

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

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

3 **Running Title:** Neuroanatomical signatures of childhood adversity

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59 **Abstract**

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

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

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

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

81

82 **Introduction**

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

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

102 We took an in-depth approach to better characterize the complex neuroanatomy of CT by investigating
103 the relationship between structural brain data and CT in the multi-center, European PRONIA cohort
104 (Personalized Prognostic Tools for Early Psychosis Management study; <https://www.pronia.eu/>).
105 Following a transdiagnostic, data-driven study design, we applied the multivariate Sparse Partial Least
106 Squares (SPLS) algorithm to identify parsimonious and interpretable phenotype-brain signatures (34).

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

114 **Methods and Materials**

115 **Study participants**

116 The PRONIA cohort includes healthy controls (HC), participants with recent-onset depression (ROD) or
117 psychosis (ROP) and patients with clinical high-risk states for psychosis (CHR). The cohort is divided
118 into a discovery sample for model generation and a replication sample for model validation
119 (Supplementary Material and Koutsouleris et al. (35)). Data from 649 participants from the discovery
120 sample (264 HC, 129 ROD, 132 ROP, 124 CHR, Table 1) and 427 individuals from the replication sample
121 (135 HC, 96 ROD, 92 ROP, 104 CHR, Table S6) were obtained for the analysis.

122 **Childhood trauma, clinical and sociodemographic features assessment**

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

129 Functioning was evaluated using the Global Assessment of Functioning Symptoms and
130 Disability/Impairment Scale (GAF:S and GAF:D/I) (39) and the Global Functioning Social and Role Scale

131 (GF:S and GF:R) (40), while depressive symptoms were quantified using the Beck Depression Inventory
132 (BDI) (41). The WHO Quality of Life Short Version (WHOQOL-BREF) was applied to measure individual
133 perception of quality of life (42). Personality domains were assessed using the NEO Five Factor
134 Inventory (NEO-FFI), quantifying personality traits along five domains: openness, conscientiousness,
135 extraversion, agreeableness and neuroticism (43).

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

139 **MRI data acquisition and preprocessing**

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

147 **Sparse Partial Least Squares Analysis**

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

156 Another characteristic of SPLS is the enforcement of sparsity, whereby weights of zero are assigned to
157 features that did not yield any relevant association. The process of weighting and selecting features
158 according to their covariance is accomplished via l_1 - and l_2 -norm constraints, similar to elastic net
159 regularization (46), and controlled by a pair of hyperparameters. Additionally, every participant can be
160 assigned a pair of latent phenotypic and brain scores. These latent phenotypic and brain scores indicate
161 how strong a participant loads on the phenotypic and brain patterns of the LV, respectively, with greater
162 latent scores values reflecting higher individual loading and vice versa. We used these latent scores for
163 post-hoc correlation analyses to investigate clinical and sociodemographic aspects of the LV signatures
164 (34).

165 **Assessment of generalizability and significance**

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

180 Univariate partial correlation analysis between the seven study sites and the input datasets was used
181 within the NCV scheme to correct for site effects (49, 50).

182 **Univariate Analysis**

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

188 **Results**

189 **Group-level differences at baseline**

190 The clinical study populations (ROD, CHR, ROP) revealed significant differences with respect to age,
191 sex, GAF, GF, Positive and Negative Symptom Scale (PANSS) and BDI (Table 1, Table S7, S8).
192 Furthermore, a significant difference for the recruitment of study groups across sites was found (Table
193 1, Table S9). The clinical study populations also displayed significant differences in antidepressant,
194 antipsychotic and sedative treatment (Table S10, S11). Moreover, the clinical study populations of the
195 discovery and replication sample did not reveal any significant differences with regards to CTQ total or
196 subscale scores (Table 2, Table S12).

197 **SPLS results: association between phenotypic and brain data**

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

201 **LV1: age (P value = 1.9×10^{-4}). Phenotypic pattern** (Figure S6A): Age received the strongest positive
202 weight, whereas further positive weights were assigned to male sex, ROP status and to the subscales
203 of sexual abuse (5 items), physical abuse (4), emotional abuse (1) and physical neglect (1). Smaller

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

207 **LV2: sexual abuse & age ($P = 1.9 \times 10^{-4}$). Phenotypic pattern** (Figure 1A): Two questions from the sexual
208 abuse subscale were positively weighted, while age was negatively weighted. **Brain pattern** (Figure
209 1B): GMV was assigned negative weights bilaterally in the prefrontal cortex (PFC), particularly in the
210 dorsolateral (DLPFC) and medial prefrontal cortex (mPFC) regions. Further negative weights were
211 found bilaterally in the superior and middle temporal gyrus as well as unilaterally in the left angular
212 gyrus. Positive weighting was detected bilaterally in the cerebellum, the premotor cortex, the cuneus,
213 the lingual gyrus and the basal ganglia.

214 **LV3: sex ($P = 1.9 \times 10^{-4}$). Phenotypic pattern** (Figure S7A): The strongest positive and negative weights
215 were detected for male and female sex, respectively. Moreover, positive weights were assigned to
216 emotional abuse (1 item), physical abuse (2), sexual abuse (3), emotional neglect (1) and physical
217 neglect (2), while smaller negative weights were distributed to age, sexual abuse (1) and denial (1).
218 **Brain pattern** (Figure S7B): GMV was positively weighted in occipital, parietal and frontal areas,
219 particularly in the precuneus region, and negatively bilaterally in prefrontal, hippocampal and parietal
220 areas.

221 **LV4: physical/sexual abuse & sex ($P = 1.2 \times 10^{-3}$). Phenotypic pattern** (Figure 2A): Physical (3 items) and
222 sexual abuse (4 items) received positive weights, while male and female sex were weighted inversely.
223 **Brain pattern** (Figure 2B): The most profound effect was detected in bilateral positive weighting of
224 GMV in the primary somatosensory cortex, the basal ganglia and the cuneus as well as unilaterally
225 reduced GMV in the left fusiform gyrus and the right DLPFC. GMV was also positively weighted
226 bilaterally in the occipital gyrus, the angular and supramarginal gyrus as well as the thalamus. Smaller
227 clusters of negative GMV weights were discovered bilaterally in the superior and middle temporal
228 gyrus, the cingulate gyrus, the (para-)hippocampus, the precuneus and the right PFC.

229 **LV5: emotional abuse/neglect ($P = 1.9 \times 10^{-4}$). Phenotypic pattern** (Figure 3A): Emotional abuse (3
230 items) and neglect (3 items) were weighted positively. **Brain pattern** (Figure 3B): The largest effects
231 were found in bilateral positive GMV weights in in the cuneus and the left primary somatosensory
232 cortex as well as bilateral negative weights in the cingulate. Smaller positive weights were found in the
233 right occipital region and the left DLPFC, whereas negative weighting was detected in the left insula,
234 the right caudate nucleus, the left supramarginal gyrus, the right hippocampus and bilaterally in the
235 fusiform gyrus.

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

240 **SPLS results: correlation between latent scores and clinical domains**

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

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

249 **LV4 (sexual/physical abuse & sex). Phenotypic scores:** We detected negative correlations for most
250 GAF, GF and WHOQOL-BREF domains as well as the NEO-FFI domains of extraversion and
251 conscientiousness (ρ : -0.09-(-0.30), P : $<10^{-3}$ -.04). Positive associations were found for NEO-FFI
252 neuroticism and BDI total scores (ρ : 0.18-0.21, P : $<10^{-3}$). **Brain scores:** Negative correlations were

253 detected for GF:S and GF:R as well as GAF:S, GAF:D/I and WHOQOL-BREF (ρ : -0.11-(-0.24), P : $<10^{-3}$ -
254 .04). We observed a positive association with NEO-FFI neuroticism ($\rho=0.11$, $P=.05$).

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

261 **External clinical validation of the SPLS trauma model**

262 Fifty-nine of 84 (70%) significant clinical associations from the discovery sample were successfully
263 validated in the replication sample, whereby 48 of 61 (79%) phenotype-level correlations and 11 of 23
264 (48%) brain-level correlations were replicated. Two phenotypic and 18 brain-level associations were
265 additionally detected, amounting to a total of 79 significant clinical associations (50 phenotypic, 29
266 brain-level) in the replication sample. Moreover, none of the significant correlations changed their
267 orientation (Table 3, Table 4).

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

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

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

279 **Sociodemographic exploration of the SPLS trauma model**

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

282 **Discovery sample: LV2 (sexual abuse & age):** Positive associations were found between brain scores
283 and population size at place of living ($\rho=0.28$, $P=.01$), whereas negative correlations were detected
284 between phenotypic scores and number of offspring, married status and years of education ($\rho=-0.29$ -
285 -0.32), $P: <10^{-3}$ -.01). **LV4 (physical/sexual abuse & sex):** Phenotypic scores were negatively associated
286 with years of education ($\rho=-0.29$, $P=.04$). **LV5 (emotional abuse/neglect):** Brain scores were negatively
287 correlated with population at place of living ($\rho=-0.26$, $P=.04$), while phenotypic scores were positively
288 associated with lower education of the mother ($\rho=0.27$, $P=.03$).

289 **Replication sample:** No significant correlations were detected.

290 **Discussion**

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

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

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

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

321 The patterns observed in LV2 and LV4 further reflect previous findings concerning brain development,
322 which showed differential developmental trajectories for female and male brains (64, 65). The brain
323 signature of LV2 comprises specifically the medial prefrontal cortex, i.e., a cortical region that fully
324 develops during adolescence (64), while the LV4 signature covers the temporal, prefrontal and

325 occipital lobes—regions in which sex has shown to have a nonlinear relationship with age (65). Thus,
326 sex exerts a modulating influence on cortical development from childhood to adulthood. The strong
327 covariation of the age and sex effects on childhood trauma signatures might be explained in a
328 developmental framework in which not only men and women differently react to trauma, but their
329 brains may also differentially develop as a result of CT.

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

337 All three CT-specific signatures yielded significant correlations with clinical measures, which were
338 largely validated in the replication sample. The phenotypic scores of the age-dependent sexual abuse
339 signature (LV2) revealed strong connections to an impaired clinical phenotype in the discovery and the
340 replication sample. The brain scores appeared dissociated from that in both populations, yielding no
341 significant associations in the discovery sample and positive associations with GAF and GF in the
342 replication sample. One possible interpretation might be that the signature of LV2 had been influenced
343 by unaccounted resilience dynamics, in which neurobiological adaptations compensate for the
344 phenomenological trauma load, thus maintaining levels of functioning (79, 80). Additional analyses
345 revealed a positive correlation between LV2 brain scores and population size at place of living as well as
346 inverse associations between LV2 phenotypic scores and number of offspring, marital status and years
347 of education in the discovery sample. These findings suggest a possible connection between resilience-
348 conferring brain adaptations and urbanicity as well as higher sexual trauma loadings and social (offspring,
349 marriage) and educational status. Moreover, LV4 and LV5 revealed the most extensive significant

350 associations with functioning, depressivity, personality domains and quality of life in the discovery and
351 the replication sample. Both trauma and brain scores of LV4 and LV5 were significantly correlated with
352 lower levels of social and role functioning, more pronounced symptom severity, increased impairment
353 as well as higher levels of depressivity and reduced quality of life. Additionally, we found a strong
354 connection between individual trauma loads and higher levels of neuroticism as well as lower levels of
355 extraversion, conscientiousness, agreeableness and openness. Finally, phenotypic loading of LV4 was
356 associated with lower educational status, whereas LV5 loading was connected to a less urban
357 environment (phenotypic scores) and lower maternal educational status (brain scores). These findings
358 confirm and extend the current body of literature on the negative clinical implications and complex
359 sociodemographic constellations of CT. It has been well established that CT has a broad negative
360 impact on mental health, ranging from a higher vulnerability for mental disorders, the presence of
361 maladaptive personality traits to decreased psychosocial functioning and quality of life (21).
362 Nonetheless, beyond these general associations, very few studies have investigated more domain-
363 specific aspects of CT (81-83). Thus, our results provide more extensive evidence for a differential
364 neurobiological, clinical and sociodemographic imprint of CT. Moreover, the connection between the
365 CT signatures and the presence of vulnerability-conferring personality domains, provides novel
366 neurobiological evidence for the long-standing and still controversially discussed hypothesis that
367 adverse childhood experiences lead to the development of dysfunctional personality structures (9, 84,
368 85).

369 As 70% of these clinical associations were successfully validated in the replication sample and 20
370 additional significant clinical correlations (18 on the brain-level) emerged, the multi-layered SPLS
371 trauma model appears robustly generalizable both at the phenotypic and neuroanatomical levels.
372 Furthermore, it emphasizes the validity and paramount clinical relevance of the multi-dimensional
373 childhood trauma concept across a broad diagnostic spectrum in two large-scale international samples
374 of young adults and adolescent individuals.

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

382 To our knowledge, this is the first study that investigated CT in a transdiagnostic sample of young adults
383 using a data-driven machine learning approach and a comprehensive, multidimensional framework for
384 CT operationalization. Our novel approach confirms that CT is composed of distinct phenotypic-
385 neuroanatomical dimensions which may have complex ramifications into clinically relevant
386 phenotypes. We found CT signatures of sexual, physical and emotional trauma with distinct
387 neuroanatomic correlates in prefronto-thalamo-cerebellar, limbic and sensory networks. Furthermore,
388 sex-dependent combined sexual and physical abuse as well as emotional trauma appeared to be
389 specifically predictive of relevant clinical state and trait phenotypes, whereas the age-dependent sexual
390 abuse signature may have been further influenced by neurobiological resilience pathways and interacted
391 with modulating factors such as urbanicity, education and family status. As these results were largely
392 validated in a large replication sample, our findings demonstrate that machine learning tools can
393 generate new and generalizable insights into complex human phenomena such as CT and might help to
394 develop superior treatments targeting CT and its psychiatric consequences at short- to long-term time
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396

397

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691 **Legends**

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

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

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

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

703 **Legend Figure 3: Emotional trauma signature of LV5**

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

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

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

716 **Legend Table 2: Group-level statistics for CTQ differences between discovery and replication 717 sample.**

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

721 **Legend Table 3: Spearman's correlation analyses between latent scores and clinical domains 722 of functioning in the discovery and replication sample.**

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

728 **Legend Table 4: Spearman's correlation analyses between latent scores and clinical domains 729 of depressivity, personality and quality of life in the discovery and replication sample.**

730 Results are states as correlation coefficient ρ , followed by its *P* value in brackets: ρ (*P* value).
731 Abbreviations: D, Discovery Sample; R, Replication Sample; BDI, Beck Depression Inventory; NEO-FFI,

732 Neuroticism-Extraversion-Openness (NEO) Five-Factor Inventory; WHOQOL-BREF, World Health
733 Organization Quality of Life Short Version. Significant *P* values are highlighted in bold font. All *P* values
734 FDR-corrected for multiple testing (family of tests with Table 3).

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739 **Tables**740 **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		

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

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

CTQ\Study groups		All	HC	ROD	CHR	ROP	H	<i>P</i>
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
	<i>P</i>	.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
	<i>P</i>	.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
	<i>P</i>	.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
	<i>P</i>	.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
	<i>P</i>	.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
	<i>P</i>	.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
	<i>P</i>	.85 ^b	.65 ^b	.88 ^b	.82 ^b	.51 ^b		

745 ^a Kruskal-Wallis-Test (H test), ^b Wilcoxon-Mann-Whitney-Test

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750 **Table 3: Spearman’s correlation analyses between latent scores and clinical domains of functioning**
 751 **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 (.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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754 **Table 4: Spearman's correlation analyses between latent scores and clinical domains of depression,**
 755 **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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