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The non-specific nature of mental health and structural brain outcomes following childhood trauma

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Abstract:	Background:Childhood trauma (CT) is associated with an increased risk of mental health disorders, however it is unknown whether this represents a diagnosis-specific risk factor for specific psychopathology mediated by structural brain changes. Our aim was to explore whether (i)a predictive CT pattern for transdiagnostic psychopathology exists, and whether (ii)CT can differentiate between distinct diagnosis-dependent psychopathology. Furthermore, we aimed to identify association between CT, psychopathology and brain structure. Methods:We used multivariate pattern analysis in data from 643 participants of the Personalised Prognostic Tools for Early Psychosis Management study (PRONIA), including healthy controls (HC), recent onset psychosis (ROP), recent onset depression (ROD) and individuals clinically at high-risk for psychosis (CHR). Participants completed structured interviews and self-report measures including the Childhood Trauma Questionnaire, SCID diagnostic interview, BDI, PANSS, Schizophrenia Proneness Instrument, Structured Interview for Prodromal Symptoms and structural MRI, analysed by voxel-based morphometry. Results:(i)Patients and HC could be distinguished by their CT pattern with a reasonable precision (balanced accuracy of 71.2% (sensitivity=72.1%, specificity=70.4%, p=<.001) (ii)Subdomains ‘emotional neglect’ and ‘emotional abuse’ were most predictive for CHR and ROP, while in ROD ‘physical abuse’ and ‘sexual abuse’ were most important. The CT pattern was significantly associated with the severity of depressive symptoms in both ROD and CHR. No associations between group-separating CT patterns and brain structure were found. Conclusions:These results indicate that CT poses a transdiagnostic risk factor for mental health disorders, possibly related to depressive symptoms. While differences in the quality of CT exposure exist, diagnostic differentiation was not possible suggesting a multi-factorial pathogenesis.

The non-specific nature of mental health and structural brain outcomes following childhood trauma

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Abstract

Background: Childhood trauma (CT) is associated with an increased risk of mental health disorders, however it is unknown whether this represents a diagnosis-specific risk factor for specific psychopathology mediated by structural brain changes. Our aim was to explore whether (i) a predictive CT pattern for transdiagnostic psychopathology exists, and whether (ii) CT can differentiate between distinct diagnosis-dependent psychopathology. Furthermore, we aimed to identify association between CT, psychopathology and brain structure.

Methods: We used multivariate pattern analysis in data from 643 participants of the Personalised Prognostic Tools for Early Psychosis Management study (PRONIA), including healthy controls (HC), recent onset psychosis (ROP), recent onset depression (ROD) and patients clinically at high-risk for psychosis (CHR). Participants completed structured interviews and self-report measures including the Childhood Trauma Questionnaire, SCID diagnostic interview, BDI-II, PANSS, Schizophrenia Proneness Instrument, Structured Interview for Prodromal Symptoms and structural MRI, analysed by voxel-based morphometry.

Results: (i) Patients and HC could be distinguished by their CT pattern with a reasonable precision (balanced accuracy of 71.2% (sensitivity=72.1%, specificity=70.4%, p=<.001) (ii) Subdomains 'emotional neglect' and 'emotional abuse' were most predictive for CHR and ROP, while in ROD 'physical abuse' and 'sexual abuse' were most important. The CT pattern was significantly associated with the severity of depressive symptoms in ROD, ROP and CHR, as well as with the PANSS total and negative domain scores in the CHR patients. No associations between group-separating CT patterns and brain structure were found.

Conclusions: These results indicate that CT poses a transdiagnostic risk factor for mental health disorders, possibly related to depressive symptoms. While differences in the quality of CT exposure exist, diagnostic differentiation was not possible suggesting a multi-factorial pathogenesis.

Introduction

Childhood trauma (CT) is a frequent form of maltreatment comprising sexual, physical, and emotional dimensions. In Western countries 30% to 40% of the adult population reported experiences with at least some form of maltreatment during childhood (Scher, Forde, McQuaid, & Stein, 2004). CT was revealed to influence the further course of life of the affected individuals, frequently leading to psychological symptoms and impairment in adulthood (Kessler et al., 2010; Scott, McLaughlin, Smith, & Ellis, 2012). It has been shown to be associated with an increased risk for psychiatric disorders such as major depression, anxiety disorders, addiction, post-traumatic stress disorder (PTSD) and psychosis, including patients at clinical high-risk for psychosis (CHR) (Kessler et al., 2010; Palmier-Claus, Berry, Bucci, Mansell, & Varese, 2016; Sahin et al., 2013; Scott et al., 2012; Varese et al., 2012). Even in the general population, CT seems to have long-standing effects on individuals' social perception (Salokangas, From, Luutonen, & Hietala, 2018). Due to its high prevalence and detrimental effects to both, mental health and associated socioeconomic costs (Fang, Brown, Florence, & Mercy, 2012), a better understanding of CT as a risk factor is essential. Furthermore, the fact that CT occurs during a period of important neurodevelopmental steps underlines the potential for prevention or better care for CT victims to contribute to lower lifetime burden of psychiatric diseases (Mikton & Butchart, 2009).

The sum of trauma exposure during childhood has been established as an important risk factor for mental health disorders. However, this has not been investigated in detail, although CT covers five different subcategories of different trauma exposure. These are in detail physical abuse (PA), physical neglect (PN), emotional abuse (EA), emotional neglect (EN) and sexual abuse (SA) (Bernstein & Fink, 1998). A promising approach to investigate the complex granularity of CT as a risk factor is multivariate pattern analysis (MVPA) which was previously shown to identify neuropsychiatric conditions based on e.g. neuroimaging data (Kambeitz et al., 2015). The initial publication from the PRONIA study was on the prediction of functional and treatment outcomes based on clinical baseline data across multiple sites (Koutsouleris et al., 2018). Furthermore, two publications from the PRONIA consortium focused on different aspects of CT: Popovic et al. (2020) identified distinct volumetric brain patterns associated

with single dimensions of CT (in particular physical and sexual abuse and emotional trauma) in a transdiagnostic approach. Salokangas et al. (2021) focused on CT in smaller patient groups and specifically investigated differences with respect to frontal lobe and hippocampal-amygdala complex volumes. In contrast, our study focuses on the potential ability of separating healthy controls and patient groups using machine learning techniques, and to identify potential clinical and volumetric brain correlates of CT in the entire cohort.

To answer these questions the present study first investigated the discriminative value of CT for the individualized identification of transdiagnostic and diagnosis-specific psychiatric disorders using MVPA. In a second step we examined whether found CT patterns correlate with measures of psychopathology and/ or altered brain structure. The investigation was carried out in the PRONIA database ('Personalized Prognostic Tools for Early Psychosis Management'; www.pronia.eu), a large, multi-site European cohort consisting of patients with recent onset depression (ROD), recent onset psychosis (ROP), individuals clinically at high-risk for psychosis (CHR) and healthy controls (HC).

Aims of the study

We aimed to investigate whether (i) a predictive pattern of childhood trauma for transdiagnostic psychopathology exists, and whether (ii) childhood trauma can differentiate between distinct diagnosis-dependent psychopathology. Moreover, our aim was to identify associations between childhood trauma, psychopathology and brain structure.

Methods

Participants

For the quality assurance of our proceedings, we followed the "Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis" (TRIPOD) checklist for prediction model development and validation (Collins, Reitsma, Altman, & Moons, 2015).

All participants were recruited within the PRONIA project ('Personalized Prognostic Tools for Early Psychosis Management'). PRONIA is a multisite observational study funded by the European Union under the 7th Framework Programme (grant agreement n° 602152). Seven clinical centers in five European countries participated in the evaluation of patients with recent onset depression (ROD), recent onset psychosis (ROP), patients clinically at high-risk for psychosis (CHR) and healthy controls (HC). Within a longitudinal study design a comprehensive battery of clinical assessment tools were used every three months over 18 months (**see supplemental Figure 1**). Neuroimaging examinations were carried out at the baseline and the 9-month follow-up points. The entire study design has been previously described detailed in Koutsouleris et al. (2018).

All adult participants provided their written informed consent prior to study inclusion. Minors provided written informed assent and guardians written informed consent. The study was registered at the German Clinical Trials Register (DRKS00005042). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/ patients were approved by the local research ethics committees.

Inclusion and exclusion criteria

The included persons were aged between 15 and 40 years and recruited into the study between 1st of February 2014 and 1st of May 2016. Patients with CHR were included by Cognitive Disturbances

(COGDIS) criteria, assessed by the Schizophrenia Proneness Instrument (SPI-A) (Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007), and/ or UHR criteria (Phillips, Yung, & McGorry, 2000), assessed using a modified version of the Structured Interview for Prodromal Syndromes (SIPS) (McGlashan, Walsh, & Woods, 2010). For ROD, specific inclusion criteria were having a DSM-IV (American Psychiatric Association, 2000) Major Depressive Episode that was present within the past three months and did not last longer than 24 months. ROP fulfilled DSM-IV criteria for affective or non-affective psychosis within the last 24 months and not before. General inclusion and exclusion criteria have been described in detail in Koutsouleris et al. (2018) and were detailed depicted in **supplemental Table S1**.

Procedure and instruments

The data used in this study were all acquired at baseline. As mentioned above, psychopathology of CHR patients was assessed using SIPS and SPI-A. ROP and ROD were diagnosed by DSM-IV. Depressive syndrome severity was additionally measured using the Beck-Depression-Inventory II (BDI-II) (Hautzinger, Bailer, Worall, & Keller, 1995). Positive and negative symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). For the assessment of CT, the Childhood Trauma Questionnaire (CTQ), developed by Bernstein and Fink (1998), was used. The CTQ is a self-assessment tool for the retrospective recording of mistreatment and neglect in childhood. It consists of 28 items, whereby three items (10, 16, 22) are used to determine denial and trivialization. It includes five subscales; emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN) and physical neglect (PN). Rating was carried out on a 5-point Likert scale (0= never to 4= very often). The convergent and discriminative validity has been reported as being good (Bernstein & Fink, 1998). In addition, the cumulative sum of the equivalent doses received until T0 was calculated for SSRIs (Hayasaka et al., 2015), chlorpromazine (Leucht, Samara, Heres, & Davis, 2016) olanzapine (Leucht et al., 2016) and benzodiazepines (diazepam) (Clinical Guidelines on Drug Misuse and Dependence Update 2017 Independent Expert Working Group, 2017).

MRI acquisition, preprocessing and analysis

Participants underwent a comprehensive imaging protocol at seven sites respecting a minimal harmonization protocol including high resolution 3D T1-weighted imaging. Detailed scanner and sequence specifications for all sites can be found in the **supplemental Table S2**. All images underwent quality control and were preprocessed using the CAT12 toolbox (version r1155; http://dbm.neuro.uni-jena.de/cat12/), an extension of SPM 12 as described previously (Koutsouleris et al., 2018). Images were smoothed with 10 mm before entering the subsequent analysis steps. The Quality Assurance framework of CAT12 was used to empirically check the quality of the GMV maps.

By computing the correlation of each image to all other 592 images, we found 11 (1.9%) images whose correlation exceeded two standard deviations from the sample mean. These images were inspected and 9 were removed because of MRI artifacts. Thus, 583 persons could be included in the VBM analysis (109 CHR patients, 115 ROD patients, 110 ROP patients and 249 HC). Notably, 98.47% of the images achieved a good overall weighted quality (B), and 83.0% of the data quality was rated with a B+ as provided by the internal quality assessment of CAT12 (Gaser & Dahnke, 2016). For analysis of brain structure and associations with CT, voxel-based morphometry (VBM) was employed. Preprocessed data entered a full-factorial general linear model design as implemented in SPM. Sex, site (coded as dummy regressors), and age were used as covariates of no interest to correct for potential confounds for VBM analyses. In order to investigate possible sex differences, male and female participants were also analyzed separately. Global proportional scaling for total intracranial volume (TIV) was used to adjust for different global brain volume differences. Contrasts were defined for main-effects and interaction analyses to assess differences in mean and slope effects of associations between CTQ-based decision scores (DS) and local GM. Threshold-free cluster enhancement (TFCE) was used as implemented in the TFCE toolbox for SPM with 5000 permutations (Smith & Nichols, 2009). Significance threshold was set at $p<0.05$, Family-wise error (FWE) corrected.

Machine learning strategies

To investigate discriminative patterns of CT experience in HC vs. the combined three patient groups (PAT), we used a L2-regularized logistic regression as provided by the LIBLINEAR library (Fan, Chang, Hsieh, & Lin, 2008), which offers methods for classifying individuals instead of describing statistical group differences.

We used our open-source machine learning toolkit NeuroMiner (https://github.com/neurominer-git/) to implement a fully automated machine learning pipeline. We trained different models to predict psychiatric disorders based on the single CTQ items;

1. **PAT vs. HC**
2. **HC vs. CHR; HC vs. ROD; HC vs. ROP**
3. **ROD vs. CHR; ROD vs. ROP; CHR vs. ROP**

We followed the internal-external validation approach recommended for the assessment of model generalizability in multi-site studies (Steyerberg & Harrell, 2016) and validated our models using nested leave-one-site-out cross-validation (LOSOCV) (see in detail **supplemental Methods**).

To compare the multivariate versus univariate methods, we repeated the HC vs. PAT analysis after replacing the L_2-regularized logistic regression (L2-LR) (Fan et al., 2008) algorithm with a univariate logistic regression model (uLR) in NeuroMiner. Algorithm performance was measured using the balanced accuracy (BAC) of the out-of-training (OOT) group membership predictions and assessed for significance using 1000 random label permutations (Golland & Fischl, 2003). Predictive features for each L2-LR model were compared by their mean weights.

A further validation analysis assessed whether our model generalized across study groups. Therefore, we used LOSOCV to train and cross-validate three binary L2-LR-based diagnostic classifiers (HC vs. CHR; HC vs. ROD; HC vs. ROP) using the identical algorithmic setup described above. Each trained classification ensemble was then applied to the CTQ data of the other two clinical study groups

following an out-of-sample cross-validation (OOCV) approach. Class membership probabilities/ DS of the patients in the held-back study groups were computed as for the OOT predictions.

These main analyses were supplemented by an investigation of univariate associations between measures of *current* psychopathology and the OOT DS of clinical participants produced by the L2-LR algorithms, which were trained in the HC vs CHR, HC vs. ROD and HC vs ROP comparisons. For the ROD, ROP and CHR groups, the correlations of the CTQ-based DS with the BDI-II, SIPS-P, SIPS-N, SIPS-D, SIPS-G, PANSS total, positive, negative and general domain scores were examined respectively. Furthermore, the relationship between the equivalent doses of the individual drug classes (neuroleptics, SSRIs, benzodiazepines) and the CTQ-based DS was calculated for each group. In order to exclude recall bias in older participants (with longer time spans between CT and study inclusion), we performed correlation analyses between CTQ-based DS and age at study inclusion as a control analysis.

Results

Study group characteristics

643 subjects (57.2% male, mean age 27.69 ± 5.99 years) were included in the analysis. These consisted of n=262 (40.7%) HC, n=122 (19.0%) CHR, n=130 (20.2%) ROD and n=129 (20.1%) ROP. CTQ total scores and subdomain scores were significantly different between PAT and HC. No group differences were found between the PAT groups ROP, ROD and CHR regarding the total CTQ score. Please see **Table 1** and **supplemental Table S3** for details. The **supplementary Table S4 shows** the mean values of the drug equivalent doses that have been taken cumulatively so far. As expected, the highest equivalent doses for antipsychotics were found in ROP patients (chlorpromazine=8072.71 mg/d, olanzapine=280.02 mg/d), followed by CHR patients (chlorpromazine= 1025.06 mg/d, olanzapine= 42.04 mg/d). Surprisingly, the highest equivalent doses for SSRIs were found in CHR patients (3864.95 mg/d), followed by ROD patients (2630.83). We did not find an association between patient age and DS, making an age-dependent recall bias unlikely to have influenced our results (see **supplementary Table S5**).

Childhood trauma profiles predict general psychopathology.

The classifier distinguishing HC from PAT performed with a BAC of 71.2% (sensitivity: 72.1%, specificity: 70.4%). Leave-site-out validation yielded good generalizability of the CTQ-based discriminative model (**see Table 2**). In order to deduct a CT profile predictive of general psychopathology, weights of CTQ single items from the MVPA were recorded and are depicted in **Figure 1**. It must be emphasized that the resulting values do not allow to conclude on the direction of the prediction. The highest weights related to items within the subdomains EN and EA, namely: **CTQ Item 5;** `There was someone in my family who helped me feel that I was important or special`**, CTQ Item 14;** `People in my family said hurtful or insulting things to me', and **CTQ Item 13;** `People in my family looked out for each other.' The uLR analyses for the same classification (HC vs. PAT) led to a BAC of 67.1% (sensitivity: 66.0%, specificity: 68.2%). For detailed results, please see **Table 2**.

Childhood trauma profiles for diagnosis-specific psychopathology

Classifying the three diagnostic groups within the PAT cohort, namely CHR, ROD, and ROP did not perform above chance level (CHR vs ROD: BAC= 46.1%, sensitivity=35.8%, specificity= 56.3%; CHR vs ROP: BAC= 47.1%, sensitivity= 42.5%, specificity= 51.7%; ROD vs ROP: BAC= 51.9 sensitivity= 58.0%, specificity= 45.3%). However, classifiers separating between HC and individual PAT groups performed well (HC vs ROD: BAC= 67.2%, sensitivity= 75.6%, specificity= 58.9%; HC vs CHR: BAC= 72.1%, sensitivity= 72.4%, specificity= 71.8%; HC vs ROP: BAC= 70.8%, sensitivity= 74.4%, specificity= 67.2%; please see **Table 2**).

Regarding the differentiation of HC vs CHR, highest weights belonged to items of the subdomain EA and EN (**see Figure 1**); **CTQ Item 14;** `People in my family said hurtful or insulting things to me', **CTQ Item 13;** `People in my family looked out for each other', and **CTQ Item 28;** ` My family was a source of strength and support.'

Analysing the profile of HC vs ROD revealed the highest weights in items of the subdomains PA, SA and EA (**see Figure 1**); **CTQ Item 17;** ` I got hit or beaten so badly that it was noticed by someone like a teacher, neighbour, or doctor', **CTQ Item 24;** ` Someone molested me', and **CTQ Item 14;** `People in my family said hurtful or insulting things to me.'

Describing the profile, which is distinguishing HC vs ROP items of the subdomains EA, EN and PN were most predictive (**see Figure 1**); **CTQ Item 25;** ` I believe that I was emotionally abused', **CTQ Item 13;** `People in my family looked out for each other', and **CTQ Item 2;** ` I knew that there was someone to take care of me and protect me.'

Correlation between childhood trauma and psychopathology

Across all groups, correlations between the CTQ-based DS and GAF symptoms (r= .388, p= <0.01) as well as disability and impairment (r= .412, p= <0.01) were moderate to strong. In the CHR group, there were no associations between the CTQ-based DS and any SIPS domain, but a weak correlation between

the DS and the BDI total score was observed (r= -.175, p= 0.028). Moreover, a weak correlation between the PANSS total and (r= -.191, p= 0.038) and the PANSS negative domain score (r=-.196, p= 0.033) was seen in the CHR patients. Regarding the ROD group, a moderate association between the CTQ-based DS and the BDI total score was found (r= -0.278, p= .001). In the ROP group, there was no significant correlation between the PANSS scores and the CTQ-based DS but a moderate association between the BDI total score and the CTQ-based DS (r= -.246, p= 0.003). For details see please **Table 3**.

Correlation between childhood trauma and medication

Across all groups, weak negative correlations were found between the CTQ-based DS and all types of medication (chlorpromazine r= -.213, p= <0.001, olanzapine r= -.213, p= <0.001, SSRI r= -.193, p= <0.001, benzodiazepine (diazepam) r= -1.28, p=0.001). Interestingly, however, no significant correlations were found in the individual groups, except for a weak positive correlation with benzodiazepine in HC individuals. For details, please see **supplemental Table S6**.

Correlation between childhood trauma and brain structure

Despite several methodological approaches and adjusted statistical thresholds, we did not find any associations between CTQ-based DS and brain morphology in our cohort. Additionally, there were no significant associations between DS and brain morphology when examining male and female participants separately, also suggesting also no sex-specific brain alterations associated with CTQ-based DS.

Discussion

We investigated CT and psychopathology in a large cohort of HC and patients with ROD, ROP and CHR using MVPA. We found that CT significantly predicted transdiagnostic psychopathology using MVPA, while separation of diagnosis-specific psychopathology was not achieved. Qualitative analysis of CT patterns emphasized the importance of EN and EA for ROP and CHR identification while PA and SA yielded importance in ROD patients. The CTQ-based DS was significantly associated with the current severity of depressive symptoms in the ROD, ROP and CHR group. Moreover, a correlation between the CTQ-based DS and the PANSS total and negative domain score was achieved in the CHR patients. However, no further associations with psychopathology or structural brain alterations were found. Weak correlations between CTQ-based DS and medication were discovered across all groups, while no correlations were observed in the single groups, except for a weak positive correlation with benzodiazepine in HC individuals. The latter might reflect negative consequences of CT at a subthreshold level, resulting in higher tension and anxiety treated with benzodiazepine.

In order to investigate the association between CT and psychopathology, we tested whether PAT and HC could be separated based on CTQ information using a machine-learning model. We found that this distinction could be made with acceptable accuracy on the individual level and that highest weights were assigned to domains pertaining to EA and EN. CT has been associated with several specific psychiatric diseases such as psychosis (Varese et al., 2012), unipolar depression (Rubino, Nanni, Pozzi, & Siracusano, 2009) and bipolar disorder (Palmier-Claus et al., 2016) and has been posited as a general risk factor for their development. Recent reviews and meta-analyses have shown that each subdomain of the CTQ is by itself significantly associated with the occurrence of psychiatric illness (Lindert et al., 2014; Nelson, Klumparendt, Doebler, & Ehring, 2017; Varese et al., 2012). These results agree with our findings showing that CT is globally associated with early-stage psychiatric disease phenotypes but predictive of these illnesses from an individualized transdiagnostic perspective.

In order to test whether CTQ profiles also allow for diagnosis-specific prediction of early mental health disorders, we applied the same machine-learning model to separate CHR, ROP, and ROD. In these analyses, we found that it was not possible to distinguish reliably between the three diagnostic groups based on trauma exposure patterns. This is in line with studies describing increased rates of CT in psychiatric patients, irrespective of the exact diagnosis (Kessler et al., 2010; Palmier-Claus et al., 2016; Sahin et al., 2013; Scott et al., 2012; Varese et al., 2012). However, other studies exist describing distinct forms of early adversity in specific patient groups. Particularly, Bruni and colleagues found escape from home, cannabis abuse, psychological abuse, physical abuse and loneliness to be more frequent in patients with schizophrenic spectrum disorder than in patients with major depression or bipolar disorder (Bruni et al., 2018). Contrary to these results, our findings suggest that CT exposure is not associated with specific disorders but instead poses a rather general and transdiagnostic risk factor for early psychiatric disorders, which is also in line with an earlier study of our group (Popovic et al., 2020).

Regarding the individual CT patterns, we performed a qualitative comparison of the three CTQ questions which were assigned the highest weights. We identified the subdomains EN and EA playing the most important role across all groups. On the single item level, especially items that reflect the family climate showed the highest predictive power. These results are in line with a recent structure equation model analysis of Salokangas et al. (2019), which indicated that subdomains EN and PA had the strongest association with depression and psychosis. Furthermore, in our analysis EN and EA were most predictive in CHR patients, while PN was additionally predictive in psychosis. In contrast, an earlier work by Trauelsen et al. (2015) showed beside EA and EN, PA to be significantly associated with psychotic disorders. Other works revealed specific associations between SA and psychosis (Bentall, Wickham, Shevlin, & Varese, 2012) and hallucinations (Upthegrove et al., 2015). Interestingly, in ROD patients, besides EA, SA and PA were particularly predictive for a later depressive illness. In line with these observations, a meta-analysis of Lindert et al. (2014) pointed out that especially SA and PA are strongly associated with later depression and anxiety disorders. Although this meta-analysis identified

SA and PA as most important risk factors of depression and anxiety disorder, which are also common in CHR patients (Albert, Tomassi, Maina, & Tosato, 2018), we found EN and EA to play the most important role across all groups. One reason for this discrepancy might be the lower frequency of SA and PA compared to other CT domains in our sample that might have led to a underestimation of their role in our cohort. Thus, our results provide more comprehensive evidence for a differentiated neurobiological imprint of the CT in different psychiatric diseases, while at the same time highlighting emotional trauma as particularly relevant to a person´s clinical phenotype.

Furthermore, we found evidence that the participants' CTQ-based DS was significantly associated with the current severity of depressive symptoms but not with psychotic symptoms (positive, negative and general) in the ROD, ROP and CHR groups. Moreover, pre-psychotic symptoms measured by the SIPS were not correlated with the DS in the CHR group but a weak relationship was detected between the CTQ-based DS and the PANSS total and negative domain scores. These results support the hypothesis that CT constitutes a dimension of vulnerability that is dependent of the current depressive state of the patients. This observation is in keeping with previous work of our group showing that an emotional trauma signature was significantly correlated with higher depression scores, lower levels of functioning, decreased quality of life and maladaptive personality traits (Popovic et al., 2020). In the past depressiveness has also been shown to be a mediating factor in the effect of CT on alcohol consumption (Salokangas, From, Luutonen, Salokangas, & Hietala, 2018) and suicidal thoughts (Salokangas et al., 2019).

No associations were found between the CTQ-based DS and brain structure. It can be assumed that the changes at the single item level of the CTQ are too subtle for individual prediction of disease. In a recent publication from our group, we performed a data-driven analysis of brain structure and phenotypic data including CT exposure and found three latent signatures specifically associated with CT. In this previous paper, and latent representations of brain-phenotype associations, SA was associated with aberrant volumes in the prefrontal cortex, the hippocampus and occipital lobe. EA and EN were associated with volumetric alterations in the occipital lobe and postcentral regions associated

with sensory processing. No associations between specific diagnostic groups and CT exposure were found, which is in line with the absence of diagnosis-specific associations between CT and early mental health diseases, and in keeping with current analysis (Popovic et al., 2020). In another previous mediation analysis of our group, PA was shown to be associated in particular with reduced volumes of the grey and white matter of the frontal lobe and amygdala-hippocampal complex in ROD and CHR patients (Salokangas et al., 2021). In addition, it was shown that the effect of PA on social anxiety in CHR patients was mediated by a reduced volume of gray matter in the frontal lobe. Since this was methodological a mediation analysis and not a machine learning approach, these results should not be regarded as contradictory.

Limitations

Limitations of our study include the observational, retrospective and cross-sectional character of the study. As with most CT assessments, the CTQ assesses trauma retrospectively, thus, running the risk of a "recall bias" depending on the individual's current mental health situation, including the influence of depression severity (Colman et al., 2016). Another possible limitation is the non-assessment of factors as the age at onset, the frequency and the extent of the suffering associated with exposure to CT. It must be critically taken into account that despite diverse adverse experiences, many victims of CT show no or only minor long-term psychological impairment, suggesting that resilience factors appear to be important mediating variables as well (Lee, Yu, & Kim, 2020). Therefore, in the future, suitable methods and longitudinal population data utilizing methods such as structure equation models, could be used to investigate the exact relationship between CT and functional or school outcome, against the background of the above-mentioned mediating variables.

Conclusions

In summary, our work has demonstrated that CT constitutes a discriminative transdiagnostic fingerprint of at-risk mental states and early-stage mental disorders. Focusing on the most predictive items of our analyses, we were able to show that a violence-free, supportive family environment as

well as protection are important aspects for good mental health in later life. Our findings support the conclusions of a paper by Hudziak (2009) who called for a routine evaluation of CT history in persons presenting to mental health services in order to identify those who may need more intensive support and additional treatment. In line with that, Marshall and colleagues (Marshall, Shannon, Meenagh, Mc Corry, & Mulholland, 2018) emphasized the importance of special preventive measures, such as therapeutic intervention aimed at sufferers of past abuse, neglect and poor parenting to prevent 'trans-generational patterns' continuing with their own children. In the future, further analyses of the longitudinally administered PRONIA sample should investigate, whether there are differences in the course of the diseases related to CT experiences. Furthermore, suitable methods, such as structural equation models, should be used to highlight the exact relationship between CT and mental illness against the background of mediating variables and resilience factors.

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Tables

Figure legends

Supplement

Supplement Tables

Supplement Table 1: Study inclusion / exclusion criteria of the study

Supplement Table 2: MR scanner systems and structural MRI sequence parameters used at the respective PRONIA sites

Supplement Table 3: Comparison of CTQ subscales across groups

Supplemental Table 4: Mean values of medication dose equivalents taken cumulatively over lifetime (mg/d)

Supplemental Table 5: CTQ-class probabilities associations with age

Supplemental Table 6: CTQ-class probabilities associations with medication dose equivalents taken cumulatively over lifetime

Supplement Figures

Supplement Figure 1: Study design

Supplement Figure 2: Consort Chart

Supplement Methods

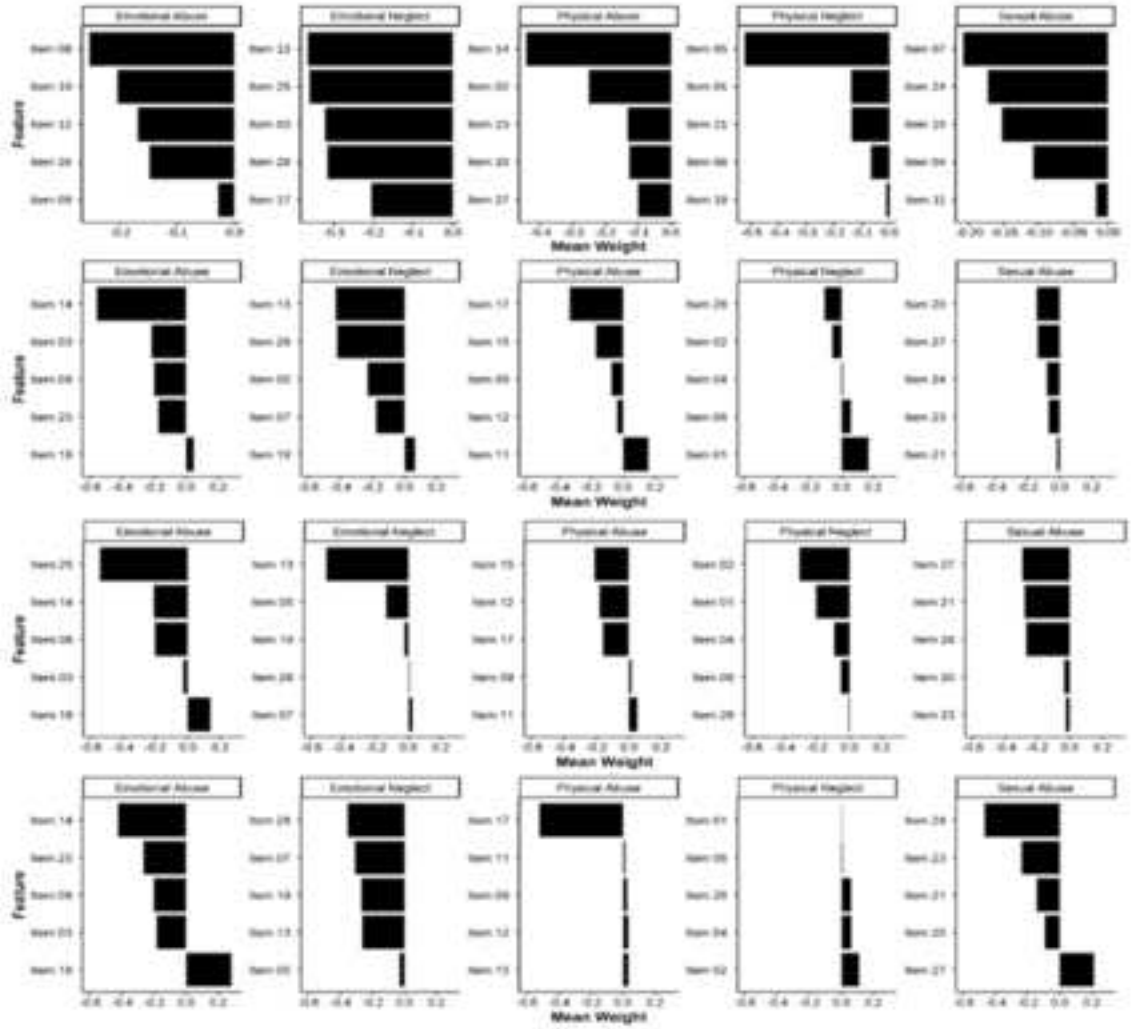
Supplement Method: Nested leave-site-out cross-validation

Conflicts of interest

None

Figure 1

Click here to access/download;Figure(s);CTQ_Figure_1_BlackandWhite.tiff



A) HC vs. PAT

B) HC vs. CHR

C) HC vs. ROP

D) HC vs. ROD

Table 3: *CTQ-class probabilities associations with psychopathology*

	r_s	p
All groups		
GAF Symptoms	.388	<.001**
GAF Disability/Impairment	.412	<.001**
CHR		
SIPS-P	-.103	.259
SIPS-N	-.116	.206
SIPS-D	-.014	.882
SIPS-G	.026	.777
BDI-II	-.175	.028*
PANSS Total	-.191	.038*
PANSS Positive	-.127	.168
PANSS Negative	-.196	.033*
PANSS General	-.126	.174
ROD		
SIPS Positive	.018	.839
SIPS Negative	.010	.908
SIPS Disorganizing	-.124	.166
SIPS General	-.106	.236
BDI-II	-.278	.001**
PANSS Total	-.017	.854
PANSS Positive	-.120	.182
PANSS Negative	-.025	.782
PANSS General	-.008	.928
ROP		
SIPS Positive	-.042	.638
SIPS Negative	-.230	.10
SIPS Disorganizing	-.139	.125
SIPS General	-.050	.581
BDI-II	-.246	.003**
PANSS-T	-.107	.117
PANSS-P	-.097	.141
PANSS-N	-.115	.100
PANSS-G	-.083	.177

CHR, Clinical High-Risk state; ROD, Recent Onset Depression; ROP, Recent Onset Psychosis; PANSS, Positive and Negative Syndrom Scale; BDI-II, Beck Depression Inventory II; SIPS, Structured Interview for Prodromal Symptoms; GAF, Global Assessment of Functioning; r_s, Spearmans Correlation Coefficient

*Significant at the level of 0.05

**Significant at the level of <0.01

Table 2: Multivariate analyses

Classifier	TP	TN	FP	FN	Sens	Spec	BAC	PPV	NPV	PSI	AUC	P[a]
Leave-site-out performance												
HC vs PAT (L2LR)	186	266	112	72	72.1	70.4	**71.2**	62.4	78.7	41.1	0.77	<.001
HC vs PAT (GLM)	173	260	121	89	66	68.2	**67.1**	58.8	74.5	33.3	0.74	<.001
ROD vs ROP	69	55	65	50	58.0	45.3	**51.9**	51.5	52.4	3.9	0.49	0.358
CHR vs ROP	51	62	58	69	42.5	51.7	**47.1**	46.8	47.3	-5.9	0.48	0.866
CHR vs ROD	43	67	52	77	35.8	56.3	**46.1**	45.3	46.5	-8.2	0.43	0.923
HC vs ROD	198	76	53	64	75.6	58.9	**67.2**	78.9	54.3	33.2	0.69	<.001
HC vs CHR	189	84	33	72	72.4	71.8	**72.1**	85.1	53.8	39.0	0.72	<.001
HC vs ROP	195	86	42	67	74.4	67.2	**70.8**	82.3	56.2	38.5	0.75	<.001
Leave-group-out performance												
HC vs CHR OOCV ROP	249	51	78	13	95	39.5	**67.3**	76.1	79.7	55.8	0.79	<.001
HC vs CHR OOCV ROD	249	38	92	13	95	29.2	**62.1**	73.0	74.5	47.5	0.74	<.001
HC vs ROD OOCV ROP	249	51	78	13	95	39.5	**67.3**	76.1	79.7	55.8	0.76	<.001
HC vs ROD OOCV CHR	249	48	74	13	95	39.3	**67.2**	77.1	78.7	55.8	0.77	<.001
HC vs ROP OOCV CHR	248	49	73	14	94.7	40.2	**67.4**	77.3	77.8	55.0	0.79	<.001
HC vs ROP OOCV ROD	248	45	85	14	94.7	34.6	**64.6**	74.5	76.3	50.7	0.71	<.001

All analyses were single item based, Abbreviations: TP = True positive, TN = True negative, FP = False positive, FN = False negative, Sens = Sensitivity, Spec = Specificity, BAC = Balanced Accuracy, PPV = Positive Predictive Value, NPV = Negative Predictive Value, PSI = Prognostic Summary Index, AUC = Area-under-the Curve, HC = Healthy controls, PAT = patients including ROP, ROD and CHR; ROD = Recent Onset Depression, ROP = Recent Onset Psychosis, CHR = Clinically High-Risk, OOCV = Out-Of-Sample Cross-Validation

Table 1: *Sociodemographic data and general psychopathology. Comparison between healthy controls and patients*

	HC	PAT	U / χ2 [a]	p [a]	CHR	ROD	ROP
n total (%)	262 (40.7%)	381 (59.3)	n.a.	n.a.	122 (19.0%)	130 (20.2%)	129 (20.1%)
Age (y), M (SD)	27.75 (6.41)	27.64 (5.68)	49854	0.932	26.26 (4.9)	28.54 (6.14)	28.02 (5.68)
Sex (♀) F (%)	164 (62.6%)	204 (53.5)	16.23	<.001	58 (47.5%)	70 (53.8%)	49 (38%)
Psychopathology [Mean (SD)]							
BDI-II	3.76 (5.27)	24.12 (13.04)	6273.5	<.001	24.89 (12.16)	26.71 (13.91)	20.79 (12.30)
CTQ	30.88 (6.4)	40.38 (12.64)	20806.5	<.001	41.28 (12.73)	39.33 (13.66)	40.57 (11.42)
PANSS Total	n.a.	56.32 (18.90)	n.a.	n.a.	50.74 (13.11)	47.80 (11.33)	70.11 (21.70)
PANSS Negative	n.a.	13.83 (6.39)	n.a.	n.a.	12.54 (5.83)	12.60 (5.00)	16.27 (7.38)
PANSS Positive	n.a.	11.97 (6.05)	n.a.	n.a.	10.27 (2.95)	7.71 (1.39)	17.84 (6.52)
PANSS General	n.a.	30.49 (9.39)	n.a.	n.a.	27.83 (6.88)	27.48 (6.97)	35.99 (11.07)
Childhood Trauma							
Emotional Abuse	6.56 (2.42)	9.64 (4.37)	24784.0	<.001	10.16 (4.43)	9.2 (4.36)	9.62 (4.29)
Physical Abuse	5.39 (1.0)	6.52 (3.08)	38805.5	<.001	6.56 (3.11)	6.45 (3.21)	6.56 (3.0)
Sexual Abuse	5.2 (1.1)	6.04 (2.95)	39828.5	<.001	5.97 (2.77)	5.88 (2.84)	6.28 (3.22)
Emotional Neglect	7.93 (3.14)	11.47 (4.58)	25248.5	<.001	11.78 (4.45)	11.25 (4.88)	11.4 (4.42)
Physical Neglect	5.87 (1.51)	7.41 (2.73)	29420.0	<.001	7.35 (2.6)	7.08 (2.81)	7.79 (2.76)
Distribution across sites (total/%)							
Munich	59 (22.5)	125 (32.8)	n.a.	n.a.	40 (32.8)	44 (33.8)	41 (31.8)
Basel	44 (16.8)	51 (13.4)	n.a.	n.a.	18 (14.8)	17 (13.1)	16 (12.4)
Cologne	56 (21.4)	69 (18.1)	n.a.	n.a.	18 (14.8)	25 (19.2)	26 (20.2)
Birmingham	42 (16.0)	34 (8.9)	n.a.	n.a.	13 (10.7)	12 (9.2)	9 (7.0)
Turku	19 (7.3)	45 (11.8)	n.a.	n.a.	14 (11.5)	11 (8.5)	20 (15.5)
Udine	31 (11.8)	31 (8.1)	n.a.	n.a.	12 (9.8)	14 (10.8)	5 (3.9)
Milan	11 (4.2)	26 (6.8)	n.a.	n.a.	7 (5.7)	7 (5.4)	12 (9.3)

Statistical comparisons: sex with χ^2 statistics ; age, BDI-II and CTQ with Mann-Whitney-U Test. Abbreviations: U, Mann-Whitney-U Test; χ^2 , chi-squared test, M, mean; SD, standard deviation; PAT= patients including ROP, ROD and CHR; HC, Healthy Controlls; CHR, Clinical High-Risk state; ROD, Recent Onset Depression; ROP, Recent Onset Psychosis; CTQ, childhood trauma questionnaire, PANSS, Positive and Negative Syndrom Scale; BDI-II, Beck Depression Inventory II,[a] comparison only between PAT and HC

Supplement Table 1: Study inclusion / exclusion criteria of the study.

Group Inclusion Criteria	Group Exclusion Criteria	General Inclusion / Exclusion / Drop-out
Clinical High-Risk Group (CHR)		**Inclusion Criteria:** 1. Age 15 to 40 years 2. Language skills sufficient for participation 3. Able to provide to consent / assent **Exclusion Criteria:** 1. IQ below 70 2. Hearing is not sufficient for neuro-cognitive testing 3. Current or past head trauma with loss of consciousness (> 5 min) 4. Current or past known neurological disorder of the brain 5. Current or past known somatic disorder potentially affecting the structure or functioning of the brain 6. Current or past alcohol dependence 7. Current poly-substance dependence or within the past six months (Note: any combination with E.6. led to exclusion) 8. Any contra-indication for MRI **Exclusion criteria for healthy controls:** 1. Any current or past DSM-IV axis disorder 2. A positive familial history (1st degree relatives) for affective or non-affective psychoses or major affective disorders; and 3. An intake of psychotropic medications or drugs more than 5 times/year and in the month before study inclusion. **Drop-out criteria:** 1. No follow-up examination after the 6-months follow-up examination (IV6) 2. Withdrawn consent / assent
Psychosis-risk syndrome defined: **EITHER** by *Attenuated Positive Symptoms (APS)*, as measured by the SIPS (requires 1 of 5 attenuated psychotic symptoms: unusual thought content/ delusional ideas, suspicious-ness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations, and disorganized communication) with a moderate to severe, but not psychotic, severity (SIPS score 3-5) that (1) began with-in the past year or was rated one or more scale points higher compared to 12 month ago, **AND** (2) occurred at an average frequency of at least once per week for at least several minutes per event in the past month **OR:** by *Brief Intermittent Psychotic Symptoms (BLIPS)*, as measured by the SIPS (as defined by one of the symptoms listed above (1) reaching a psychotic level of intensity in each of the past 3 months for at least several minutes per day, **OR** (2) reaching a psychotic level of intensity in the past month, occurring at an average frequency of at least once per week for at least several minutes per event in the past month, or occurring at least for a cumulative period of more than one hour within the past month, **AND** (1+2) remitting spontaneously within one week (i.e. without antipsychotic medication) **OR:** by a *Genetic Risk and Functional Decline Psychosis-Risk Syndrome (GRFD)* defined by a current 30% or greater reduction in the functional disability score of the split version of the Global Assessment of Functioning Scale (GAF-F) compared with the highest lifetime level of functioning, **AND** (having a first-degree relative with a history of any psychotic disorder, **OR** having a DSM-IV-TR schizotypal personality disorder). **OR:** by a *Cognitive Disturbance Syndrome* (COGDIS) as measured by the SPI-A (requires at least 2 of 9 cognitive basic symptoms with at least weekly occurrence (score ≥3) during the last 3 months)	1. Any intake of antipsychotic medication for more than 30 cumulative days at or above the minimum dosage threshold defined by the DGPPN S3 Guidelines for the treatment of first-episode psychosis[1] 2. Any intake of antipsychotic drugs within the past 3 months before psychopathological baseline assessments at or above the minimum dosage threshold. 3. Occurrence of the CHR syndrome is better explained by other DSM-IV disorder	
Recent-Onset Depression (ROD)		
Recent-onset Depression as defined by DSM-IV-TR + ALL of the following criteria: 1. First life-time depressive episode, 2. Duration of current depressive episode no longer than 24 months, 3. Diagnostic criteria fulfilled within past three months	1. Occurrence of the major depressive episode is better explained by other DSM-IV disorder 2. See CHR exclusion criteria	
Recent-Onset Psychosis (ROP)		
Recent-onset Psychosis as defined by DSM-IV-TR (affective and non-affective) + ALL of the following criteria: 1. First life-time psychotic episode, 2. Duration of current psychotic episode no longer than 24 months, **3.** Diagnostic criteria fulfilled within past three months	1. Occurrence of the psychotic episode is better explained by other DSM-IV disorder 2. Antipsychotic medication for more than 90 days at or above the minimum dosage defined by the DGPPN S3 Guidelines for the treatment of first-episode psychosis[1]	

[1] Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde. DGPPN S3 Treatment Guideline Schizophrenia / Psychotic Disorders. *AWMF* 2006.

Supplement Table 2: MR scanner systems and structural MRI sequence parameters used at the respective PRONIA sites

PRONIA Site	Model	Field strength [3T]	Coil channels	Flip angle [deg]	TR [ms]	TE [ms]	Voxel size [mm]	FOV	Slice number
Munich	Philips Ingenia	3	32	8	9.5	5.5	0.97x0.97x1.0	250 x 250	190
Milan Niguarda	Philips Achieva Intera	1.5	8	12	Shortest (8.1)	Shortest (3.7)	0.93x0.93x1.0	240 x 240	170
Basel	Siemens Verio	3	12	8	2000	3.4	1.0x1.0x1.0	256 x 256	176
Cologne	Philips Achieva	3	8	8	9.5	5.5	0.97x0.97x1.0	250 x 250	190
Birmingham	Philips Achieva	3	32	8	8.4	3.8	1.0x1.0x1.0	288 x 288	175
Turku	Philips Ingenuity	3	32	7	8.1	3.7	1.0x1.0x1.0	256 x 256	176
Udine	Philips Achieva	3	8	12	Shortest (8.1)	Shortest (3.7)	0.93x0.93x1.0	240 x 240	170

Supplement Table 3: Comparison of CTQ subscales across groups

CTQ Subscale			Average difference	Standard error	p
Emotional Abuse					
		CHR	-3.60*	0.41	<.001
	HC	ROD	-2.6*	0.4	<.001
		ROP	-3.06*	0.4	<.001
		HC	3.60*	0.41	<.001
	CHR	ROD	0.99	0.47	0.15
		ROP	0.53	0.47	0.67
		HC	2.6*	0.4	<.001
	ROD	CHR	-0.99	0.47	0.15
		ROP	-0.46	0.46	0.76
		HC	3.06*	0.4	<.001
	ROP	CHR	-0.53	0.47	0.67
		ROD	0.46	0.46	0.76
Physical Abuse					
		CHR	-1.17*	0.27	<.001
	HC	ROD	-1.05*	0.27	<.001
		ROP	-1.17*	0.27	<.001
		HC	1.17*	0.27	<.001
	CHR	ROD	0.11	0.31	0.98
		ROP	-0.004	0.31	1.00
		HC	1.05*	0.27	<.001
	ROD	CHR	-0.11	0.31	0.98
		ROP	-0.12	0.31	0.98
		HC	1.17*	0.27	<.001
	ROP	CHR	0.004	0.31	1.00
		ROD	0.12	0.31	0.98
Sexual Abuse					
		CHR	-0.77*	0.26	0.02
	HC	ROD	-0.69*	0.26	0.04
		ROP	-1.09*	0.26	<.001
		HC	0.77*	0.26	0.02
	CHR	ROD	0.08	0.3	0.99
		ROP	-0.32	0.3	0.72
		HC	0.69*	0.26	0.04
	ROD	CHR	-0.08	0.3	0.99
		ROP	-0.4	0.3	0.53
		HC	1.09*	0.26	<.001
	ROP	CHR	0.32	0.3	0.72
		ROD	0.4	0.3	0.53
Emotional Neglect					
		CHR	-3.85*	0.45	<.001
	HC	ROD	-3.31*	0.44	<.001
		ROP	-3.47*	0.44	<.001
		HC	3.85*	0.45	<.001
	CHR	ROD	0.54	0.52	0.73
		ROP	0.39	0.52	0.88
		HC	3.31*	0.44	<.001
	ROD	CHR	-0.54	0.52	0.73
		ROP	-0.15	0.51	0.99
		HC	3.47*	0.44	<.001
	ROP	CHR	-0.38	0.52	0.88
		ROD	0.15	0.51	0.99

Physical Neglect

	CHR	-1.48*	0.26	<.001
HC	ROD	-1.21*	0.25	<.001
	ROP	-1.92*	0.25	<.001
	HC	1.48*	0.26	<.001
CHR	ROD	0.27	0.29	0.79
	ROP	-0.43	0.29	0.45
	HC	1.21*	0.25	<.001
ROD	CHR	-0.27	0.29	0.79
	ROP	-0.71	0.29	0.07
	HC	1.92*	0.25	<.001
ROP	CHR	0.43	0.29	0.45
	ROD	0.71	0.29	0.07

Abbreviations: HC, Healthy Controlls; CHR, Clinical High-Risk state; ROD, Recent Onset Depression; ROP, Recent Onset Psychosis; CTQ, childhood trauma questionnaire
*Significant at the level of 0.05

Supplement Table 4: *Mean values of medication dose equivalents taken cumulatively over lifetime (mg/d)*

		CHLORPROMAZINE	OLANZAPINE	SSRI	BENZODIAZEPINE
ALL GROUPS	M	1919.98	68.16	1617.69	121.52
	N	623	623	623	623
	SD	8906.37	307.86	6417.95	651.69
HC	M	0	0	0	16.10
	N	250	250	250	250
	SD	0	0	0	232.24
ROD	M	504.47	19.05	2630.83	142.59
	N	129	129	129	129
	SD	2033.96	78.42	6682.12	556.91
CHR	M	1025.06	42.04	3864.95	123.49
	N	119	119	119	119
	SD	5463.24	235.20	8371.53	649.41
ROP	M	8072.71	280.02	1668.10	308.74
	N	125	125	125	125
	SD	17798.21	598.88	9090.62	1114.60

M, mean; SD, standard deviation; HC, Healthy Controlls; CHR, Clinical High-Risk state; ROD, Recent Onset Depression; ROP, Recent Onset Psychosis; Chlorpromazine; Chlorpromazine equivalent, Olanzapine; Olanzapine equivalent, SSRI; SSRI equivalent, Benzodiazepine; Benzodiazepine (Diazepam) equivalent

Supplement Table S5: *CTQ-class probabilities associations with age*

	r_s	p
All groups	-.018	.648
HC	.029	.640
CHR	-.157	0.83
ROD	-0.034	.703
ROP	-.002	.986

CHR, Clinical High-Risk state; ROD, Recent Onset Depression; ROP, Recent Onset Psychosis; r_s, Spearmans Correlation Coefficient

Supplement Table S6: *CTQ-class probabilities associations with medication dose equivalents taken cumulatively over lifetime*

	r_s	p
All groups		
Chlorpromazine	-.213	<0.001
Olanzapine	-.213	<0.001
SSRI	-.193	<0.001
Benzodiazepine	-.128	0.001
HC		
Chlorpromazine	n.a.	n.a.
Olanzapine	n.a.	n.a.
SSRI	n.a.	n.a.
Benzodiazepine	.141	0.013
CHR		
Chlorpromazine	-0.045	0.314
Olanzapine	-0.043	0.319
SSRI	0.015	0.437
Benzodiazepine	-0.038	0.341
ROD		
Chlorpromazine	0.058	0.255
Olanzapine	0.059	0.254
SSRI	0.047	0.298
Benzodiazepine	0.058	0.258
ROP		
Chlorpromazine	-0.002	.491
Olanzapine	-0.006	.472
SSRI	0.004	.481
Benzodiazepine	0.029	.374

CHR, Clinical High-Risk state; ROD, Recent Onset Depression; ROP, Recent Onset Psychosis; r_s, Spearmans Correlation Coefficient, Chlorpromazine; Chlorpromazine equivalent, Olanzapine; Olanzapine equivalent, SSRI; SSRI equivalent, Benzodiazepine; Benzodiazepine (Diazepam) equivalent

Supplement Method: Nested leave-site-out cross-validation

On the outer LOSOCV cycle (CV_2), the entire population was split into the seven sites. Each of these samples was iteratively held back as validation data, while the six remaining samples entered the inner CV loop. Hence, this outer CV loop provided a robust and unbiased estimate of the classification generalizability because all validation samples were strictly separated from the entire training process taking place at the inner loop (CV_1). A 10-fold CV with 10 repetitions was used at this inner loop, to generate classifier ensembles and the outer loop was repeated 5 times to further increase robustness of the generalizability assessments.

Specifically, in each of these training partitions, the CTQ-items were scaled feature-wise to a range of [0, 1]. Because of missing values (3.8% missing), we used a nearest neighbor-based imputation approach employing the Hamming distance[1] suitable for ordinal data. Then, the scaled and imputed data matrix was z-normalized to the training sample's means and standard deviations before it entered sequential backward elimination (SBE) algorithm that employed L_2-regularized logistic regression (L2-LR)[2] as provided by the LIBLINEAR library[2] in NeuroMiner. The SBE algorithm iteratively removed CTQ items from the item pool that decreased average model performance in the CV_1 training and CV_1 test data. An early stopping criterion at 50% of the variables remaining in the pool was introduced to avoid an overfitting of the algorithm. To further increase feature extraction stability, a probabilistic feature extraction step identified those CTQ items that were selected by at least 90% of the CV_1 models in the given CV_2 training partition. CTQ items not meeting this criterion were pruned from the feature pool and models were retrained with the remaining features using the entire CV_1 data partition.

To predict the group membership of unknown individuals in the CV_2 validation partitions, the scaling, imputation and z-normalization models developed in the training sample were first applied to these cases, followed by the computation of class membership probabilities by means of the trained L2-LR models. The class membership predictions produced by these CV_1 models for the unseen validation cases in each held-back site were bagged into an classification ensemble by means of averaging and majority voting[3]. Thus, an average CTQ-based class probability / decision score (DS) was calculated for each individual, predicting its out-of-training (OOT) group membership.

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Supplement Figure 1

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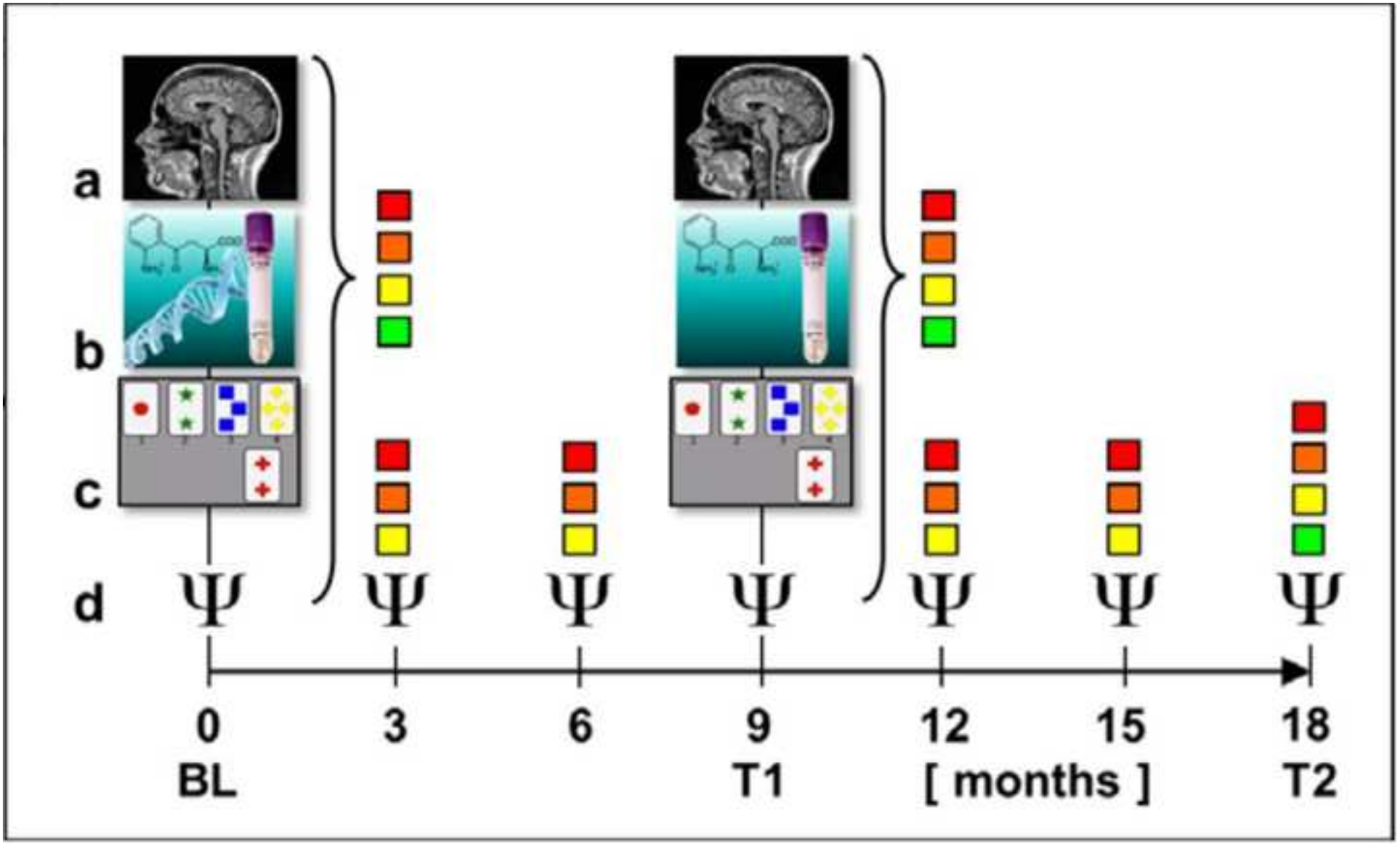

Supplement Figure 2

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