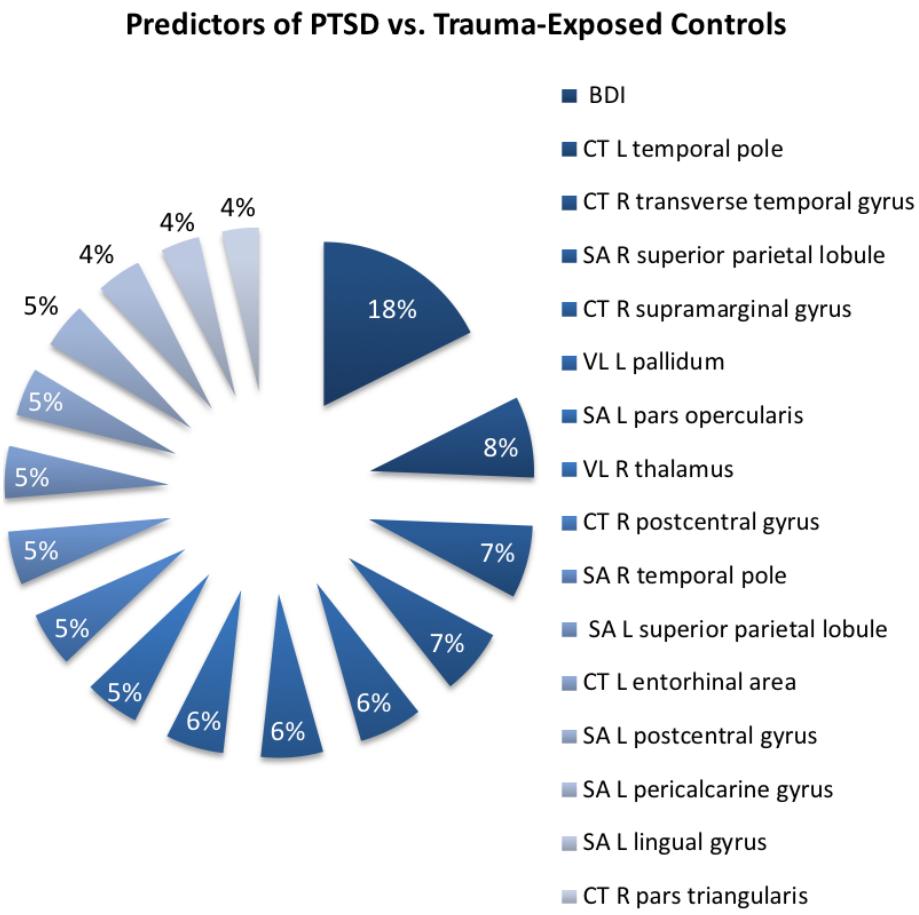

Figure 2. Feature importance results for the 16 individual predictors identified by the best performance with EPIC, displayed in rank order. Percentages are based on relative SVM coefficient weights for each ROI. SA= surface area, CT= cortical thickness, VL= volume, R= right hemisphere, L= left hemisphere.

Model performance declined significantly when we tested the classifier on inputs that were residualized for BDI scores. Neither the original FreeSurfer segmentation, nor the EPIC classifier could distinguish PTSD groups from controls, with similarly low predictive power between the methods (37.5% accuracy vs. 38.1% accuracy, respectively). Given this low predictive power, we did not apply this approach for other analyses that differed on BDI scores.

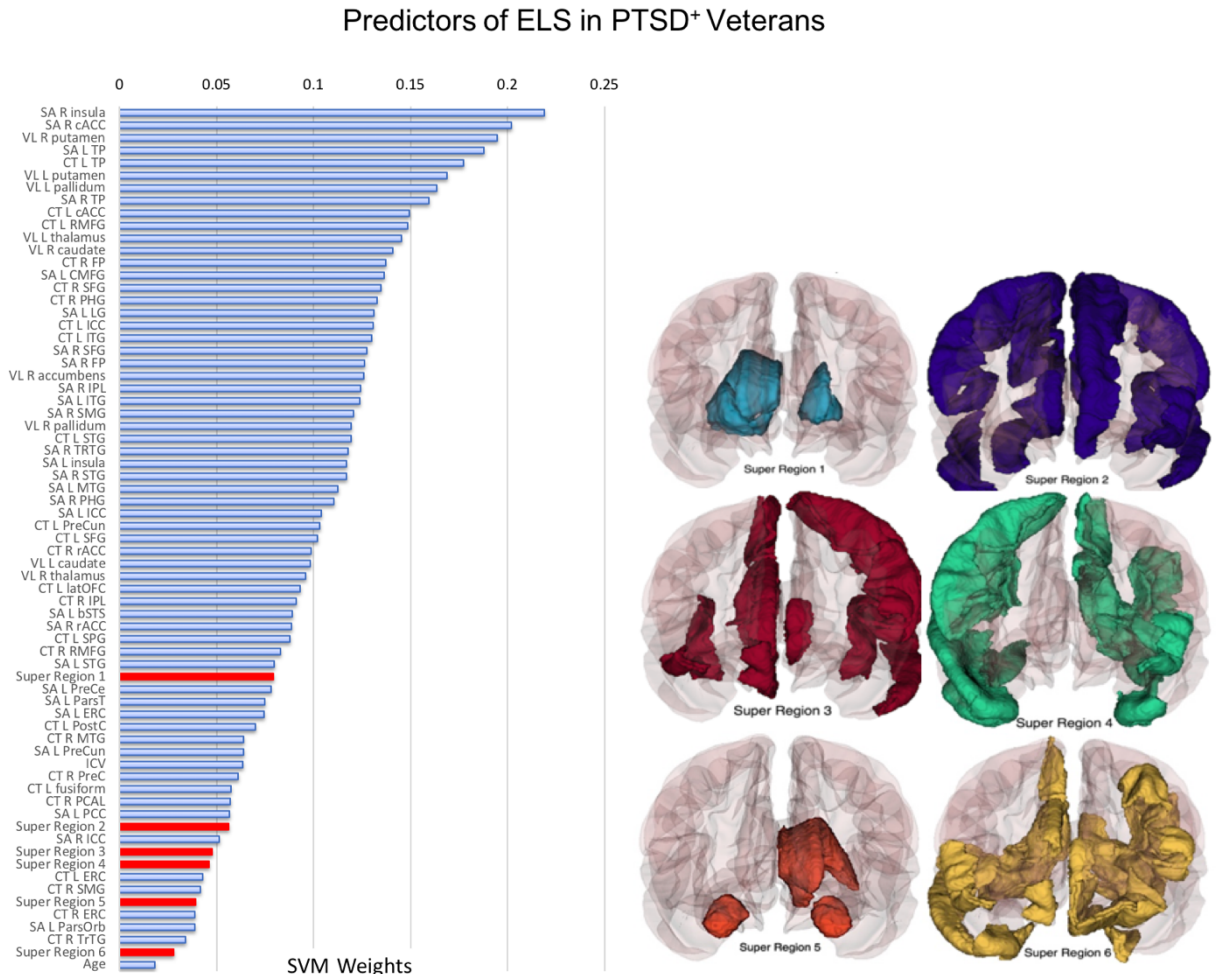

Figure 3. SVM weights of individual predictors and super regions that discriminated PTSD+ subjects with and without ELS are depicted in rank order. EPIC discovered 6 super-regions of individual ROIs and merged regions are shown on the brain maps. **Super Region 1 (VL):** Bilateral hippocampus+ L amygdala+ L accumbens. **Super Region 2 (VL)**: Bilateral Lat Ventricle+ R amygdala. **Super Region 3 (CT)**: Bilateral bSTS (banks of superior temporal sulcus)+ Bilateral insula+ Bilateral ParsOperc (parsopercularis)+ Bilateral ParsOrb (parsorbitalis)+ Bilateral ParsT (parstriangularis)+ L CMFG (caudal middle frontal gyrus)+ L latOCC (lateral occipital)+ Bilateral LG (lingual gyrus)+ L mOFC (medial orbitofrontal)+ L MTG (middle temporal gyrus)+ L PHG (parahippocampal gyrus)+ L rACC (rostral anterior cingulate)+ L TrTG (transverse temporal)+ R latOFC (lateral orbitofrontal)+ R PostC (post central)+ R TP (temporal pole). **Super Region 4 (CT):** Bilateral Cun (cuneus)+ Bilateral ParaC (paracentral)+ Bilateral PCC (posterior cingulate)+ L IPL (inferior parietal)+ L PCAL (pericalcarine)+ L PreCe (precentral)+ L SMG (supramarginal)+ L FP (frontal pole)+ R cACC (caudal ACC)+ R CMFG+ R fusiform+ R ITG (inferior temporal)+ R ICC (isthmus cingulate)+ R latOCC+ R mOFC+ R PreCun (precuneus)+ R SPG (superior parietal gyrus)+ R STG (superior temporal gyrus). **Super Region 5 (SA)**: Bilateral fusiform+ Bilateral PCAL+ Bilateral latOFC+ Bilateral mOFC+ Bilateral RMFG+ L Cun+ L IPL+ L PHG+ L ParaC+ L ParsOrb+ L PostC+ L SPG+ R FP+ R bSTS+ R ITG+ R latOCC + R MTG+ R ParsOperc+ R PCC+ R PreCun. **Super Region 6 (SA)**: L cACC+ L latOCC+ L rACC+ L SFG (superior frontal gyrus)+ L SMG+ L TrTG+ R CMFG+ R Cun+ R ERC (entorhinal)+ R LG+ R ParaC+ R ParsOrb+ R ParsT+ R PostC+ R PreCe+ R SPG.

PTSD$^+$ veterans with and without ELS

PTSD$^+$ groups did not differ significantly on BDI scores (ELS$^+$: *M*=16.4, *SD*=12.2; ELS$^-$: *M*=15.5, *SD*=10.7) or adult trauma exposure (ELS$^+$: *M*=13.6, *SD*=8.5; ELS$^-$: *M*=10, *SD*=10.1), so these variables were not used here as input features. On average, EPIC modestly improved classification accuracy for ELS status in PTSD$^+$ veterans, with 65% accuracy using the individual input features, to 67% accuracy using EPIC (IBA= 66% accuracy). Across repeats, the best performance with EPIC resulted in classification accuracy of 80% (IBA=79%), with 63% sensitivity and 92% specificity. This was a 5% improvement in overall accuracy using the best classifier performance from the original FreeSurfer segmentation. The SVM revealed 72 predictors that contributed to improve classification accuracy. Six super-regions were included among these predictors (Figure 3). The strongest individual predictors represented CT of the right parahippocampal and superior frontal gyri, right PCC, and left caudal anterior cingulate (cACC), as well as SA in the left superior parietal and transverse temporal gyri, and VL of the left hippocampus (*w*'s >0.15).

Trauma-exposed controls with and without ELS

BDI scores and adult trauma exposure differed significantly between ELS$^+$ (BDI, *M*=6.9, *SD*=7.1; TLEQ, *M*=13.1, *SD*=5.8) and ELS$^-$ controls (BDI, *M*=3.1, *SD*=4.2, *p*=0.016; TLEQ, *M*=13.1, *SD*=5.8, *p*=0.001), so these variables were included as covariates in this analysis. On average, EPIC improved classification of ELS from 68% (individual input features) to 70% accuracy (IBA=69%), with 81% specificity and 43% sensitivity. Across repeats, the best performance with EPIC accurately classified 75% (IBA=74%) of participants (63% Sensitivity, 80% Specificity), resulting in 4% improvement from the best performance using the FreeSurfer segmentation. Predictors are listed in rank order in Figure 4, including 4 super-regions that optimized prediction. The two best predictors of ELS included adult trauma exposure and total scores on the BDI, followed by CT in the right PCC and SA in the left isthmus cingulate (ICC).

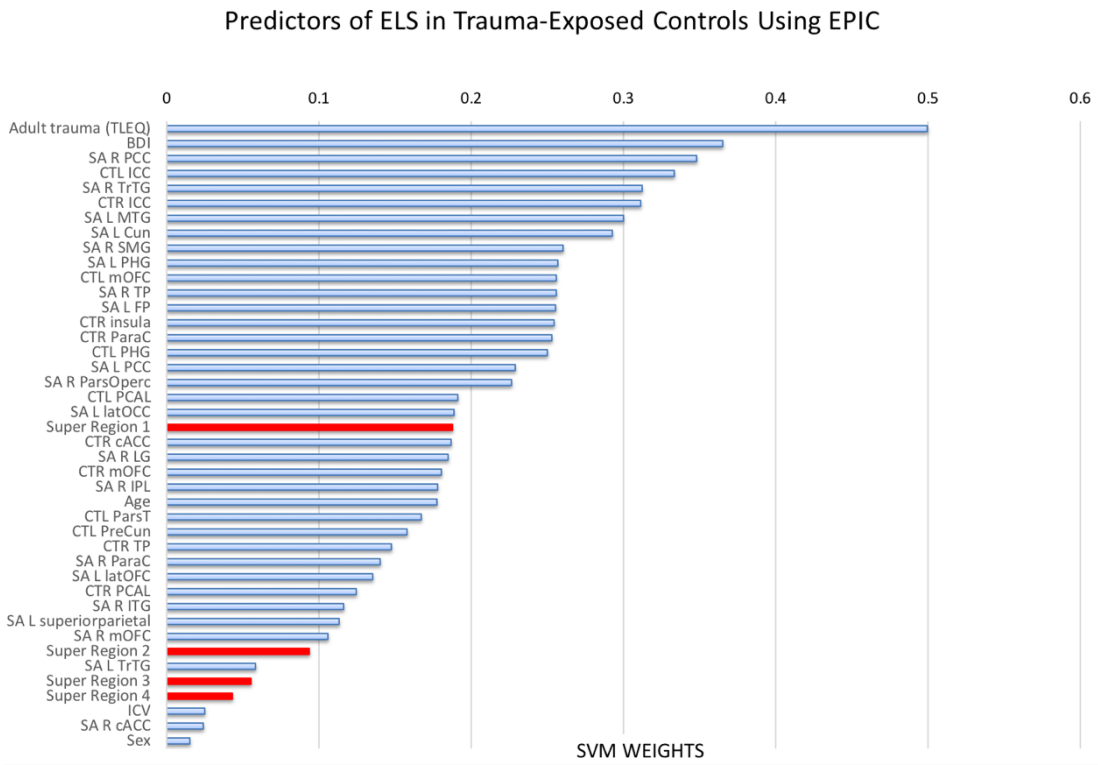

Figure 4. SVM weights of individual predictors and super regions that discriminated control subjects with and without ELS are depicted in rank order. EPIC discovered the following 4 super-regions: **Super Region 1 (SA)**: Bilateral CMFG + Bilateral ICC + Bilateral STG + Bilateral PostC + Bilateral PCAL + Bilateral PreCun + Bilateral STG + L bSTS + L cACC + L IPL + L LG + L ParsOperc + L ParsT + L rACC + L SFG + L SMG + L insula + R Cun + R ERC + R latOCC + R MTG + R PreCe. **Super Region 2 (CT)**: Bilateral bSTS + Bilateral CMFG + Bilateral Cun + Bilateral ITG + Bilateral FP + Bilateral ParsOrb + Bilateral SPG + L cACC + L fusiform + L latOCC + L ParaC + L PostC + L PreCe + L RMFG + L TrTG + L insula + R ParsT + R PreCun + R STG + R SMG. **Super Region 3 (CT)**: Bilateral ERC + Bilateral IPL + Bilateral latOFC + Bilateral LG + Bilateral MTG + Bilateral ParsOperc + Bilateral PCC + Bilateral SFG + L rACC + L STG + L SMG + L TP + R fusiform + R latOCC + R PHG + R PostC + R PreCe + R RMFG R SFG + R SPG + R TrTG. **Super Region 4 (SA):** Bilateral fusiform + Bilateral ParsOrb + Bilateral RMFG + L ERC + L ITG + L mOFC + L ParaC + L PreCe + L TP + R bSTS + R PHG + R ParsT + R rACC + R SFG + R SPG + R FP + R insula.

Discussion

Our machine learning method, EPIC, revealed groups of features that modestly improved classification accuracy for PTSD and ELS relative to individual brain measures in this cohort of military veterans. BDI scores were the strongest predictors of group classification in PTSD^{+} veterans compared to trauma-exposed controls, followed by measures from temporoparietal regions involved in somatosensory function and semantic processing. These regions distinguished individuals with PTSD *after* adjusting for BDI scores, suggesting that traditionally defined PTSD brain abnormalities in the hippocampus and amygdala may be due to co-morbid depression rather than features unique to PTSD (e.g., startle). The

hippocampus and amygdala were merged with the nucleus accumbens to form a super-region in the PTSD$^+$ analysis, but this merged region was a weak predictor of PTSD. Further work is needed to determine how this subcortical cluster may be involved in PTSD versus other comorbidities in military and PTSD populations.

The top predictors of ELS in the PTSD$^+$ group included brain regions that tap emotion regulation, reward sensitivity, and executive control – functional domains that tend to be abnormal in PTSD[17]. Among these regions was the ACC, a commonly disrupted structure in ELS$^+$ populations[6]. ELS may prime brain regions that subserve these functions to exhibit a chronic and exaggerated threat response that disrupts brain structure and increases risk for PTSD following adult trauma exposure.

For trauma-exposed controls, adult trauma exposure and BDI scores were the strongest predictors of ELS classification. The strong predictive influence of adult trauma exposure on ELS classification is consistent with evidence that ELS is linked with high risk for subsequent trauma exposure in adults [21], which may be due to increased risk-taking behaviors in ELS$^+$ individuals [22]. Additional work shows significantly higher prevalence of ELS in military samples, which may reflect an escape from adversity among those who voluntarily enlist [18]. The observation that depression was a top predictor of ELS classification in controls is consistent with studies that show higher symptoms of depression and emotional dysregulation among otherwise healthy individuals with a history of ELS compared to unexposed controls [23-24]. The strongest neuroimaging predictor of ELS was the PCC – an important brain region for processing emotionally salient stimuli [25]. EPIC also identified four super-regions of merged cortical regions in key areas known to underlie behavioral dysfunction in depression and anxiety [26].

Several limitations should be acknowledged. 1) EPIC combined neuroimaging features to boost classification accuracy in each analysis, but these super-regions showed reduced feature importance relative to the individual regions. Combining neuroimaging metrics into super-regions may reduce noise in the individual measures that are most relevant to group classification, thereby improving accuracy

relative to using each feature individually[12]. 2) Sensitivity was low in all analyses, ranging from 43% - 58%, on average. This is not necessarily surprising because all participants in this study were exposed to military combat. Lifetime trauma exposure in military veterans may yield a unique phenotype that is independent of PTSD and ELS, limiting the detection rate of either "condition". Sensitivity was lowest for detection of ELS in the control group (43% accuracy on average), likely because the control group consists of non-clinical participants who should not have any gross brain abnormalities. Importantly, the high specificity observed in controls with ELS suggests that EPIC can distinguish participants with subtle brain differences that are within the normal range of variance that would be expected in a non-clinical sample. 3) Although our sample size is consistent with several previous studies of machine learning in neuroimaging and psychiatry, numbers were small when considering the subdivisions of cases and controls used for training, cross-validation, and testing; this may have limited our ability to detect more robust effects across the target groups. However, recent work from the ENIGMA consortium reveals comparable rates of classification accuracy for bipolar disease [27] in over 3,000 individuals, suggesting that sample size was not an issue in our study. Using the Research Domain Criteria (RDoC) approach to guide future machine learning studies may significantly improve classification and prediction of complex psychiatric diseases [28] ; this is currently a goal of several Working Groups within the ENIGMA consortium. 4) We did not examine the ability of EPIC to distinguish ELS^+ from ELS^- controls independent of PTSD because there are multiple projects within the ENIGMA consortium that are pursuing this research topic in larger samples [29]. Thus, we cannot determine from the information presented whether PTSD is easier to detect and classify than ELS. This is an important research question to address using clinically diverse datasets to provide a more stable understanding of nuanced phenotypes of ELS, PTSD, and major depression. 5) This cohort was exposed to military combat and results may not generalize to civilians. However, the most salient predictive features of PTSD and ELS are consistent with civilian studies, so they may represent the larger $PTSD^+$ and ELS^+ populations.

EPIC adapts regions of interest to improve classification, and a similar approach could be implemented for functional imaging data. Here we focused on structural MRI features to compare classifier results to the large body of literature showing structural brain disruptions among individuals with PTSD and ELS. In functional connectivity analyses, however, the seed regions that act as nodes of the network could be adaptively refined to improve classification of the target groups, and some regions could be merged or split to adapt the set of predictors. This is an interesting topic for future work and a current goal of the PGC-ENIGMA PTSD Working Group - the larger data source from which this work stems.

In sum, our results show region-specific distinctions in the neuroimaging profiles of PTSD and ELS in military veterans. We also report a specific function of self-reported depression and adult trauma exposure as important non-imaging markers that may distinguish people with PTSD and ELS in future data-driven designs. Further work will determine the generalizability of these findings in other cohorts with additional sources of clinical heterogeneity that are characteristic of PTSD populations.

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