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The effect of childhood trauma on blood transcriptome expression in major depressive disorder

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ABSTRACT

Childhood trauma (CT) increases the likelihood of developing severe mental illnesses, such as major depressive disorder (MDD), during adulthood. Several studies have suggested an inflammatory immune system dysregulation as a biological mediator; however, the molecular mechanisms underlying this relationship remain largely undetermined. Moreover, different types of CT, in particular, emotional abuse and neglect, confer a higher risk of developing MDD, and recent meta-analyses showed that each CT can be associated with different pro-inflammatory biomarkers. However, no studies using a hypothesis-free approach have been performed. For this reason, we carried out a reanalysis of transcriptome data from a large mRNA sequencing dataset to investigate different types of CT in MDD patients. Gene expression analysis followed by principal component and gene-set enrichment analyses were carried out to identify genes and pathways differentially expressed in 368 patients who experienced four different types of CT (sexual abuse, physical abuse, emotional abuse and neglect). Expression analysis of single genes revealed a significant association between the neglect CT and the *MED22* gene ($p = 1.11 \times 10^{-6}$; FDR = 0.016). Furthermore, analyses of the principal components of expression data support a dysregulation of cytokine system pathways, such as interferon (IFN) α/β and γ signaling, as a consequence of emotional abuse in depressed patients. Our results corroborate the hypothesis that specific types of CT affect distinct molecular pathways, and in particular, emotional abuse and neglect exert the strongest impact on gene expression in MDD.

1. Introduction

It has been widely demonstrated that trauma, particularly when experienced during childhood and adolescence, increases the risk of developing a mental disorder with a relatively unfavorable related treatment outcome (Brietzke et al., 2012; Danese and Baldwin, 2017; Sachs-Ericsson et al., 2009; Stoddard, 2014).

Recent literature has focused on understanding the preeminent role of childhood abuse and neglect in vulnerability to major depressive disorder (MDD) and putative underlying neurobiological mechanisms (Baumeister et al., 2016; Nemeroff and Binder, 2014). To date, childhood maltreatment is related to increased levels of C-reactive protein (CRP), fibrogen and proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (Baumeister et al., 2016; Coelho et al., 2014; Lu et al., 2013; Spindola et al., 2017). Furthermore, stress-related alterations in expression levels of immune response genes have been associated with several different environmental adversity, such as childhood abuse and neglect, post-traumatic stress disorder (PTSD, or severe physical diseases as cancer (Bower et al., 2011; O'Donovan et al., 2011; Schwaiger et al., 2016). In the largest mRNA sequencing study performed to date in MDD (Mostafavi et al., 2014), the global impact of childhood trauma (CT) was investigated by a factorial analysis, and no significant results were obtained. Overall, data are still limited, and no conclusive findings have emerged. Indeed, the literature addressing this issue yields several non-significant results, most studies lack a hypothesis-free approach, and few have investigated specific types of CT. Most research has so far focused on physical and sexual abuse, whereas fewer studies have examined the effects of emotional abuse or neglect (Infurna et al., 2016). Molecular research on these types of CT is important because emotional/physical neglect and emotional abuse seem to confer the highest risk for depressive states in adulthood (Infurna et al., 2016; Mandelli et al., 2015). In particular, the results of these meta-analyses point to the importance of considering neglect and emotional abuse as having a relevant impact in adult depression, while sexual and physical abuse, which have been traditionally considered as major risk factors for depression and though maintaining a strong association with this condition, may be less specific for this disorder (Infurna et al., 2016; Mandelli et al., 2015). Concerning

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neglect, a recent study reported in detail that only emotional neglect was associated with depressive symptomatology (van Veen et al., 2013). Furthermore, a recent meta-analysis found evidence that exposure to specific types of CT has a different impact on the inflammatory markers investigated (Baumeister et al., 2016). In particular, Baumeister and collaborators have shown that physical and sexual abuse were associated with significant increased TNF-α and IL-6, but not CRP that instead it seemed to be related to parental absence during early development.

Based on the above findings, to better understand the biological mechanisms associated with different types of CT in MDD, we carried out a re-analysis of expression data using the RNA-sequencing of whole-blood RNA dataset originally described by Mostafavi and colleagues (Mostafavi et al., 2014).

2. Material and methods

2.1. Sample

We evaluated clinical and biological data from dataset 7 (Levinson RNA Sequencing Data from NIMH Study 88/Site 621), encompassing 922 individuals (463 MDD and 459 controls), available upon request from the National Institute of Mental Health (NIMH) Center for Collaborative Genomic Studies on Mental Disorders (https://www.nimhgenetics.org/access_data_biomaterial.php), and originally described by Mostafavi and collaborators (Mostafavi et al., 2014).

From the whole sample, we selected only MDD patients with at least moderate depression episode and without lifetime mania symptoms, and healthy volunteers without a history of drug or alcohol abuse or dependence and without a personal history of psychiatric disorders. Furthermore, we excluded subjects with neurological disorders such as Parkinson's, epilepsy, and Tourette syndrome; inflammatory diseases such as hepatitis, HIV, HPV, LES, Flajani-Basedow-Graves disease, Lyme disease, Sjogren's syndrome, and rheumatoid arthritis; unusual medical comorbidities such as Ehlers-Danlos Syndrome, Kartagener syndrome, von Willebrand disease, and Marfan Syndrome; and subjects with a current cancer diagnosis. The resulting samples consisted of 367 cases and 344 controls.

2.2. Childhood trauma assessment and classification

The CT were assessed with the Childhood Trauma Scale. Because there is no scoring key for this questionnaire, we classified the groups as having experienced each childhood abuse in the following way (see Supplementary File 1 for details). The subjects were classified as having experienced sexual childhood abuse (SA) when they responded at least “once” to the two items concerning the corresponding abuse. For the other kinds of trauma, because the items were evaluated by multiple-choice responses that assess the subjective perception of the events, we established the response choice thresholds that represents a vulnerability to developing MDD by a cell chi-squared test for frequency distribution between MDD and controls. The contingency table cells that resulted to be significantly different in the two groups were considered the response choice thresholds (see Supplementary File 1 for details).

According to this classification, we divided controls and MDD patients in subgroups for four type of trauma; SA, physical abuse (PA), emotional abuse (EA), emotional Neglect (Ne).

Gene expression analyses were carried out only in MDD patients (N = Sample size 368 MDD patients; 285 females, mean age 43.74) and no analyses were carried out in controls because the goal of the study was to examine biological pathways associated with exposure to CT in MDD. In particular, we compared MDD patients with and without SA (N = 150 vs. N = 218), MDD patients with and without PA (N = 70 vs. N = 186), MDD patients with and without EA (N = 139 vs. N = 229), and patients with and without Ne (N = 157 vs. N = 211).

The principal sociodemographic and clinical features of considered groups are reported in tables S2, S3 and S4 of Supplementary File 1.

2.3. Genes selected for the association analysis

Starting from RNA-seq raw reads calculated on RefSeq genes, as in the Mostafavi study (Mostafavi et al., 2014), we considered only genes with at least 10 reads in at least 100 individuals in our dataset, resulting in 14,832 addressable genes. As described in the Mostafavi study (Mostafavi et al., 2014), to normalize data and remove confounding effects due to technical factors (i.e., differences in sequencing performances) and differences in blood samples, subsequent analyses were conducted on residuals from ridge regression of raw counts against 36 technical variables.

2.4. Expression principal components (EPC) estimation

Twenty expression principal components (EPC) were calculated on the subsets of subjects selected for this study. Because the variance explained by these EPCs plateau at the 8th EPC (Supplementary file 1, Figure S1), we considered only the first 8 components for further analysis. The EPC analysis was performed using SVS 8 software (Golden Helix, Bozeman, MT, USA).

2.5. Selection of relevant clinical, demographic and environmental covariates

Among the clinical, demographic and environmental variables available, we selected only those reported in at least 20 individuals and that correlated with trauma status or EPCs. By Fisher's exact tests or Spearman's rank correlation tests, we identified 30 variables that correlated at a p-value lower than 0.05 (Supplementary File 1 Table S5). False discovery rate (FDR) was used for multiple hypothesis correction.

2.6. Association of single gene expression levels with different types of trauma

Gene expression analysis was performed based on the method described by Mostafavi and colleagues (Mostafavi et al., 2014). Based on the analysis showed in the original paper, we examine the relationship between gene expression levels (reported as RNA-seq count data normalized by ridge regression) and each type of CT described above, using a likelihood ratio test (LRT). Given CT as dependent variable, the LRT compares the log likelihood of logistic regression model including only covariates (null model) and including covariates and gene expression (full model).

In order to reduce the impact of putative confounding factors we included in our model as “background” covariates the 30 environmental, physiological or medical variables reported in Supplementary File 1 Table S5. Moreover, because about 39% of MDD patients with trauma experienced two or more types of trauma (Supplementary File 1 Figure S2), we corrected for the concomitant presence of the others childhood trauma. Finally, to correct for population stratification, we included the five genotyping principal components (GPCs) extracted from the original data (Mostafavi et al., 2014). Due to the large number of covariates included in the LRT model that could inflate the p-values, nominal p-values were validated using permutation test.

In addition, given the high degree of multi-exposure of CT, a LRT analysis with the same covariates reported above was performed for evaluating cumulative effects of CT. Cumulative effect was measured as quantitative variable ranging from 0 to 4 according to the number of maltreatment types experienced.

Spearman's rank correlation tests and hypergeometric test were applied to verify any correlation between top genes associated with different types of trauma.

Gene set enrichment analysis was performed separately for genes