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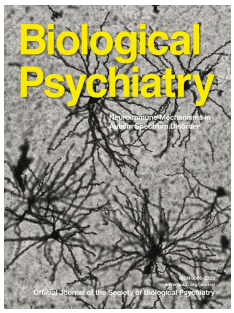

Traces of trauma – a multivariate pattern analysis of childhood trauma, brain structure and clinical phenotypes

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Traces of trauma – a multivariate pattern analysis of childhood trauma, brain structure and clinical phenotypes

Running Title: Neuroanatomical signatures of childhood adversity

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Abstract

Background: Childhood trauma (CT) is a major, yet elusive psychiatric risk factor, whose multidimensional conceptualization and heterogeneous effects on brain morphology might demand advanced mathematical modelling. Therefore, we present an unsupervised machine learning approach to characterize the clinical and neuroanatomical complexity of CT in a larger, transdiagnostic context.

Methods: We used a multi-center European cohort of 1076 female and male individuals (discovery, n=649; replication, n=427) comprising young, minimally medicated patients with clinical high-risk states for psychosis, patients with recent-onset depression or psychosis, and healthy volunteers. We employed multivariate Sparse Partial Least Squares Analysis to detect parsimonious associations between combinations of items from the Childhood Trauma Questionnaire and grey matter volume (GMV) and tested their generalizability via nested cross-validation as well as external validation. We investigated the associations of these CT signatures with state (functioning, depressivity, quality of life), trait (personality) and sociodemographic levels.

Results: We discovered signatures of age-dependent sexual abuse, sex-dependent physical and sexual abuse as well as emotional trauma, which projected onto GMV patterns in prefronto-cerebellar, limbic and sensory networks. These signatures were associated with predominantly impaired clinical state- and trait-level phenotypes, while pointing towards an interaction between sexual abuse, age, urbanicity and education. We validated the clinical profiles for all three CT signatures in the replication sample.

Conclusions: Our results suggest distinct multi-layered associations between partially age- and sex-dependent patterns of CT, distributed neuroanatomical networks and clinical profiles. Hence, our study highlights how machine learning approaches can shape future, more fine-grained CT research.

Introduction

Childhood trauma (CT) is defined as any act that results in harm, potential or threat of harm to a child (1) and is generally operationalized along the dimensions of physical, sexual and emotional abuse or neglect (2). CT acts as a transdiagnostic risk factor for a variety of psychiatric disorders (3-5), reduces an individual's quality of life (6), impairs levels of functioning (7) and is associated with dysfunctional personality development (8, 9). Furthermore, neuroimaging studies have suggested associations between CT and grey matter volume (GMV), reporting alterations in subcortical, temporal and frontal regions (10-13). Yet, these findings have been highly heterogeneous and so far neither a distinct correlate of CT (14-19) nor a link between CT-related brain changes and observable clinical phenotypes has been established (20, 21).

A better neurobiological understanding of CT is important as it could mitigate the long-term adverse effects of CT through early recognition and targeted multimodal intervention programs (22, 23). Still, most studies investigating CT use voxel-wise mass-univariate strategies, which assume highly localized functional specialization and statistical independence of voxels (24). This approach does not reflect the state-of-the-art understanding of neuroanatomical variation being encoded along distributed clusters of voxels, cortical regions and brain systems (25-27), potentially leading to subtle and distributed effects of CT on brain morphology (28). The diverse effects of CT might be better understood in a larger context by investigating the more generalized, transdiagnostic effects of CT, and its important interactions with age and sex (29-32). Therefore, advanced methods are needed to capture the complexity of CT and potentially associated structural brain surrogates (33).

We took an in-depth approach to better characterize the complex neuroanatomy of CT by investigating the relationship between structural brain data and CT in the multi-center, European PRONIA cohort (Personalized Prognostic Tools for Early Psychosis Management study; https://www.pronia.eu/). Following a transdiagnostic, data-driven study design, we applied the multivariate Sparse Partial Least Squares (SPLS) algorithm to identify parsimonious and interpretable

phenotype-brain signatures (34). Specifically, we used the strength of SPLS to model complex patterns of interactions between CT-related phenotypic features and brain voxels, possibly yielding new and distinct CT signatures. Finally, we wanted to examine the clinical and sociodemographic implications of these novel CT dimensions by performing correlation analyses between participants' loadings onto the CT signatures and measures of functioning, depressivity, quality of life, personality and sociodemographic information. We expected to find transdiagnostic CT signatures linked to clinical and sociodemographic characteristics, providing further insights into the multidimensional fingerprints of CT.

Methods and Materials

Study participants

The PRONIA cohort includes healthy controls (HC), participants with recent-onset depression (ROD) or psychosis (ROP) and patients with clinical high-risk states for psychosis (CHR). The cohort is divided into a discovery sample for model generation and a replication sample for model validation (Supplementary Material and Koutsouleris et al. (35)). Data from 649 participants from the discovery sample (264 HC, 129 ROD, 132 ROP, 124 CHR, Table 1) and 427 individuals from the replication sample (135 HC, 96 ROD, 92 ROP, 104 CHR, Table S6) were obtained for the analysis.

Childhood trauma, clinical and sociodemographic features assessment

Childhood trauma was measured using the Childhood Trauma Questionnaire (CTQ) (36, 37). The CTQ is a 28-items self-report questionnaire, which assesses five types of maltreatment–emotional, physical, and sexual abuse as well as emotional and physical neglect–and contains an additional denial measure. A 5-point Likert scale is used to record responses ranging from "Never True" to "Very Often True". Internal consistency scores of the CTQ subscales range from 0.66 (physical neglect) to 0.94 (sexual abuse), while the test-retest coefficient over a 3.5 month period was calculated at 0.80 (36-38).

Functioning was evaluated using the Global Assessment of Functioning Symptoms and Disability/Impairment Scale (GAF:S and GAF:D/I) (39) and the Global Functioning Social and Role Scale (GF:S and GF:R) (40), while depressive symptoms were quantified using the Beck Depression Inventory (BDI) (41). The WHO Quality of Life Short Version (WHOQOL-BREF) was applied to measure individual perception of quality of life (42). Personality domains were assessed using the NEO Five Factor Inventory (NEO-FFI), quantifying personality traits along five domains: openness, conscientiousness, extraversion, agreeableness and neuroticism (43).

Sociodemographic features were assessed along the domains of participant's ethnicity, urbanicity, religion, parental education background, family and relationship status as well as participant's education level and employment status.

MRI data acquisition and preprocessing

T1-weighted structural magnetic resonance imaging (MRI) data were acquired from the study participants (Supplementary Methods). All images were examined for artifacts, gross anatomical abnormalities and signs of neurological disease by trained clinical neuroradiologists. Structural MRI data were preprocessed using the CAT12 toolbox (version 1206 available at http://www.neuro.uni-jena.de/cat/), an extension of the SPM12 software (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), and final grey matter volumes (GMV) were corrected for total intracranial volume (TIV).

Sparse Partial Least Squares Analysis

We used phenotypic and brain data as input for the SPLS algorithm. Our phenotypic dataset contained all 28 CTQ items, age and sex as well-established modulators of CT (31, 32, 44, 45), and study group. The brain dataset consisted of vectorized whole-brain GMV (resliced to 3mm) for all individuals. Given these two datasets, SPLS uses singular value decomposition to compute a latent variable (LV) capturing a specific associative effect between phenotypic and brain data. For each dataset, the LV contains a vector with feature weights (values ranging from -1 to 1) measuring the covariance between

the two datasets. Therefore, the LV consists of paired multivariate profiles measuring how the phenotypic features (phenotypic pattern) relate to the brain features (brain pattern) (Supplementary Methods). Another characteristic of SPLS is the enforcement of sparsity, whereby weights of zero are assigned to features that did not yield any relevant association. The process of weighting and selecting features according to their covariance is accomplished via l_1- and l_2-norm constraints, similar to elastic net regularization (46), and controlled by a pair of hyperparameters. Additionally, every participant can be assigned a pair of latent phenotypic and brain scores. These latent phenotypic and brain scores indicate how strong a participant loads on the phenotypic and brain patterns of the LV, respectively, with greater latent scores values reflecting higher individual loading and vice versa. We used these latent scores for post-hoc correlation analyses to investigate clinical and sociodemographic aspects of the LV signatures (34).

Assessment of generalizability and significance

We implemented a nested cross-validation (NCV) framework, which robustly prevents information leakage between participants used for training and validating the models (47, 48) (see Figure S2). We used 10 inner folds for hyperparameter optimization of the l_1- and l_2-norm constraints and 10 outer folds to test the optimized model against a previously held-out dataset. Before entering the SPLS analysis, Z-transformation models were generated in the training data and then applied to the test data within the NCV structure. Significance testing of each LV was done by comparing the performance of the optimized model against 5000 permutations of the dataset. If an LV proved significant, the respective covariance component was removed from the two datasets via projection deflation and the next LV was computed on the deflated datasets. This process was repeated until an LV failed to reach significance, thus generating several layers of significant, associative effects. LV are labelled according to the order of their computation (Supplementary Methods). The generalizability of the CT model was further validated by applying data from the replication sample onto the phenotypic and neuroanatomic patterns of all its LV, thus generating latent phenotypic and brain scores in the replication sample.

These latent scores were correlated to our predefined set of clinical and sociodemographic parameters. Univariate partial correlation analysis between the seven study sites and the input datasets was used within the NCV scheme to correct for site effects (49, 50).

Univariate Analysis

Group-level sociodemographic and clinical differences were assessed using non-parametric tests (Kruskal-Wallis-H-Test, Wilcoxon-Mann-Whitney-Test, Dunn's post-hoc multiple comparison test, χ^2-test). Latent trauma and brain scores were correlated to clinical and sociodemographic features using Spearman's correlation coefficient (ρ). Analyses were FDR-corrected for multiple testing at a significance threshold of $q<0.05$ (51).

Results

Group-level differences at baseline

The clinical study populations (ROD, CHR, ROP) revealed significant differences with respect to age, sex, GAF, GF, Positive and Negative Symptom Scale (PANSS) and BDI (Table 1, Table S7, S8). Furthermore, a significant difference for the recruitment of study groups across sites was found (Table 1, Table S9). The clinical study populations also displayed significant differences in antidepressant, antipsychotic and sedative treatment (Table S10, S11). Moreover, the clinical study populations of the discovery and replication sample did not reveal any significant differences with regards to CTQ total or subscale scores (Table 2, Table S12).

SPLS results: association between phenotypic and brain data

SPLS analysis of all 649 discovery sample subjects yielded five significant LV (LV1-LV5), representing different layers of association between phenotypic and brain patterns (Table S13 and S14 for CTQ item list and atlas readouts, Figure S20 for visualization of phenotype-brain correlations).

LV1: age (*P* value = 1.9×10^{-4}). Phenotypic pattern (Figure S6A): Age received the strongest positive weight, whereas further positive weights were assigned to male sex, ROP status and to the subscales

of sexual abuse (5 items), physical abuse (4), emotional abuse (1) and physical neglect (1). Smaller negative weights were distributed to emotional abuse (1), denial (1) and female sex. **Brain pattern** (Figure S6B): GMV was widely negatively weighted across frontal, temporal, parietal and occipital regions as well as subcortical areas. Positive GMV weights were sparsely found in the thalamus region.

LV2: sexual abuse & age (P = 1.9x10^{-4}). Phenotypic pattern (Figure 1A)**:** Two questions from the sexual abuse subscale were positively weighted, while age was negatively weighted. **Brain pattern** (Figure 1B)**:** GMV was assigned negative weights bilaterally in the prefrontal cortex (PFC), particularly in the dorsolateral (DLPFC) and medial prefrontal cortex (mPFC) regions. Further negative weights were found bilaterally in the superior and middle temporal gyrus as well as unilaterally in the left angular gyrus. Positive weighting was detected bilaterally in the cerebellum, the premotor cortex, the cuneus, the lingual gyrus and the basal ganglia.

LV3: sex (P = 1.9x10^{-4}). Phenotypic pattern (Figure S7A): The strongest positive and negative weights were detected for male and female sex, respectively. Moreover, positive weights were assigned to emotional abuse (1 item), physical abuse (2), sexual abuse (3), emotional neglect (1) and physical neglect (2), while smaller negative weights were distributed to age, sexual abuse (1) and denial (1). **Brain pattern** (Figure S7B): GMV was positively weighted in occipital, parietal and frontal areas, particularly in the precuneus region, and negatively bilaterally in prefrontal, hippocampal and parietal areas.

LV4: physical/sexual abuse & sex (P = 1.2x10^{-3}). Phenotypic pattern (Figure 2A)**:** Physical (3 items) and sexual abuse (4 items) received positive weights, while male and female sex were weighted inversely. **Brain pattern** (Figure 2B): The most profound effect was detected in bilateral positive weighting of GMV in the primary somatosensory cortex, the basal ganglia and the cuneus as well as unilaterally reduced GMV in the left fusiform gyrus and the right DLPFC. GMV was also positively weighted bilaterally in the occipital gyrus, the angular and supramarginal gyrus as well as the

thalamus. Smaller clusters of negative GMV weights were discovered bilaterally in the superior and middle temporal gyrus, the cingulate gyrus, the (para-)hippocampus, the precuneus and the right PFC.

LV5: emotional abuse/neglect (P = 1.9x10^{-4}). Phenotypic pattern (Figure 3A)**:** Emotional abuse (3 items) and neglect (3 items) were weighted positively. **Brain pattern** (Figure 3B)**:** The largest effects were found in bilateral positive GMV weights in in the cuneus and the left primary somatosensory cortex as well as bilateral negative weights in the cingulate. Smaller positive weights were found in the right occipital region and the left DLPFC, whereas negative weighting was detected in the left insula, the right caudate nucleus, the left supramarginal gyrus, the right hippocampus and bilaterally in the fusiform gyrus.

In summary, LV1 and LV3 represented mostly patterns of age- and sex-related brain maturation processes respectively, whereas the other three LV were more trauma-specific with LV2 reflecting an age-informed sexual abuse pattern, LV4 displaying a sex-dependent signature of physical and sexual abuse and LV5 containing an emotional trauma pattern.

SPLS results: correlation between latent scores and clinical domains

In the discovery sample, correlation analyses between clinical domains and latent scores yielded several significant results for all three CT-specific LV (Table 3, Table 4) and for LV1 and LV3 as well (Tables S15, S16).

LV2 (sexual abuse & age). Phenotypic scores: Negative correlations were observed for GF:S, GF:R, GAF:S, GAF:D/I and WHOQOL-BREF as well as NEO-FFI extraversion, openness, agreeableness, conscientiousness (ρ-range: -0.09-(-0.30), P-range: <10^{-3}-.04). Positive correlations were detected for NEO-FFI neuroticism and BDI scores (ρ: -0.09-(-0.30), P: <10^{-3}-.04). **Brain scores:** No significant associations were detected.

LV4 (sexual/physical abuse & sex). Phenotypic scores: We detected negative correlations for most GAF, GF and WHOQOL-BREF domains as well as the NEO-FFI domains of extraversion and conscientiousness (ρ: -0.09-(-0.30), *P*: <10^{-3}-.04). Positive associations were found for NEO-FFI neuroticism and BDI total scores (ρ: 0.18-0.21, *P*: <10^{-3}). **Brain scores:** Negative correlations were detected for GF:S and GF:R as well as GAF:S, GAF:D/I and WHOQOL-BREF (ρ: -0.11-(-0.24), *P*: <10^{-3}-.04). We observed a positive association with NEO-FFI neuroticism (ρ=0.11, *P*=.05).

LV5 (emotional abuse/neglect). Phenotypic scores: Negative correlations were detected for all GAF, GF and WHOQOL-BREF domains as well as NEO-FFI extraversion, agreeableness and conscientiousness (ρ: -0.22-(-0.47), *P*: <10^{-3}-.04). Positive correlations were found for BDI and NEO-FFI neuroticism levels (ρ = 0.44-0.48, *P*<10^{-3}). **Brain scores:** Negative correlations were found for GAF, GF and WHOQOL-BREF domains as well as NEO-FFI extraversion and conscientiousness (ρ: = -0.09-(-0.18), *P*: <10^{-3}-0.04). Positive correlations were observed for BDI and NEO-FFI neuroticism (ρ: 0.13-0.19, *P*: <10^{-3}).

External clinical validation of the SPLS trauma model

Fifty-nine of 84 (70%) significant clinical associations from the discovery sample were successfully validated in the replication sample, whereby 48 of 61 (79%) phenotype-level correlations and 11 of 23 (48%) brain-level correlations were replicated. Two phenotypic and 18 brain-level associations were additionally detected, amounting to a total of 79 significant clinical associations (50 phenotypic, 29 brain-level) in the replication sample. Moreover, none of the significant correlations changed their orientation (Table 3, Table 4).

LV2 (sexual abuse & age). Phenotypic scores: 12 of 18 (67%) associations were replicated. Additional significant associations were found for GAF:S Past Month (ρ=-0.19, *P*<10^{-3}) and NEO-FFI extraversion (ρ=-0.18), *P*<10^{-3}). **Brain scores:** Additional significant, positive associations were detected for 8 GAF and GF measures (ρ: 0.13-0.20, *P*: <10^{-3}-.03).

LV4 (sexual/physical abuse & sex). Phenotypic scores: 13 of 20 (65%) associations were replicated, whereas additional correlations were not found. **Brain scores:** 3 of 3 (100%) correlations were replicated, while further correlations were found for GAF and GF, NEO-FFI extraversion and WHOQOL-BREF physical (ρ: -0.11-(-0.19), *P*: <10^{-3}-.04) as well as BDI (ρ=0.18, *P*<10^{-3}).

LV5 (emotional abuse/neglect). Phenotypic scores: 23 of 23 (100%) associations were replicated and no additional correlations were detected. **Brain scores:** 8 of 20 (40%) associations were replicated and one additional correlation was detected for GAF:S Lifetime (ρ=-0.15, *P*=.01).

Sociodemographic exploration of the SPLS trauma model

Correlation analyses between individual latent scores of LV2, LV4 and LV5 and sociodemographic features yielded several significant results (Tables S17-S24).

Discovery sample: LV2 (sexual abuse & age): Positive associations were found between brain scores and population size at place of living (ρ=0.28, *P*=.01), whereas negative correlations were detected between phenotypic scores and number of offspring, married status and years of education (ρ=-0.29-(-0.32), *P*: <10^{-3}-.01). **LV4 (physical/sexual abuse & sex):** Phenotypic scores were negatively associated with years of education (ρ=-0.29, *P*=.04). **LV5 (emotional abuse/neglect):** Brain scores were negatively correlated with population at place of living (ρ=-0.26, *P*=.04), while phenotypic scores were positively associated with lower education of the mother (ρ=0.27, *P*=.03).

Replication sample: No significant correlations were detected.

Discussion

The goal of this study was a novel, comprehensive investigation of CT using a naturalistic and transdiagnostic machine learning approach. We performed SPLS analysis of CT-related phenotypic data and GMV in order to generate a transdiagnostic and multi-layered CT model. We explored the clinical validity and sociodemographic ramifications of this CT model and confirmed the majority of our findings in a prospectively acquired replication sample.

We found five significant LV, of which three (LV2, LV4, LV5) were more specifically linked to CT, while the other two (LV1, LV3) represented predominantly age- and sex-related effects (Supplementary Results). As all three CT-specific LV did not contain any weighting for study group, they can be regarded as transdiagnostic signatures.

The highly parsimonious signature of LV2 links sexual abuse in younger individuals to GMV alterations along the prefronto-thalamo-cerebellar axis. Further GMV variation associated with CT involved the temporal and angular gyrus as well as the basal ganglia and the cuneus region. While the PFC has been among the most well-established GMV correlates of childhood trauma, the other brain regions in this signature have not yet been consistently associated with CT (20, 52, 53). Instead, the prefronto-thalamo-cerebellar axis has been implicated in various aspects of (social) cognition (54, 55) and associative learning (56). Additionally, it has been proposed as a key system involved in psychiatric disorders, including affective (57, 58) and non-affective psychoses (59-61). Hence, the LV2 signature may point to disease-connected alterations in the prefronto-thalamo-cerebellar axis associated with sexual trauma experiences.

In LV4, a pattern of sexual and physical abuse was associated with a dense GMV signature involving the postcentral gyrus, hippocampus and PFC (20) as well as limbic brain regions associated with emotional learning and social cognitive processes (62, 63). This signature was inversely expressed in male and female individuals. This supports previous studies, which reported contrary volumetric and connectivity changes in the PFC, the hippocampus, the amygdala and the anterior cingulate cortex for male and female individuals after exposure to CT (44). Moreover, the LV4 trauma signature aligns with a recent study reporting an interaction between childhood trauma and sex on hippocampal volume, which could be predicted by neglect in males and abuse in females (45). This evidence emphasizes that the limbic system and key CT-associated regions are inversely affected by abuse in men and women and highlights the paramount need for further gender-specific CT research and gender-tailored therapeutic approaches in traumatized individuals.

The patterns observed in LV2 and LV4 further reflect previous findings concerning brain development, which showed differential developmental trajectories for female and male brains (64, 65). The brain signature of LV2 comprises specifically the medial prefrontal cortex, i.e., a cortical region that fully develops during adolescence (64), while the LV4 signature covers the temporal, prefrontal and occipital lobes—regions in which sex has shown to have a nonlinear relationship with age (65). Thus, sex exerts a modulating influence on cortical development from childhood to adulthood. The strong covariation of the age and sex effects on childhood trauma signatures might be explained in a developmental framework in which not only men and women differently react to trauma, but their brains may also differentially develop as a result of CT.

LV5 links emotional abuse and neglect to a brain pattern consisting of diverse GMV changes. First, emotional trauma is connected to brain regions responsible for sensory processing via the postcentral gyrus and the occipital lobe (66, 67). Second, associations with the DLPFC, the insula and the cingulate gyrus relate emotional trauma to key brain systems subserving emotional processing (68-70), memory formation (71, 72) and risk for psychiatric disorders (73-75). These findings support the hypothesis that trauma experience is connected to sensory and perceptive dysregulations, which could also be accessed therapeutically (76-78).

All three CT-specific signatures yielded significant correlations with clinical measures, which were largely validated in the replication sample. The phenotypic scores of the age-dependent sexual abuse signature (LV2) revealed strong connections to an impaired clinical phenotype in the discovery and the replication sample. The brain scores appeared dissociated from that in both populations, yielding no significant associations in the discovery sample and positive associations with GAF and GF in the replication sample. One possible interpretation might be that the signature of LV2 had been influenced by unaccounted resilience dynamics, in which neurobiological adaptations compensate for the phenomenological trauma load, thus maintaining levels of functioning (79, 80). Additional analyses revealed a positive correlation between LV2 brain scores and population size at place of living as well as

inverse associations between LV2 phenotypic scores and number of offspring, marital status and years of education in the discovery sample. These findings suggest a possible connection between resilience-conferring brain adaptations and urbanicity as well as higher sexual trauma loadings and social (offspring, marriage) and educational status. Moreover, LV4 and LV5 revealed the most extensive significant associations with functioning, depressivity, personality domains and quality of life in the discovery and the replication sample. Both trauma and brain scores of LV4 and LV5 were significantly correlated with lower levels of social and role functioning, more pronounced symptom severity, increased impairment as well as higher levels of depressivity and reduced quality of life. Additionally, we found a strong connection between individual trauma loads and higher levels of neuroticism as well as lower levels of extraversion, conscientiousness, agreeableness and openness. Finally, phenotypic loading of LV4 was associated with lower educational status, whereas LV5 loading was connected to a less urban environment (phenotypic scores) and lower maternal educational status (brain scores). These findings confirm and extend the current body of literature on the negative clinical implications and complex sociodemographic constellations of CT. It has been well established that CT has a broad negative impact on mental health, ranging from a higher vulnerability for mental disorders, the presence of maladaptive personality traits to decreased psychosocial functioning and quality of life (21). Nonetheless, beyond these general associations, very few studies have investigated more domain-specific aspects of CT (81-83). Thus, our results provide more extensive evidence for a differential neurobiological, clinical and sociodemographic imprint of CT. Moreover, the connection between the CT signatures and the presence of vulnerability-conferring personality domains, provides novel neurobiological evidence for the long-standing and still controversially discussed hypothesis that adverse childhood experiences lead to the development of dysfunctional personality structures (9, 84, 85).

As 70% of these clinical associations were successfully validated in the replication sample and 20 additional significant clinical correlations (18 on the brain-level) emerged, the multi-layered SPLS trauma model appears robustly generalizable both at the phenotypic and neuroanatomical levels.

Furthermore, it emphasizes the validity and paramount clinical relevance of the multi-dimensional childhood trauma concept across a broad diagnostic spectrum in two large-scale international samples of young adults and adolescent individuals.

Potential limitations of the study need to be considered. Some of the brain variance might be attributed to psychopharmacological treatment. Yet, our transdiagnostic study design should provide a robust framework against such confounders. Moreover, some LV signatures were partly associated with MRI data quality, albeit the impact being minimal. Additional SPLS analyses further supported the main results (Supplementary Results). Furthermore, the associative nature of our results should not lead to causal assumptions. Directed network analysis and supervised machine learning could help elucidate the inner workings of CT and assess their predictive value for psychiatric disorders.

To our knowledge, this is the first study that investigated CT in a transdiagnostic sample of young adults using a data-driven machine learning approach and a comprehensive, multidimensional framework for CT operationalization. Our novel approach confirms that CT is composed of distinct phenotypic-neuroanatomical dimensions which may have complex ramifications into clinically relevant phenotypes. We found CT signatures of sexual, physical and emotional trauma with distinct neuroanatomic correlates in prefronto-thalamo-cerebellar, limbic and sensory networks. Furthermore, sex-dependent combined sexual and physical abuse as well as emotional trauma appeared to be specifically predictive of relevant clinical state and trait phenotypes, whereas the age-dependent sexual abuse signature may have been further influenced by neurobiological resilience pathways and interacted with modulating factors such as urbanicity, education and family status. As these results were largely validated in a large replication sample, our findings demonstrate that machine learning tools can generate new and generalizable insights into complex human phenomena such as CT and might help to develop superior treatments targeting CT and its psychiatric consequences at short- to long-term time scales.

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Legends

Legend Figure 1: Age-dependent sexual abuse signature of LV2

A) The barplot visualizes the direction and the values of the weights included in the phenotypic pattern of LV2. 2 questions from the CTQ sexual abuse subscale (CTQ21, CTQ24) received a positive weight, while age received a negative weight. B) Depicted is the brain pattern of LV2, with positive weighting of voxels displayed in red and negative weighting displayed in blue color scale.

Legend Figure 2: Sex-dependent sexual and physical abuse signature of LV4

A) The barplot visualizes the direction and the values of the weights included in the phenotypic pattern of LV4. Three questions from the CTQ physical abuse subscale (CTQ09, CTQ12, CTQ15) and four questions from the sexual abuse subscale (CTQ20, CTQ23, CTQ24, CTQ27) received positive weights. Male sex received a negative and female sex a positive weight. B) Depicted is the brain pattern of LV4, with positive weighting of voxels displayed in red and negative weighting displayed in blue color scale.

Legend Figure 3: Emotional trauma signature of LV5

A) The barplot visualizes the direction and the values of the weights included in the phenotypic pattern of LV5. Three questions each from the CTQ subscales of emotional abuse (CTQ03, CTQ14, CTQ18) and emotional neglect (CTQ07, CTQ13, CTQ28) received positive weights. B) Depicted is the brain pattern of LV5, with positive weighting of voxels displayed in red and negative weighting displayed in blue color scale.

Legend Table 1: Clinical and demographic characteristics of the discovery sample.

Abbreviations: HC, healthy control; ROD, recent-onset of depression; CHR, clinical high-risk state; ROP, recent-onset of psychosis; SD, standard deviation; NA, not available; GAF:S, Global Assessment of Functioning Social Scale; GAF:D/I, GAF Disability/Impairment Scale; GF:S, Global Functioning Social Scale; GF:R, GF Role Scale; PANSS, Positive and Negative Symptom Scale; BDI, Beck Depression Inventory. Significant *P* values are highlighted in bold font. *P* values are stated after FDR-correction for multiple testing.

Legend Table 2: Group-level statistics for CTQ differences between discovery and replication sample.

Abbreviations: HC, healthy control; ROD, recent-onset of depression; CHR, clinical high-risk state; ROP, recent-onset of psychosis; SD, standard deviation; H, Kruskal-Wallis-H-test statistic (χ^2). *P* values are stated after FDR-correction for multiple testing.

Legend Table 3: Spearman's correlation analyses between latent scores and clinical domains of functioning in the discovery and replication sample.

Results are states as correlation coefficient ρ, followed by its *P* value in brackets: ρ (*P* value). Abbreviations: D, Discovery Sample; R, Replication Sample; GAF:S, Global Assessment of Functioning Social Scale; GAF:D/I, GAF Disability/Impairment Scale; GF:S, Global Functioning Social Scale; GF:R, GF Role Scale. Significant *P* values are highlighted in bold font. All *P* values FDR-corrected for multiple testing (family of tests with Table 4).

Legend Table 4: Spearman's correlation analyses between latent scores and clinical domains of depressivity, personality and quality of life in the discovery and replication sample.

Results are states as correlation coefficient ρ, followed by its *P* value in brackets: ρ (*P* value). Abbreviations: D, Discovery Sample; R, Replication Sample; BDI, Beck Depression Inventory; NEO-FFI, Neuroticism-Extraversion-Openness (NEO) Five-Factor Inventory; WHOQOL-BREF, World Health Organization Quality of Life Short Version. Significant *P* values are highlighted in bold font. All *P* values FDR-corrected for multiple testing (family of tests with Table 3).

Tables

Table 1: Clinical and demographic characteristics of the discovery sample.

	All	HC	ROD	CHR	ROP	H/χ^2	*P* Value
Age, mean, years	28.39	28.50	29.09	27.02	28.73	8.98[a]	**.011**
SD	6.00	6.45	6.21	4.84	5.63		
Sex, women/men %	53	62	54	48	38	7.41[b]	**.024**
Years of Education, mean, years	14.77	15.69	14.70	13.78	13.93	5.56[a]	.062
SD	3.25	3.17	3.16	3.03	3.15		
GAF:S, mean	65.15	86.52	55.76	54.95	41.13	86.63[a]	**$<10^{-3}$**
SD	21.12	6.51	12.48	11.00	13.22		
GAF:D/I, mean	65.57	85.16	56.36	55.93	44.44	59.82[a]	**$<10^{-3}$**
SD	20.1	5.86	14.42	13.94	12.23		
GF:S, mean	7.15	8.51	6.47	6.51	5.68	28.11[a]	**$<10^{-3}$**
SD	1.67	0.84	1.34	1.36	1.47		
GF:R, mean	6.97	8.56	6.23	6.18	5.24	29.66[a]	**$<10^{-3}$**
SD	1.90	0.75	1.69	1.44	1.65		
Handedness, right-handed, %	91	94	90	88	90	0.41[b]	.82
PANSS total, mean	55.97	NA	47.55	50.57	69.29	87.93[a]	**$<10^{-3}$**
SD	18.83	NA	10.91	13.23	21.92		
PANSS positive, mean	11.92	NA	7.67	10.23	17.68	204.19[a]	**$<10^{-3}$**
SD	6.00	NA	1.24	2.96	6.50		
PANSS negative, mean	13.77	NA	12.56	12.53	16.14	21.62[a]	**$<10^{-3}$**
SD	6.40	NA	4.98	5.88	7.37		
PANSS general, mean	30.25	NA	27.31	27.78	35.47	50.54[a]	**$<10^{-3}$**
SD	9.38	NA	6.73	6.90	11.23		
BDI, mean	15.78	3.73	26.23	25.49	21.05	11.05[a]	**.004**
SD	14.62	5.27	13.82	12.24	12.49		
Study center						149.87[b]	**$<10^{-3}$**
Munich	181	58	44	38	41		
Basel	84	37	15	17	15		
Cologne	131	59	24	20	28		
Birmingham	80	43	14	13	10		
Milan	37	13	6	7	11		
Turku	74	23	12	17	22		
Udine	62	31	14	12	5		
Total	649	264	129	124	132		

[a] Kruskal-Wallis-Test (H test), [b] χ^2-test

Table 2: Group-level statistics for CTQ differences between discovery and replication sample.

CTQ\Study groups		All	HC	ROD	CHR	ROP	H	*P*
Total	D	30.0 (12.1)	23.8 (5.8)	33.0 (14.6)	34.8 (13.1)	34.9 (12.5)	5.08	.55 [a]
	R	31.3 (13.1)	24.0 (6.9)	33.6 (11.9)	35.6 (13.7)	34.8 (15.8)	1.20	.76 [a]
	P	.50 [b]	.91 [b]	.59 [b]	.84 [b]	.61 [b]		
Emotional Abuse	D	8.4 (4.0)	6.5 (2.4)	9.2 (4.5)	10.2 (4.4)	9.8 (4.4)	5.20	.52 [a]
	R	9.0 (4.5)	6.4 (2.0)	9.4 (4.1)	10.8 (4.9)	10.1 (5.2)	3.70	.50 [a]
	P	.50 [b]	.71 [b]	.69 [b]	.72 [b]	.97 [b]		
Physical Abuse	D	6.0 (2.5)	5.4 (1.0)	6.5 (3.3)	6.5 (3.1)	6.5 (2.9)	1.33	.95 [a]
	R	6.2 (2.6)	5.5 (1.5)	6.3 (2.4)	6.6 (3.0)	6.6 (3.3)	0.25	.98 [a]
	P	.56 [b]	.77 [b]	.64 [b]	.72 [b]	.89 [b]		
Sexual Abuse	D	5.7 (2.4)	5.2 (0.9)	5.9 (2.8)	6.0 (2.8)	6.3 (3.1)	2.84	.50 [a]
	R	5.8 (2.6)	5.1 (0.9)	5.9 (2.9)	6.1 (2.9)	6.3 (3.2)	2.39	.60 [a]
	P	.95 [b]	.71 [b]	.76 [b]	.92 [b]	.87 [b]		
Emotional Neglect	D	5.0 (4.4)	2.9 (3.0)	6.3 (5.1)	6.8 (4.5)	6.4 (4.4)	1.73	.80 [a]
	R	5.4 (4.6)	3.0 (3.2)	6.8 (4.8)	6.7 (4.4)	6.1 (5.0)	1.46	.72 [a]
	P	.54 [b]	.95 [b]	.61 [b]	.86 [b]	.70 [b]		
Physical Neglect	D	4.8 (2.4)	3.8 (1.4)	5.1 (2.9)	5.3 (2.6)	5.8 (2.8)	9.70	.05 [a]
	R	4.9 (2.5)	3.9 (1.6)	5.1 (2.3)	5.4 (2.6)	5.6 (3.1)	0.19	.99 [a]
	P	.63 [b]	.74 [b]	.62 [b]	.99 [b]	.51 [b]		
Denial	D	0.6 (0.9)	0.7 (1.0)	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)	1.22	.99 [a]
	R	0.6 (0.9)	0.8 (1.1)	0.4 (0.8)	0.3 (0.8)	0.6 (0.9)	7.73	.15 [a]
	P	.85 [b]	.65 [b]	.88 [b]	.82 [b]	.51 [b]		

[a] Kruskal-Wallis-Test (H test), [b] Wilcoxon-Mann-Whitney-Test

761 **Table 3: Spearman's correlation analyses between latent scores and clinical domains of functioning**
762 **in the discovery and replication sample.**

		LV2		LV4		LV5	
		Sexual abuse & age		Sexual/physical abuse & sex		Emotional abuse/neglect	
		Phenotypic score	Brain score	Phenotypic score	Brain score	Phenotypic score	Brain score
GAF:S							
Lifetime	D	**-0.17 (<10^{-3})**	0.01 (.99)	**-0.15 (<10^{-3})**	**-0.13 (.01)**	**-0.24 (<10^{-3})**	-0.05 (.32)
	R	**-0.20 (<10^{-3})**	0.07 (.52)	**-0.17 (<10^{-3})**	**-0.24 (<10^{-3})**	**-0.29 (<10^{-3})**	**-0.15 (.01)**
Past Year	D	**-0.13 (<10^{-3})**	0.03 (.7)	**-0.13 (<10^{-3})**	-0.09 (.18)	**-0.32 (<10^{-3})**	**-0.09 (.03)**
	R	**-0.17 (<10^{-3})**	0.12 (.07)	**-0.20 (<10^{-3})**	**-0.13 (.03)**	**-0.38 (<10^{-3})**	-0.05 (.7)
Past Month	D	-0.07 (.15)	0.10 (.33)	**-0.09 (.03)**	-0.02 (.73)	**-0.36 (<10^{-3})**	**-0.11 (.01)**
	R	**-0.19 (<10^{-3})**	**0.15 (.01)**	**-0.19 (<10^{-3})**	**-0.15 (.01)**	**-0.38 (<10^{-3})**	**-0.12 (.04)**
GAF:D/I							
Lifetime	D	**-0.17 (<10^{-3})**	0.02 (.8)	**-0.14 (<10^{-3})**	-0.10 (.08)	**-0.29 (<10^{-3})**	**-0.18 (<10^{-3})**
	R	**-0.19 (<10^{-3})**	0.05 (.9)	**-0.14 (.02)**	**-0.17 (<10^{-3})**	**-0.28 (<10^{-3})**	**-0.16 (.01)**
Past Year	D	**-0.16 (<10^{-3})**	0.04 (.64)	**-0.14 (<10^{-3})**	-0.08 (.3)	**-0.35 (<10^{-3})**	**-0.16 (<10^{-3})**
	R	**-0.14 (.02)**	**0.13 (.03)**	**-0.14 (.02)**	-0.08 (.32)	**-0.36 (<10^{-3})**	-0.07 (.44)
Past Month	D	-0.09 (.05)	0.08 (.75)	**-0.10 (.01)**	-0.05 (.55)	**-0.38 (<10^{-3})**	**-0.15 (<10^{-3})**
	R	-0.10 (.14)	**0.16 (<10^{-3})**	-0.11 (.11)	-0.09 (.19)	**-0.35 (<10^{-3})**	**-0.13 (.03)**
GF:S							
Current	D	**-0.11 (.01)**	0.10 (.3)	**-0.12 (<10^{-3})**	0.01 (.99)	**-0.35 (<10^{-3})**	**-0.12 (<10^{-3})**
	R	-0.10 (.17)	**0.16 (.01)**	**-0.13 (.04)**	-0.10 (.12)	**-0.37 (<10^{-3})**	-0.10 (.12)
Low Past Year	D	**-0.10 (.02)**	0.07 (.52)	**-0.12 (<10^{-3})**	0.02 (.83)	**-0.34 (<10^{-3})**	**-0.11 (.01)**
	R	-0.08 (.31)	**0.17 (<10^{-3})**	-0.11 (.09)	-0.06 (.68)	**-0.38 (<10^{-3})**	-0.07 (.37)
High Past Year	D	**-0.15 (<10^{-3})**	0.04 (.64)	**-0.15 (<10^{-3})**	-0.04 (.62)	**-0.31 (<10^{-3})**	**-0.09 (.04)**
	R	-0.10 (.14)	0.11 (.11)	-0.11 (.09)	**-0.14 (.02)**	**-0.31 (<10^{-3})**	-0.09 (.19)
High Lifetime	D	**-0.15 (<10^{-3})**	0.06 (.55)	**-0.14 (<10^{-3})**	-0.08 (.43)	**-0.30 (<10^{-3})**	**-0.15 (<10^{-3})**
	R	**-0.13 (0.03)**	0.02 (.76)	-0.09 (.18)	**-0.14 (.02)**	**-0.22 (<10^{-3})**	-0.10 (.16)
GF:R							
Current	D	**-0.09 (.04)**	0.11 (.09)	-0.08 (.05)	0.01 (.99)	**-0.38 (<10^{-3})**	**-0.18 (<10^{-3})**
	R	-0.11 (.08)	**0.19 (<10^{-3})**	-0.11 (.09)	-0.11 (.08)	**-0.30 (<10^{-3})**	**-0.15 (.01)**
Low Past Year	D	-0.07 (.13)	0.10 (.25)	-0.07 (.08)	0.02 (.75)	**-0.37 (<10^{-3})**	**-0.18 (<10^{-3})**
	R	-0.09 (.22)	**0.20 (<10^{-3})**	-0.10 (.15)	-0.08 (.28)	**-0.32 (<10^{-3})**	**-0.14 (.01)**
High Past Year	D	**-0.14 (<10^{-3})**	0.08 (.5)	**-0.09 (.02)**	-0.02 (.79)	**-0.30 (<10^{-3})**	**-0.15 (<10^{-3})**
	R	**-0.13 (.04)**	**0.15 (.01)**	-0.09 (.22)	-0.04 (.5)	**-0.25 (<10^{-3})**	-0.08 (.3)
High Lifetime	D	**-0.13 (<10^{-3})**	0.10 (.21)	**-0.08 (.05)**	-0.05 (.53)	**-0.22 (.05)**	**-0.14 (<10^{-3})**
	R	**-0.19 (<10^{-3})**	0.04 (.52)	**-0.11 (.12)**	**-0.12 (.05)**	**-0.16 (.01)**	**-0.12 (.04)**

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765 **Table 4: Spearman's correlation analyses between latent scores and clinical domains of**
766 **depressivity, personality and quality of life in the discovery and replication sample.**

		LV2		LV4		LV5	
		Sexual abuse + age		Sexual/physical abuse + sex		Emotional abuse/neglect	
		Phenotypic score	Brain score	Phenotypic score	Brain score	Phenotypic score	Brain score
BDI							
Total score	D	**0.11 (.01)**	-0.08 (.84)	**0.18 (<10^{-3})**	0.09 (.25)	**0.48 (<10^{-3})**	**0.19 (<10^{-3})**
	R	**0.21 (<10^{-3})**	-0.08 (.32)	**0.3 (<10^{-3})**	**0.18 (<10^{-3})**	**0.48 (<10^{-3})**	**0.14 (.02)**
NEO-FFI							
Neuroticism	D	**0.15 (<10^{-3})**	-0.01 (.9)	**0.21 (<10^{-3})**	**0.11 (.05)**	**0.44 (<10^{-3})**	**0.13 (<10^{-3})**
	R	**0.17 (<10^{-3})**	0.01 (.99)	0.29 (<10^{-3})	**0.23 (<10^{-3})**	**0.43 (<10^{-3})**	0.05 (.86)
Extraversion	D	-0.04 (.45)	0.05 (.58)	**-0.08 (.05)**	0.01 (.84)	**-0.30 (<10^{-3})**	**-0.12 (.01)**
	R	**-0.18 (<10^{-3})**	-0.01 (.98)	**-0.21 (<10^{-3})**	**-0.17 (<10^{-3})**	**-0.33 (<10^{-3})**	-0.06 (.63)
Openness	D	-0.08 (.07)	-0.02 (.81)	-0.06 (.19)	-0.04 (.61)	0.02 (.5)	0.06 (.27)
	R	0.01 (.92)	-0.02 (.69)	0.01 (.98)	0.01 (.88)	-0.07 (.47)	0.07 (.46)
Agreeableness	D	**-0.16 (<10^{-3})**	-0.07 (.51)	-0.07 (.11)	0.06 (.5)	**-0.23 (.01)**	0.02 (.5)
	R	-0.11 (.11)	0.02 (.73)	0.02 (.84)	0.01 (.99)	**-0.15 (.01)**	0.01 (.99)
Conscientiousness	D	**-0.17 (<10^{-3})**	-0.05 (.59)	**-0.1 (.01)**	0.03 (.71)	**-0.33 (<10^{-3})**	**-0.1 (.02)**
	R	**-0.3 (<10^{-3})**	-0.07 (.47)	**-0.2 (<10^{-3})**	-0.07 (.51)	**-0.32 (<10^{-3})**	-0.01 (.5)
WHOQOL-BREF							
Physical	D	**-0.09 (.04)**	0.03 (.68)	**-0.15 (<10^{-3})**	-0.07 (.54)	**-0.44 (<10^{-3})**	**-0.12 (.01)**
	R	**-0.12 (.05)**	0.1 (.18)	**-0.22 (<10^{-3})**	**-0.15 (.01)**	**-0.45 (<10^{-3})**	**-0.13 (.03)**
Psychosocial	D	**-0.13 (<10^{-3})**	0.03 (.71)	**-0.2 (<10^{-3})**	**-0.11 (.05)**	**-0.47 (<10^{-3})**	**-0.12 (<10^{-3})**
	R	**-0.21 (<10^{-3})**	0.05 (.8)	**-0.3 (<10^{-3})**	**-0.19 (<10^{-3})**	**-0.45 (<10^{-3})**	-0.11 (.09)
Social Relationships	D	**-0.11 (.01)**	0.07 (.52)	**-0.11 (.01)**	-0.01 (.85)	**-0.41 (<10^{-3})**	**-0.11 (.01)**
	R	-0.09 (.18)	0.07 (.41)	**-0.15 (.01)**	-0.07 (.55)	**-0.41 (<10^{-3})**	-0.1 (.15)
Environment	D	-0.08 (.08)	0.01 (.92)	-0.05 (.54)	**-0.17 (<10^{-3})**	-0.06 (.28)	**-0.45 (<10^{-3})**
	R	-0.04 (.5)	0.11 (.1)	-0.06 (.68)	-0.1 (.12)	-0.06 (.66)	**-0.36 (<10^{-3})**

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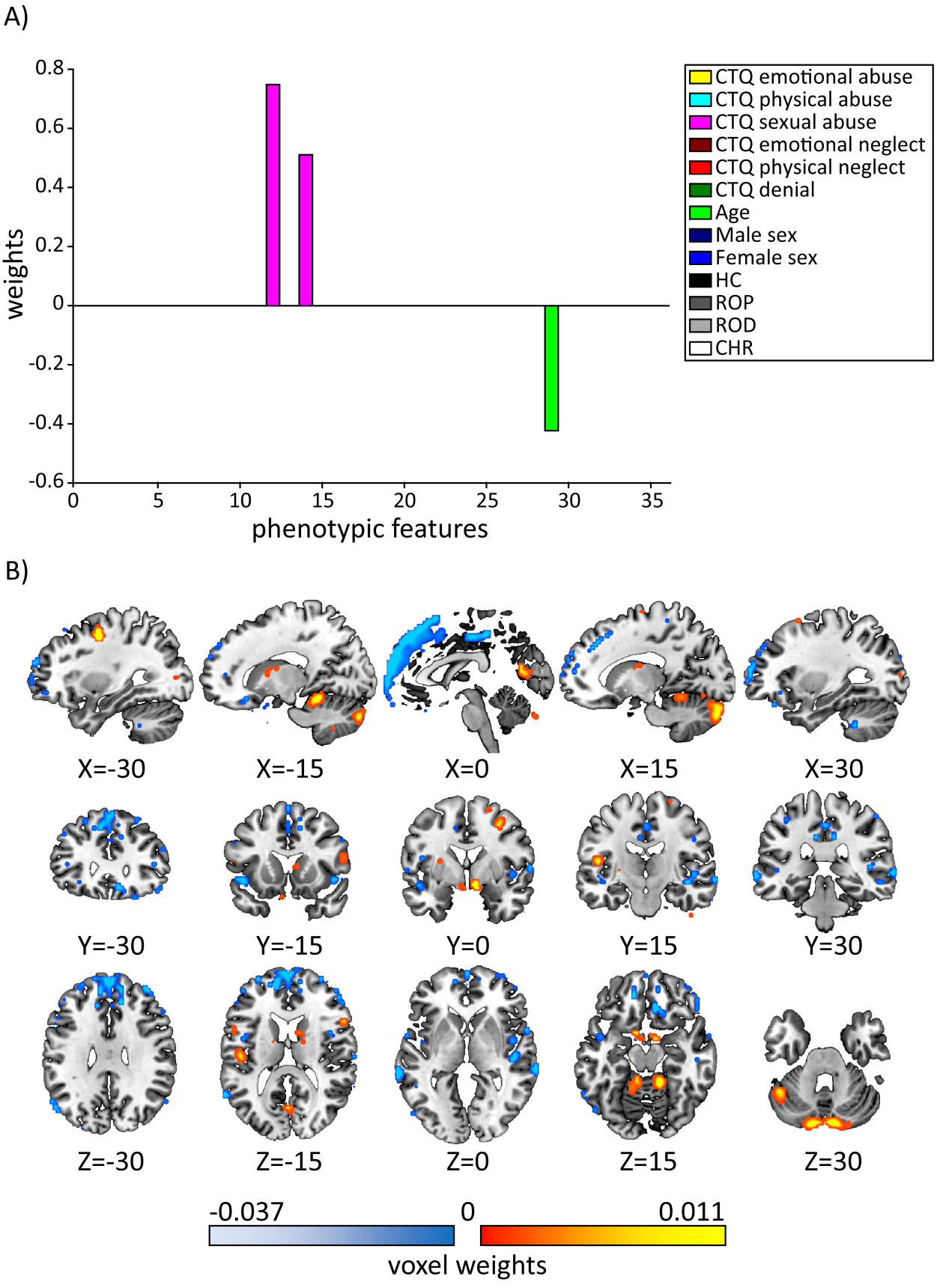
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CTQ emotional neglect
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CTQ denial
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Male sex
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HC
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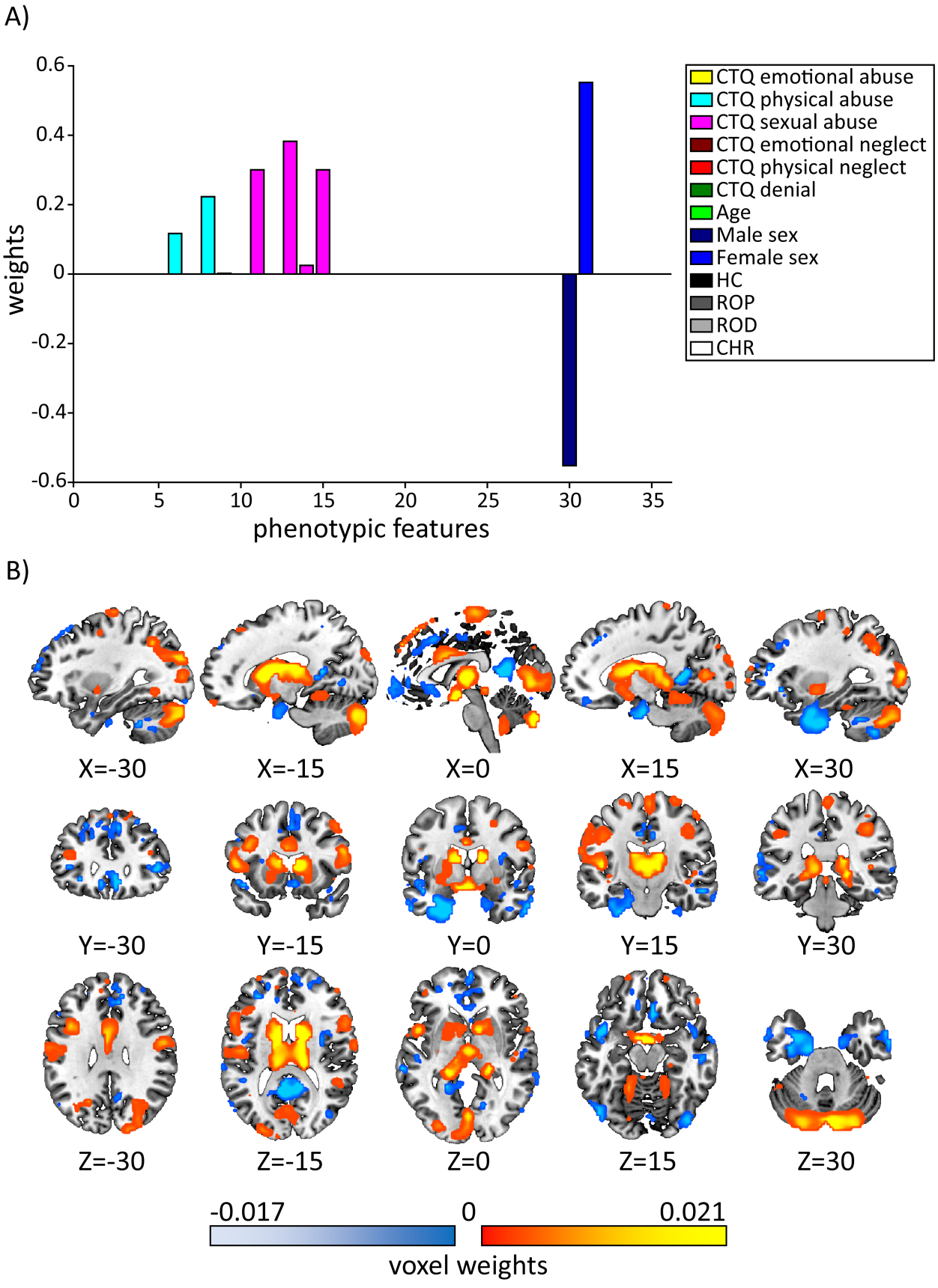
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CTQ sexual abuse
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CTQ denial
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ROP
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CHR
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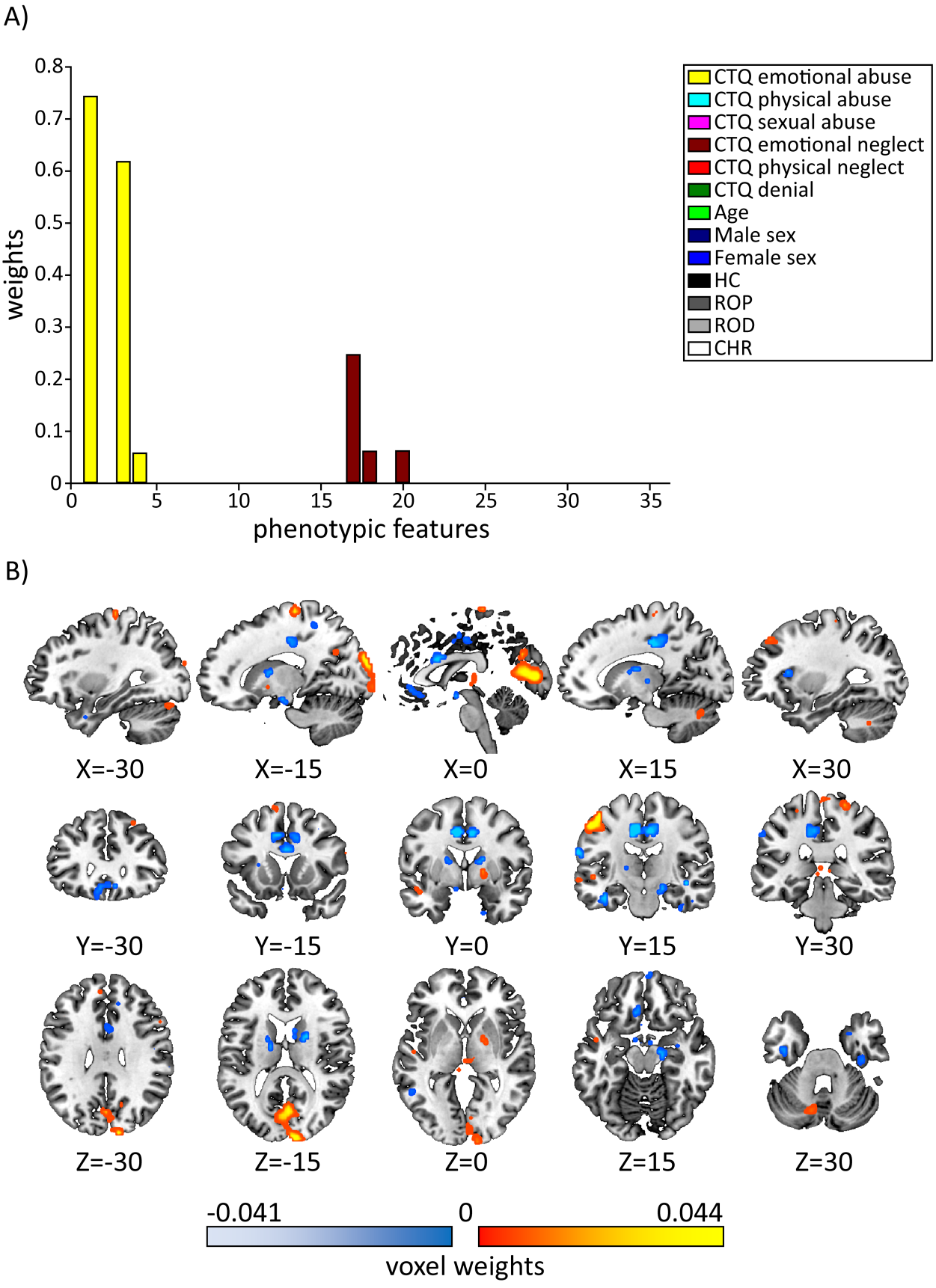
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phenotypic features
CTQ emotional abuse
CTQ physical abuse
CTQ sexual abuse
CTQ emotional neglect
CTQ physical neglect
CTQ denial
Age
Male sex
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HC
ROP
ROD
CHR
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