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ORIGINAL ARTICLE

In major affective disorders, early life trauma predict increased nitro-oxidative stress, lipid peroxidation and protein oxidation and recurrence of major affective disorders, suicidal behaviors and a lowered quality of life

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Abstract

Early life trauma (ELT) may increase the risk towards bipolar disorder (BD) and major depression (MDD), disorders associated with activated neuro-oxidative and neuro-nitrosative stress (O&NS) pathways. It has remained elusive whether ELTs are associated with O&NS and which ELTs are associated with distinct affective disorder phenotypes. This case-control study examined patients with BD ($n = 68$) and MDD ($n = 37$) and healthy controls ($n = 66$). The Child Trauma Questionnaire (CTQ) was used to assess specific ELT. We measured malondialdehyde (MDA), lipid hydroperoxides (LOOH), superoxide dismutase (SOD), catalase, advanced oxidation protein products (AOPP); NO metabolites (NOx), paraoxonase 1 activity, zinc, albumin, high density lipoprotein cholesterol and -SH groups and computed z-unit weighted composite scores. Physical neglect significantly predicts higher z-unit weighted composite scores of LOOH+SOD, LOOH+SOD+NOx, LOOH+SOD+NOx + MDA and LOOH+SOD+NOx + AOPP. Sexual abuse was associated with a significantly lower composite score of zinc+albumin+SH. Emotional abuse was associated with severity of depression and anxiety, number of depressive and manic episodes, alcohol and hypnotics use, lifetime suicidal behavior and lowered quality of life. Sexual abuse was associated with an increased risk towards BD, but not MDD. ELT, especially physical neglect, may drive increased (nitro-)oxidative stress coupled with lipid and protein oxidation, which - together with emotional abuse - may play a role in severity of illness, lowered quality of life and MDD. ELTs are also associated with the onset of BD, but this link did not appear to be related to activated O&NS pathways. These novel findings deserve confirmation in prospective studies.

Keywords Depressive disorder · Bipolar disorder · Child abuse · Oxidative stress · Antioxidants · Suicide

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Introduction

The major affective disorders (MAFD) bipolar disorder (BD) and major depressive disorder (MDD) are heterogeneous clinical phenotypes, whose patho-etiology appears to be explained by a complex interaction of genetic and environmental factors (Murray et al. 2013; Walker et al. 2015). Both MAFD types are highly prevalent and recurring disorders with a higher risk for suicidal behavior (American Psychiatric Association 2013; Bolton et al. 2015; Miret et al. 2013; Novick et al. 2010). Replicated evidence indicates that both MDD and BD are associated with impairments in health-related quality of life (HRQoL) and significant disabilities (Birnbaum et al. 2010; Dean et al. 2004; Depp et al. 2012; GBD 2015 DALYs and HALE Collaborators 2016).

Early life trauma (ELT), defined as early life adverse experiences including physical, sexual and emotional abuse and neglect, are putative environmental risk factors for BD and MDD (Alvarez et al. 2011; Bergink et al. 2016: Heim et al., 2010). Different types of childhood adversity, such as parental discord and bullying may contribute to the onset of psychopathology (Catone et al. 2015; Fisher et al. 2010; Takizawa et al. 2014). Meta-analytic evidence indicates that a history of childhood maltreatment has a significant deleterious impact on the long-term course of both MAFD, including a more recurring course (Agnew-Blais and Danese 2016; Jansen et al. 2016), greater illness severity, higher rates of co-occurring substance misuse disorders (Agnew-Blais and Danese 2016; Schoedl et al. 2010) and increased risk towards suicidal behaviors (Heim et al. 2010; Kendler et al. 2002; Runyan et al. 2002; Schoedl et al. 2010). In children and adult survivors of child abuse, ELT has a negative impact on HRQoL while affecting disability even decades after the experienced trauma (Afifi et al. 2007; Chahine 2014). Nevertheless, it is emphasized that the investigation of possible mechanisms underpinning the consequences of ELT among patients with affective disorders remains relatively unexplored (Aas et al. 2016).

There is now replicated evidence that MAFD is accompanied by activated neuro-oxidative and neuro-nitrosative stress (O&NS) pathways, lowered levels of antioxidants and antioxidant enzymes, which are often interrelated with activated immune-inflammatory pathways (Anderson and Maes 2015; Andreazza et al. 2008; Berk et al. 2011; Brown et al. 2014; Kohler et al. 2017a, b; Liu et al. 2015; Maes et al. 2009, 2011). The key findings are: a) lowered protection against lipid peroxidation as indicated by lower levels of high-density lipoprotein (HDL) cholesterol, cholesterol esters, omega-3 polyunsatutared fatty acids and paraoxonase 1 activities (Bilici et al. 2001; Bortolasci et al. 2014; Maes et al. 2000, 1999, 1994, 1997; Moreira et al. 2017; Nunes et al. 2015; Peet et al. 1998; Sobczak et al. 2004; Tsuboi et al. 2006); b) increased reactive oxygen species (ROS, including superoxide radicals and hydroxyl) as indicated by increased levels of superoxide dismutase (SOD) and peroxides coupled with lowered levels of catalase (Liu et al. 2015; Maes et al. 2010); c) oxidative damage to lipids as indicated by increased malondialdehyde (MDA) levels and IgG/IgM-mediated autoimmune responses to oxidized low-density lipoprotein (LDL) cholesterol, MDA and anchorage molecules, including palmitic and myristic acid (Bengesser et al. 2015; Bilici et al. 2001; Chowdhury et al. 2017; Khanzode et al. 2003; Kunz et al. 2008; Machado-Vieira et al. 2007; Maes et al. 2013a, b; Ozcan et al. 2004; Ranjekar et al. 2003; Sarandol et al. 2007); d) increased reactive nitrogen species (RNS) as indicated by increased production of nitric oxide (NO) metabolites (NOx) and inducible NO synthase (Galecki et al. 2011; Liu et al. 2015; Maes et al. 2011; Morris et al. 2017); e) lowered levels of key antioxidants including albumin, zinc and sulfhydryl (-SH) groups on proteins (Gomes et al. 2017; Liu et al. 2015; Maes et al. 1991; Nowak 2015; Swardfager et al. 2013); and f) increased protein oxidation as indicated by higher advanced oxidation protein products (AOPP) (Gomes et al. 2017), which may be induced by increased peroxynitrite (as a consequence of increased superoxide and NO) and myeloperxidase increasing hypochlorous acid (HOCl) (Vaccarino et al. 2008).

Psychological stressors, including ELT, may induce neuro-oxidative and immune-inflammatory pathways (do Prado et al. 2016; Maes et al. 2011). Therefore, exposure to ELT, including childhood maltreatment, may influence the pathophysiology of mood disorders at least in part through deleterious interactions involving neuro-oxidative and neuro-immune pathways (Heim et al. 2010; Maes et al. 2011; Simcek et al. 2016). Limited available data in BD patients indicates that ELT is associated with increased inflammatory biomarkers, including C-reactive protein (CRP) (Coelho et al. 2014; Dargel et al. 2015; Fernandes et al. 2016) with ELT differentially associating with increased CRP levels (Moraes et al. 2017). Although BD is associated with exposure to various subtypes of ELT, increased CRP levels were significantly and independently associated only with sexual abuse in BD patients (Moraes et al. 2017). To our knowledge no previous study has assessed the association of ELT and O&NS stress biomarkers among individuals with MAFD.

Therefore, the current study aims to delineate the relationships between ELT (and its subtypes: sexual, physical and emotional abuse, physical and emotional neglect) and peripheral biomarkers of O&NS and clinical characteristics of affective disorders. The a priori hypotheses are that ELTs are associated with increased levels of O&NS biomarkers and that previous ELT exposure will associate with clinical variables indicative of more severe forms of these disorders via O&NS processes.

Methods

Study population

This cross-sectional study examined participants with Bipolar Disorders ($n = 68$) and Major Depressive Disorder ($n = 37$) recruited from the Psychiatry outpatient clinics at the University Hospital of the Universidade Estadual de Londrina (UEL), Parana, Brazil. All patients were in remission or partial remission and none of the BD patients was in a manic phase. A sample of healthy controls (HC, $n = 66$) was recruited from the same catchment area. Participants of either gender, ages 18 to 65 years and from all ethnicities were included. The study was conducted from June 2015 through March 2016. All participants provided written informed consent to take part in the study, with the experimental procedures being approved by the Research Ethics Committee at UEL (protocol number: CAAE 34935814.2.0000.5231).

The following exclusion criteria were applied: a) participants with mental retardation, schizophrenia, neurocognitive disorders, or otherwise cognitively impaired, b) pregnant women, c) individuals using nonsteroidal anti-inflammatory drugs, glucocorticoids, interferon, omega-3 polyunsaturated fatty acids and antioxidant agents, such as N-acetylcysteine during the past 4 weeks prior to study enrollment, and d) participants with medical conditions, which are known to involve peripheral inflammation and cell-mediated immune activation, including HIV infection, hepatitis B and C virus infection, the postpartum period, chronic and acute renal failure, neurodegenerative disorders (e.g. Alzheimer's and Parkinson's disease), cancers, chronic obstructive pulmonary disease, inflammatory bowel disease, and autoimmune diseases including Crohn's disease, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus and type I diabetes (Maes et al. 2011).

Methods

All participants completed a semi-structured interview, which comprised socio-demographic data (education, work status, marital status, etc) and clinical data, including the number of depressive and manic episodes, the use of drugs of abuse, first-degree family history of mood disorders and substance-related disorders, as well as first-degree family history of suicide, use of psychopharmacological agents, namely antidepressants, antipsychotic drugs and mood stabilizers, including lithium and anticonvulsants.

Diagnoses of BD, MDD and tobacco use disorder (TUD) were established by trained research psychiatrists using the Structured Clinical Interview for the DSM-IV-TR clinical version translated and validated for application in Brazilian samples (Del-Ben et al. 2001). Depression symptom severity was measured with the 17-item Hamilton Depression Rating Scale (HAM-D), which was previously translated and adapted for use with Brazilian samples (Moreno and Moreno 1998). The severity of anxiety symptoms was assessed by means of the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1959), and the severity of manic symptoms was evaluated using the Brazilian Portuguese version of the Young Mania Rating Scale (YMRS) (Vilela et al. 2005). Current suicidal ideation and previous suicide attempts were assessed using the Columbia Suicide Rating Scale (Posner et al. 2011). In this study, we used three items of this scale, namely current and lifetime suicidal ideation and lifetime suicidal attempts (all scored as yes or no).

The Childhood Trauma Questionnaire (CTQ) is a self-administered instrument for adolescents and adults that investigates a history of abuse and neglect during childhood. The instrument features scores on a five point Likert scale as to the frequency of reported events in childhood. It rates childhood maltreatment in 5 domains, namely sexual abuse, physical abuse, emotional abuse, emotional neglect and physical neglect (Bernstein et al. 2003). Its 28-item version has been validated to Brazilian Portuguese (Grassi-Oliveira et al. 2006).

The assessment of substance misuse was made through the ASSIST (Alcohol, Smoking and Substance Involvement Screening Test), a screening questionnaire developed by the World Health Organization (WHO ASSIST Working Group 2002), translated and adapted to Brazilian Portuguese (Henrique et al. 2004). This study used items pertaining to the use of alcohol and hypnotics. The Sheehan Disability Scale is a widely employed measure of disability used for research in populations with mood disorders. It is a self-administered scale which rates three main areas: 1) occupational, 2) social life, leisure, 3) family life, activities, household activities. A score of 0–10 is rated in each domain. Scores of 0–3 indicate mild psychosocial dysfunction, 4–6 moderate dysfunction and 7–10 severe disability (Sheehan et al. 1996). We used the WHO Quality of Life Instrument-Abbreviated Version (WHOQOL-BREF) (Skevington et al. 2004) in a validated Brazilian Portuguese translation (Fleck et al. 2000) to assess HRQL. In this study, we used the sum of the 26 items as an overall index of HRQL. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2).

Peripheral blood samples were obtained at 8 a.m. after 12 h fasting on the day of clinical data collection. We assessed the concentrations of O&NS biomarkers, i.e. malondialdehyde (MDA), lipid hydroperoxides (LOOH), superoxide dismutase (SOD), catalase (CAT), advanced oxidation protein products (AOPP), NO metabolites (NOx), paraoxonase 1 (PON1) activity, zinc, albumin, high density lipoprotein (HDL-) cholesterol and -SH groups. MDA levels were measured through complexation with two molecules of thiobarbituric acid (TBA) using

MDA estimation through high performance liquid chromatography (HPLC Alliance e2695, Waters', Barueri, SP, Brasil) (Bastos et al. 2012). Experimental conditions included the use of a column Eclipse XDB-C18 (Agilent, USA); mobile phase consisting of 65% phosphate buffer (50 nM pH 7.0) and 35% HPLC grade methanol; flow rate of 1.0 mL/min; temperature of 30 ºC; wavelength of 532 nm. MDA concentration in the samples was quantified based on a calibration curve and are expressed in æmol of MDA/mg proteins. Lipid peroxides (LOOH) are assayed by chemiluminescence (CL-LOOH) (Gonzalez Flecha et al. 1991; Panis et al. 2012). This method uses the compound tert-butyl hydroperoxide to start a lipid chain reaction that can be detected by photon emission during the formation of lipid hydroperoxides. Readings were performed in a Glomax luminometer (TD 20/20 Turner Designers, USA) over 1 h at 1 reading per second. Results are expressed as relative units of light. SOD activity in erythrocytes was determined using the pyrogallol method described by Marklund and Marklund (1974). This technique is based on the inhibition of pyrogallol self-oxidation by SOD in aqueous solution. The assay was conducted in a spectrophotometer Helios à, Thermo Spectronics (Waltham, MA, USA) at 420 nm and 37 ºC. During 5 min, variation in optical density (OD) was recorded every minute. The level of SOD that inhibited 50% of the pyrogallol oxidation was defined as one unit of enzymatic activity. The results were expressed U/mg Hb. Measurement of catalase activity was estimated through the difference between the initial reading and the reading conducted 30 s after the addition of 200 mM H2O2 30% at 240 nm in a microplate reader (model EnSpire, Perkin Elmer, USA) with the temperature maintained at 25 °C. The catalase values are expressed as U/mg of hemoglobin (Hb). AOPP was quantified using the method described by Hanasand et al. (2012) in a microplate reader, Perkin Elmer, model EnSpire (Waltham, MA, EUA) at a wavelength of 340 nm (Hanasand et al. 2012). AOPP concentration was expressed in μM of equivalent chloramine T. NO metabolite (NOx) levels were assessed indirectly by determining the plasma nitrite concentration using an adaptation of the technique described (Navarro-Gonzalvez et al. 1998). This method is based on the reduction of the nitrate present in the sample to nitrite by oxidation-reduction reactions mediated by the system cadmium-copper reagent. Thereafter, Griess reagent was added to induce diazotization, forming a colored complex and subsequent detection at 540 nm. The quantification of NOx was made in a microplate reader Asys Expert Plus, Biochrom (Holliston, MA, USA). The nitric oxide concentration was expressed in μM.

Total plasmatic activity of PON1 was determined by the method described by Richter et al. (2008). The rate of hydrolysis of phenyl acetate was determined in a microplate reader EnSpire, Perkin Elmer (Waltham, MA, USA) at 270 nm and the temperature maintained at 25 °C. Measures were recorded for 4 min each 15 s. The activity was expressed in U/mL based on the phenyl acetate molar extinction coefficient of 1.31 mMol/L cm-1. PON1 activity was adjusted for Q192R polymorphism, which was determined through kinetic assays (Richter et al. 2008) in a spectrophotometer microplate reader (EnSpire, Perkin Elmer, USA). Individuals were stratified in functional genotypes for PON1 Q192R polymorphism (QQ, QR and RR). Total plasmatic PON1 activity was determined by measuring rates of phenylacetate (PA, Sigma, USA) hydrolysis at low salt concentration since under this assay condition, the PON1 Q192R polymorphism does not influence PON1 catalytic activity against PA (Furlong et al. 2006; Moreira et al. 2017). Zinc was assayed using a method described by Barceloux and Barceloux (1999). Briefly, 0.5 mL of serum sample was diluted with 2.0 mL ultrapure water (PureLab Ultra, ELGA, USA), and carried out using an Analyst model 5110 (Perkin Elmer, USA) atomic absorption spectrometer with flame atomization (8= 213.9 nm, slit 0.7), operating with ultra air and acetylene (99.999%, Air Liquid, Brazil). The accuracy of the results was evaluated using the standard reference material BioRad serum (Biorad 26,400, level 1). All the analyses were performed in an ISO Class 7 cleanroom facility. Albumim was assayed using an automated method in a clinical chemistry system (Dimension RxL,Siemens Healthcare Diagnostics Inc., Newark, DE, USA). HDL-C was assayed by automated methods using the Dimension RxL (Deerfield, IL, USA) and i2000SR Architect (Abbott, IL, USA). Sulfhydryl (-SH) groups from proteins were evaluated by the method described by Hu (1994), which is based on the reaction of 5,5-dithiobis-2 nitrobenzoic acid (DTNB) with sulfhydryl groups. Determination was conducted in a spectrophotometer Helios à, Thermo Spectronic (Waltham, MA, USA) at 412 nm. Results are expressed as :M/mg of plasmatic protein. The inter-assay coefficients of variability for all analytes were less than 10%.

Raw O&NS biomarker data were converted in z scores and consequently used to compute z-unit weighted composite scores reflecting different pathways:

- zLOOH+SOD: index of ROS, computed as z value LOOH (zLOOH) + zSOD. The rationale is that increased superoxide induces SOD thereby catalyzing superoxide radicals into peroxides and lead to production of lipid hydroperoxides ((Hayyan et al. 2016).
- zLOOH+SOD+NOx: index of nitro-oxidative stress reflecting ROS and NO production, and thus the potential to form peroxynitrite (Pacher et al. 2007).
- zLOOH+SOD+NOx + MDA: an index of nitro-oxidative stress coupled with lipid peroxidation reflecting the pathway from nitro-oxidative stress to lipid peroxidation (Maes et al. 2011);
- zLOOH+SOD+NOx + AOPP: an index of nitro-oxidative stress coupled with protein oxidation (AOPP), which is the consequence of increased nitro-oxidative stress,

peroxynitrite production, myeloperoxidase activity and hypochlorous acid (HOCl) production (Marsche et al. 2009).
- zLOOH+SOD+NOx + MDA + AOPP: index of overall nitro-oxidative stress with damage to lipids and proteins, including superoxide, NO and (probably) peroxynitrite, myeloperoxidase and HOCl production.
- zCAT+PON1 + HDL: index of anti-lipid peroxidation potential. Catalase catalyzes peroxides into water thereby removing peroxides (Chelikani et al. 2004). Both PON1 and HDL-cholelesterol protect lipids against oxidation (Moreira et al. 2017).
- zAlb+Zn + SH: index of general anti-oxidant potential consisting of three major antioxidant defenses, namely albumin (Maes et al. 2011), zinc (Nowak 2015) and -SH groups (Cichoń et al. 2015).
- All values were computed as the sums of the z transformed biomarkers. In another study, we will report on the effects of BD and MDD and other relevant predictors on the separate oxidative and antioxidant markers.

Statistics

We used analyses of contingency Tables (X^2-test) to assess associations between categorical variables and analyses of variance (ANOVA) to check differences among clinical, socio-demographic and biomarker data between categories. Automatic stepwise (forward entry) multinomial logistic regression analyses were employed to delineate the significant explanatory variables separating BD from MDD and controls. We used automatic forward (LR method, entry probability 0.05 and removal probability 0.051) binary logistic regression analyses with suicidal ideation/attempts or MAFD as dependent variables and with O&NS biomarkers and ELT domains (and other relevant clinical variables) as explanatory variables. We employed multivariate general linear model (GLM) analyses to delineate the associations between interrelated dependent variables (e.g. the CTQ subscales or clinical variables) and explanatory variables, while controlling for background variables where needed. Tests for between-subject effects were employed to examine the univariate effects of significant predictor variables on dependent variables. We entered the 5 ELT subtypes and the total CTQ score in all multivariate analyses in order to delineate the most significant predictors of clinical phenomenology. Automatic (forward) stepwise (entry probability 0.05 and removal probability 0.051) linear regression analyses were employed to examine the effects of predictor variables (including ELT subtypes) on dependent variables (including the biomarkers). All regression analyses were checked for multicollinearity. All tests were two-tailed, and an alpha level of 0.05 was regarded as statistically significant. All analyses were performed using the IMB-SPSS software version 22 for Windows.

Results

Descriptive statistics

Table 1 shows the socio-demographic, clinical and biomarker data in all individuals subdivided into three subgroups according to q25 and q75 values of the total CTQ score. We did not use any p-corrections as we did not aim to assess the multiple statistical analyses on socio-demographic, clinical and biomarker data. Indeed, these univariate statistical data (together with their intercorrelation matrices) were employed to select independent variables that were considered as possible independent variables in multivariable GLM analyses. Therefore, we did not compute post-hoc analyses to determine the multiple comparisons between treatment means.

Associations between ELT and O&NS

Table 2 shows the results of automatic stepwise linear regression analysis with the O&NS biomarkers are dependent variables and ELT subtypes as explanatory variables (while also entering age, sex, and TUD). Regression #1, 2, 3 and 4 show that zLOOH+SOD, zLOOH+SOD+NOx, zLOOH+SOD+NOx + MDA and zLOOH+SOD+NOx + AOPP are significantly and positively associated with physical neglect. Bivariate correlations showed that the other ELT subtypes were not significantly associated with the biomarkers. Regression #5 shows that the zZinc+Albumin+SH score was significantly and inversely associated with sexual abuse (after adjusting for sex). Bivariate correlations did not show that the other ELTs were significantly associated with this biomarker. Regression #6 shows that the overall index of nitro-oxidative damage to lipids and proteins is predicted by physical neglect coupled with lowered antioxidant defenses, which protect against lipid peroxidation (namely zPON+CAT+HDL).

Association between ELT, O&NS and number of episodes

Table 3 shows the outcome of different GLM analyses, a first with number of episodes as dependent variables and ELT subtypes and familial history of psychiatric disorders as explanatory variables. Multivariate regression #1 shows that emotional abuse and familial histories of MDD and BD significantly predicted number of depressive and manic episodes. Tests for between-subject effects showed that the number of depressive episodes was best predicted by emotional abuse and a familial history of MDD, while the number of manic episodes was best predicted by emotional abuse and a familial history of BD. The effects of emotional abuse ($F = 6.49$, $df = 2/152$, $p = 0.002$) remained significant after entry of sex, age and HAM-D. We have also examined whether there were any associations between the O&NS biomarkers measured here and number of episodes but none could be detected.

Table 1 Socio-demographic, clinical and biomarker data in patients with mood disorders and healthy controls (HC) subdivided into three subgroups according to the total Childhood Trauma Questionnaire score (CTQ)

Variables	Low CTQ < 32	Moderate 32 < CTQ < 48.66	Severe CTQ ≥ 48.66	F/χ^2	df	*p*
CTQ total sum	28.5 (2.3)	39.2 (4.8)	67.1 (13.1)	344.32	2/168	< 0.001
Sexual abuse score	5.1 (0.4)	5.6 (1.5)	8.8 (5.2)	23.46	2/168	< 0.001
Physical abuse score	5.8 (1.1)	7.1 (2.5)	12.9 (4.4)	94.32	2/168	< 0.001
Emotional abuse score	5.8 (1.2)	9.1 (2.9)	16.5 (4.7)	166.98	2/168	< 0.001
Emotional neglect score	6.3 (1.6)	9.9 (3.8)	17.5 (4.0)	176.96	2/168	< 0.001
Physical neglect score	5.6 (1.2)	7.6 (2.6)	11.4 (3.8)	66.65	2/168	< 0.001
Age (years)	41.8 (11.0)	44.33 (12.2)	42.83 (11.1)	0.77	2/168	0.463
Gender (F/M)	39 / 20	38 / 17	51 / 6	9.84	2	0.007
Education (years)	12.5 (6.1)	11.3 (4.8)	9.8 (4.1)	3.99	2/167	0.020
Family income (minimal salaries)	3.77 (1.45)	3.35 (1.36)	2.89 (1.38)	5.59	2/166	0.004
# Depressive episodes	1.61 (4.07)	2.43 (3.17)	5.78 (4.73)	16.28	2/159	< 0.001
# (Hypo)manic episodes	0.54 (1.71)	3.38 (5.85)	4.26 (6.45)	8.49	2/168	< 0.001
Diagnosis HC/BD/MDD	40 / 8 / 11	18 / 24 / 13	8 / 36 / 13	41.06	4	<0.001
Diagnosis HC/BDI/BDII/MDD	40 / 3 / 5/ 11	18 / 18 / 6 / 13	8 / 24 / 12/ 13	42.98	6	<0.001
HAM-D	4.1 (5.8)	6.6 (5.8)	10.9 (6.3)	19.15	2/168	< 0.001
YMRS	0.97 (2.5)	1.62 (2.5)	1.72 (2.5)	1.56	2/168	0.214
HAM-A	7.2 (8.0)	11.6 (9.9)	17.0 (9.8)	15.37	2/157	<0.001
Current suicidal ideation (No/Yes)	52 / 7	53 / 2	36 / 21	23.34	2	<0.001
Lifetime suicidal ideation (No/Yes)	44 / 15	33 / 22	15 / 42	28.42	2	< 0.001
Lifetime suicide attempts (No/Yes)	54 / 5	47 / 8	32 / 25	23.76	2	< 0.001
ASSIST–Alcohol use	2.76 (3.68)	4.80 (7.04)	4.51 (7.73)	1.73	2/168	0.180
ASSIST–Hypnotic use	0.76 (2.46)	1.36 (3.46)	2.88 (6.09)	3.73	2/168	0.026
Sheehan disability score	5.6 (8.9)	11.0 (9.2)	15.9 (9.6)	18.03	2/167	< 0.001
WHOQOL-BREF	92.8 (13.5)	85.1 (14.9)	71.2 (14.6)	33.74	2/167	< 0.001
zLOOH+SOD (z score)	−0.14 (1.69)	−0.10 (1.62)	+0.24 (1.19)	0.96	2/142	0.386
zLOOH+SOD+NOx (z score)	−0.24 (1.94)	−0.04 (1.76)	+0.24 (1.75)	0.87	2/142	0.420
zLOOH+SOD+NOx + MDA (z score)	−0.30 (2.52)	+0.10 (2.30)	+0.24 (1.94)	0.76	2/141	0.468
zLOOH+SOD+NOx + AOPP (z score)	−0.40 (2.53)	+0.06 (2.14)	+0.30 (1.96)	1.29	2/142	0.278
zLOOH+SOD+NOx + MDA + AOPP (zscore)	−0.46 (3.07)	+0.21 (2.46)	+0.31 (2.17)	1.28	2/141	0.280
zCAT+PON1 + HDL (z score)	+0.33 (1.96)	−0.19 (1.83)	−0.11 (1.86)	1.07	2/141	0.348
zAlb+Zn + SH (z score)	+0.15 (2.16)	+0.08 (1.72)	−0.21 (2.30)	0.41	2/145	0.662

HC, healthy controls; *BD*, Bipolar Disorder (Types I and II); *BD I*, Bipolar Disorder Type I; *BD II*, Bipolar Disorder Type II; *MDD*, Major Depression; *HAM-D*, Hamilton Depression Rating Scale; *YMRS*, Young Mania Rating Scale; *HAM-A*, Hamilton Anxiety Rating Scale; *ASSIST–Alcohol*, Alcohol, Smoking and Substance Involvement Screening Test score for alcohol; *ASSIST–Hypnotics*, Alcohol, Smoking and Substance Involvement Screening Test score for hypnotics; *BMI*, Body Mass Index; *Sheehan DS*, Sheehan Disability Scale total score; *WHOQOL-BREF*, World Health Organization Quality-of-Life Scale total score; *LOOH*, lipid hydroperoxides; *SOD*, superoxide dismutase; *NOx*, nitric oxide metabolites; *MDA*, malondaldehyde; *AOPP*, advanced oxidation protein products; *CAT*, catalase; *PON1*, paraoxonase 1 activity; *HDL*, high density lipoproteine cholesterol; *alb*, albumin; *Zn*, zinc; *-SH*, -SH groups; *zLOOH+SOD*, index of oxidative stress (computed as z value LOOH (zLOOH) + zSOD); *zLOOH+SOD+NOx*, index of nitro-oxidative stress; *zLOOH+SOD+NOx + MDA*, index of nitro-oxidative stress coupled with lipid peroxidation; *zLOOH+SOD+NOx + AOPP*, index of nitro-oxidative stress coupled with protein oxidation; *zLOOH+SOD+NOx + MDA + AOPP*, index of nitro-oxidative stress which caused damage to lipids and proteins; *zCAT + PON1 + HDL*, index of anti-lipid peroxidation potential; *zAlb + Zn + -SH*, index of general anti-oxidant potential (all values are computed as the sums of the z transformed biomarkers)

In Table 4 we compare the effects of emotional abuse (partial eta squared of 0.154, see Table 3) with that of the other ELT types using GLM regression #1. The effects of total CTQ score was also highly significant, whereas the impact of emotional neglect, physical abuse, physical neglect and sexual abuse were less important.

Association between ELT, O&NS and severity of illness

Table 3 multivariate regression #2 shows the outcome of multivariate GLM analysis with three severity of illness rating scales (HAM-A, HAM-D, YMRS) as dependent variables and ELT subtypes and familial histories of MDD and BD as explanatory variables. The multivariate test showed a highly significant effect of emotional abuse and a mild effect of familial history of BD. Tests of between-subject effects showed strong positive associations of emotional abuse with HAM-D, HAM-A and YMRS. A familial history of BD was associated with HAM-D only. In Table 4 we compare the effects of emotional abuse (partial eta squared 0.200, see Table 3) with that of the other ELT types using multivariate regression #2. The effects of total CTQ score was also highly significant, whereas the impact of emotional neglect, physical abuse, physical neglect and sexual abuse were less significant.

Table 3 shows also the outcome of automatic stepwise univariate regression analyses. We found that 27.7% of the variance in HAM-D (regression #1) and 27.9% of the variance in HAM-A (regression #2) was explained by zLOOH+SOD+NOx + MDA + AOPP, number of

Table 2 Results of automatic stepwise regression analyses with oxidative and nitrosative stress biomarkers as dependent variables and early life trauma as explanatory variables

Dependent variables	Explanatory variables	*t*	*p*	Model			
				R^2 (%)	F	df	*p*
#1. zLOOH+SOD	Physical neglect	+2.00	0.047	21.7%	18.27	2 / 132	<0.001
	TUD	+5.59	<0.001				
#2. zLOOH+SOD+NOx	Physical neglect	+2.19	0.030	18.4%	9.83	3 / 131	<0.001
	TUD	+3.76	0.004				
	Age	+2.19	0.031				
#3. zLOOH+SOD+NOx + MDA	Physical neglect	+2.33	0.021	25.9%	15.11	3 / 130	<0.001
	TUD	+4.92	<0.001				
	Age	+2.59	0.011				
#4. zLOOH+SOD+NOx + AOPP	Physical neglect	+2.95	0.004	22.4%	9.38	4 / 130	<0.001
	TUD	+2.50	0.014				
	Age	+2.48	0.015				
	Sex	+3.68	<0.001				
#5. zZn + Alb+SH	Sexual abuse	−2.72	0.007	24.3%	14.32	3 / 134	<0.001
	Sex	+4.86	<0.001				
#6. zLOOH+SOD+NOx + MDA + AOPP	Physical neglect	+2.74	0.007	33.8%	12.89	5 / 126	<0.001
	zPON+CAT+HDL	−2.91	0.004				
	TUD	+3.53	0.001				
	Age	+2.89	0.005				
	Sex	+3.28	0.001				

(all values are computed as the sums of the z transformed biomarkers)

TUD, tobacco use disorder; *LOOH*, lipid hydroperoxides; *SOD*, superoxide dismutase; *NOx*, nitric oxide metabolites; *MDA*, malondaldehyde; *AOPP*, advanced oxidation protein products; *CAT*, catalase; *PON1*, paraoxonase 1 activity; *HDL*, high density lipoproteine cholesterol; *alb*, albumin; *Zn*, zinc; -*SH*, -SH groups; *zLOOH+SOD*, index of oxidative stress (computed as z value LOOH (zLOOH) + zSOD); *zLOOH+SOD+NOx*, index of nitro-oxidative stress; *zLOOH+SOD+NOx + MDA*, index of nitro-oxidative stress coupled with lipid peroxidation; *zLOOH+SOD+NOx + AOPP*, index of nitro-oxidative stress coupled with protein oxidation; *zLOOH+SOD+NOx + MDA + AOPP*, index of nitro-oxidative stress which caused damage to lipids and proteins; *zAlb+Zn + SH*, index of general anti-oxidant potential; *zCAT+PON1 + HDL*, index of anti-lipid peroxidation/antioxidant potential

depressive episodes and emotional abuse (all positively) (age and sex were not significant in this regression).

Association between ELT, O&NS and ASSIST scores

Table 3, regression #3 shows the results of a multivariate analysis with ASSIST hypnotics and alcohol use as dependent variables and the ELT subtypes as explanatory variables, while adjusting for gender (age and education were not significant). We found that emotional abuse was again the most significant predictor variable, while also sex had a significant effect. Tests for between-subjects effects showed that use of hypnotics and alcohol was positively associated with emotional abuse and that sex had a significant effect on alcohol use. In Table 4 we compare the effects of emotional abuse with that of the other ELT types. The total score, emotional neglect and sexual abuse had significant effects, while physical abuse and physical neglect were not significant. We have also examined whether there were any associations between the O&NS biomarkers measured here and the ASSIST scores but none could be detected.

Associations between ETL, O&NS and suicidal behaviors

In Table 5 we examine whether ELT may predict suicidal behaviors. Toward this end we have performed logistic regression analyses with suicidal behaviors as dependent variables and ELT subtypes as primary explanatory variables while also entering HAM-D, diagnosis, number of depressive and (hypo)maniac episodes, and familial histories (see Table 3) as explanatory variables. Current suicidal ideation was significantly predicted by physical abuse, HAM-D and number of depressive episodes ($X^2 = 34.63$, $df = 3$, $p < 0.001$, Nagelkerke = 0.321). Lifetime suicidal ideation was predicted by emotional abuse and a diagnosis of mood disorder ($X^2 = 58.89$, $df = 2$, $p < 0.001$, Nagelkerke = 0.392). Lifetime suicide attempts were predicted by emotional abuse and a family history of suicide ($X^2 = 38.39$, $df = 2$, $p < 0.001$, Nagelkerke = 0.313). We have also examined whether there were any associations between the O&NS biomarkers measured here and suicidal behaviors but none could be detected when controlling for the other predictors.

Associations between ELT, O&NS, HRQol and disabilities

Table 6 examines the effects of ELT on quality of life and disabilities. Toward this end we have adjusted the regression analysis for possible confounding variables, namely number of depressive and manic episodes, age, sex, income, education, TUD, severity of illness. The first

Table 3 Results of three different multivariate GLM analyses with number of depressive episodes, and number of hypo(manic) episodes; severity of illness as measured with the Hamilton Depression rating Scale (HAM-D), Hamilton Anxiety score (HAM-A) and the Young Mania rating Scale (YMRS), or two ASSIST scores, namely - Alcohol and use of Hypnotics - as dependent variables

Type	Dependent variables	Significant explanatory variables	F	df	*p*	Partial Eta squared
Multivariate GLM #1	# Depressive episodes, # (Hypo)manic episodes	Emotional abuse	13.99	2/154	< 0.001	0.154
		FH BD	9.90	2/154	<0.001	0.114
		FH MDD	3.70	2/154	0.027	0.046
Between-subject effects	# Depressive episodes	Emotional abuse	28.05	1/155	< 0.001	0.153
	# (Hypo)manic episodes	FH MDD	4.68	1/155	0.032	0.029
		Emotional abuse	7.63	1/155	0.006	0.047
		FH BD	17.95	1/155	<0.001	0.104
Multivariate GLM #2	HAM-D, HAM-A, YMRS	Emotional abuse	12.70	3/152	<0.001	0.200
		FH BD	3.20	3/152	0.025	0.059
Between-subject effects	HAM-D	Emotional abuse	27.56	1/154	<0.001	0.152
	HAM-A	FH BD	6.53	1/154	0.012	0.041
	YMRS	Emotional abuse	28.33	1/154	<0.001	0.155
		Emotional abuse	11.10	1/154	0.001	0.067
Multivariate GLM #3	ASSIST- Alcohol + ASSIST- Hypnotics	Emotional abuse	5.83	2/164	0.004	0.066
		Sex	6.74	2/164	0.002	0.076
Between-subject effects	ASSIST - Hypnotics	Emotional abuse	5.59	1/165	0.019	0.033
	ASSIST - Alcohol	Emotional abuse	5.23	1/165	0.023	0.031
		Sex (Male > female)	13.33	1/165	<0.001	0.004
Dependent variables in univariate analyses	Explanatory variables	*t* and *p*	F (model)	df (model)	*p* (model)	R^2
#1. HAM-D	zLOOH+SOD+NOx + MDA + AOPP	$t = +2.57$, $p = 0.011$	16.37	3/128	<0.001	0.277
	# depressive episodes	$t = +4.08$, $p < 0.001$				
	Emotional abuse	$t = +2.92$, $p = 0.004$				
#2. HAM-A	zLOOH+SOD+NOx + MDA + AOPP	$t = +2.72$, $p = 0.007$	15.58	3/121	<0.001	0.279
	# depressive episodes	$t = +3.18$, $p = 0.002$				
	Emotional abuse	$t = +3.72$, $p < 0.001$				

ASSIST–Alcohol, Alcohol, Smoking and Substance Involvement Screening Test score for Alcohol; *ASSIST–Hypnotics*, Alcohol, Smoking and Substance Involvement Screening Test score for Hypnotics; *FH-BD/MM*, familial history of bipolar disorder and major depression, respectively; *HAM-D*, Hamilton Depression Rating Scale score; *HAM-A*, Hamilton Anxiety Rating Scale; *YMRS*, Young Mania Rating Scale; *LOOH*, lipid hydroperoxides; *SOD*, superoxide dismutase; *NOx*, nitric oxide metabolites; *MDA*, malondaldehyde; *AOPP*, advanced oxidation protein products; *zLOOH+SOD+NOx + MDA + AOPP*, index of nitro-oxidative stress which caused damage to lipids and proteins

multivariate regression shows that emotional abuse had significant effects (partial eta squared 0.125) on WHOQol-BREF and disability ratings (after adjusting for the significant confounding variables, namely depressive episodes, age, income, and HAM-D). Tests for between-subject effects showed that WHOQOL-BREF score was significantly predicted by these 5 explanatory variables, whereas disability was associated with emotional abuse, age, income and severity of depression. Total CTQ score ($F = 8.11$, $df = 2/150$, $p < 0.001$; partial eta squared 0.098), emotional neglect ($F = 6.51$, df==2/150, $p = 0.002$; partial eta squared 0.080) and physical neglect ($F = 4.60$, $df = 2/150$, $p = 0.011$; partial eta squared 0.058) had less impact than emotional abuse, whilst physical abuse and sexual abuse were not significant.

Table 6 shows (univariate regression) that 9.7% of the variance in WHOQOL-BREF score was explained by zLOOH+SOD+NOx + MDA + AOPP after controlling for sex (age and TUD were not significant in this analysis). Nevertheless, after introducing the ELT subtypes in this automatic stepwise regression analysis these associations with ELT disappeared with emotional abuse being highly significant ($t = -8.01$, $p < 0.001$).

Associations between ELT, O&NS and MAFD

In order to examine whether there are differences between MDD and BD in ELT we have carried out multivariate GLM analyses. Table 7 shows the outcome of these regression analyses. We found significant effects of diagnosis (BD versus MDD versus controls) ($F = 5.03$, $df = 10/326$, $p < 0.001$) on the 5 ELTs and the total CTQ score, while there were no significant effects of sex ($F = 1.86$, $df = 5/162$, $p = 0.104$). Tests for between-subject effects and protected post-hoc effects showed that total CTQ score was significantly different between the three groups with the lowest values in controls and the highest values in BD patients. Sexual abuse was significantly higher in BD patients than in controls and MDD patients. The physical

Table 4 Results of different multivariate GLM analyses (see Table 3) with number of depressive episodes, and number of hypo(manic) episodes; severity of illness as measured with the Hamilton Depression rating Scale (HAM-D), Hamilton Anxiety score (HAM-A) and the Young Mania rating Scale (YMRS), or two ASSIST scores, namely - Alcohol and use of Hypnotics - as dependent variables and early lifetime trauma (ELT) other than emotional abuse as explanatory variables

Tests (see Table 3)	Dependent variables	Explanatory variables	F	df	*p*	Partial Eta squared
Multivariate GLM analyses #1*	# Depressive episodes, # (Hypo)manic episodes	Total CTQ score	15.12	2/154	<0.001	0.164
		Physical abuse	10.42	2/154	<0.001	0.119
		Emotional neglect	9.28	2/154	<0.001	0.108
		Physical neglect	6.63	2/154	0.002	0.079
		Sexual abuse	4.87	2/154	0.009	0.060
Multivariate GLM analyses #2**	HAM-D, HAM-A, YMRS	Total CTQ score	8.72	3/152	<0.001	0.147
		Emotional neglect	4.28	3/152	0.006	0.078
		Physical abuse	4.07	3/152	0.008	0.074
		Physical neglect	3.69	3/152	0.013	0.068
		Sexual abuse	3.85	3/152	0.011	0.071
Multivariate GLM analyses #3***	ASSIST- Alcohol + ASSIST- Hypnotics	Total CTQ score	5.55	2/164	0.005	0.063
		Emotional neglect	5.56	2/164	0.005	0.064
		Sexual abuse	5.58	2/164	0.005	0.064

ASSIST–Alcohol, Alcohol, Smoking and Substance Involvement Screening Test score for Alcohol; *ASSIST–Hypnotics*, Alcohol, Smoking and Substance Involvement Screening Test score for Hypnotics; *HAM-D*, Hamilton Depression Rating Scale score; *HAM-A*, Hamilton Anxiety Rating Scale; *YMRS*, Young Mania Rating Scale; *Total CTQ score*, total Childhood Trauma Questionnaire (CTQ) score

*This regression adjusted data for familial history of bipolar disorder and major depression (see regreesion#1, Table 3)

**This regression adjusted data for Hamilton Depression Rating Scale score and Hamilton Anxiety Rating Scale (see regression #2, Table 3)

***This regression adjusted data for sex (see regression #3, Table 3)

abuse score was significantly higher in BD patients than in controls, while MDD took up an intermediate position. Scores of emotional abuse, emotional neglect and physical neglect were higher in both BD and MDD than in controls. There were no significant differences in any of these ELTs between bipolar 1 and bipolar 2 patients. In order to delineate the best predictor of MAFD versus controls we performed an automatic binary logistic regression analysis with diagnosis as dependent variable and the 5 ELT as explanatory variables. Emotional abuse was the single best predictor of MAFD (X2 = 39.04, df = 1, p < 0.001; Nagelkerke = 0.278; Odds ratio = 3.62, 95% confidence interval: 2.19–5.97).

In order to examine whether ELT and the O&NS biomarkers may have a cumulative effect explaining differences among MDD and BD and controls, we have performed automatic stepwise multinomial logistic regression analysis with BD and MDD as dependent variables (and normal controls) and sexual abuse and emotional abuse (the two most significant ELT separating these groups in Table 7) together with zLOOH+SOD+NOx + MDA + AOPP as explanatory variables (while controlling for HAM-D, TUD, age and sex). Table 8 shows that sexual abuse ($X^2 = 9.77$, df = 2, $p = 0.008$), emotional abuse ($X^2 = 13.30$, df = 2, $p = 0.001$) and the composite score zLOOH+SOD+NOx + MDA + AOPP ($X^2 = 10.21$, df = 2, $p = 0.006$) were significant in this multinomial logistic regression analysis. Parameter estimates show that BD was best separated from normal controls using emotional abuse, while the O&NS index was the best predictor variable of MDD versus controls. BD was best differentiated

Table 5 Results of 3 different automatic stepwise binary logistic regression analyses with suicidal ideation or attempts as dependent variables and early life trauma as explanatory variables, while adjusting for characteristics of major affective disorders

Dependent variables	Explanatory variables	Wald	df	*P*	OR	95% CI
#1. Current Suicidal Ideation	Physical abuse	5.35	1	0.021	1.12	1.02–1.24
	HAM-D	8.56	1	0.003	1.12	1.04–1.21
	# Depressive episodes	4.53	1	0.033	1.11	1.01–1.23
#2. Lifetime Suicidal Ideation	Emotional abuse	20.28	1	< 0.001	1.20	1.11–1.30
	Diagnosis	16.67	1	< 0.001	2.86	1.73–4.73
#3. Lifetime Suicide attempts	Emotional abuse	20.08	1	< 0.001	1.19	1.10–1.28
	FH Suicide	7.50	1	0.006	3.44	1.42–8.35

95CI%, 95% Confidence Interval, upper and lower limits; *OR*, Odds Ratio; *HAM-D*, Hamilton Depression Rating Scale score; *Diagnosis*, healthy controls versus mood disorder patients; *FH Suicide*, Family History of Suicide Attempt or Complete Suicide in first-degree relatives

Table 6 Results of multivariate GLM analyses with the total scores on the WHOQoL-BREF (WHOQoL) scale and Sheehan scale as dependent variables

Type tests	Dependent variable	Significant explanatory variables	F	df	*p*
Multivariate	WHOQOL-BREF	Emotional abuse	10.69	2/150	< 0.001
	+ Sheehan DS	# Depressive episodes	5.98	2/150	0.003
		Age	6.21	2/150	0.003
		Family income	11.86	2/150	< 0.001
		HAM-D	40.85	2/150	< 0.001
Between-subject effects	WHOQOL-BREF	Emotional abuse	20.85	1/151	< 0.001
		# Depressive episodes	12.00	1/151	0.001
		Age	13.36	1/151	0.001
		Income	23.49	1/151	< 0.001
		HAM-D	77.85	1/151	< 0.001
Between-subject effects	Sheehan DS	Emotional abuse	6.47	1/151	0.012
		Age	5.32	1/151	0.022
		HAM-D	28.96	1/151	<0.001
		Income	23.49	1/151	0.014
Dependent variables in univariate analyses	Explanatory variables	*t* and *p* values	F (model)	df (model)	*p* (model)
WHOQOL-BREF	zLOOH+SOD+NOx + MDA + AOPP	$t = -2.88$, $p = 0.005$	7.37	2/138	0.001
	Sex	$t = +3.30$, $p = 0.001$			

WHOQOL-BREF, World Health Organization Quality-of-Life Scale total score; *Sheehan DS*, Sheehan Disability Scale total score; *HAM-D*, Hamilton Depression Rating Scale score; *HAM-A*, Hamilton Anxiety Rating Scale; *LOOH*, lipid hydroperoxides; *SOD*, superoxide dismutase; *NOx*, nitric oxide metabolites; *MDA*, malondaldehyde; *AOPP*, advanced oxidation protein products; *zLOOH+SOD+NOx + MDA + AOPP*, index of nitro-oxidative stress which caused damage to lipids and proteins

from MDD using sexual abuse and emotional abuse (both positively) and the z composite score of general O&NS (inversely associated) as predictor variables.

We have also examined whether the drug state of the patients may affect the O&NS results. Therefore we have entered use of antidepressants ($n = 39$), antipsychotics ($n = 23$), lithium ($n = 27$) and mood stabilizers ($n = 25$) as explanatory variables in a multivariate GLM analysis. Tests for between-subject effects did not show significant effects of the 4 dug state variables on any of the 7 O&NS biomarkers (even at the $p = 0.05$ level).

Discussion

The first major finding of this study is that physical neglect, but not the other ELT types, is significantly associated with increased O&NS biomarkers, including indices of ROS, RNS, nitro-oxidative stress and lipid and protein oxidation. Thus, the first composite score, which is associated with physical neglect, is an index of increased SOD and lipid hydroperoxides thus indicating increased ROS production (Hayyan et al. 2016). The second composite score, which was predicted by physical neglect, reflects increased ROS and NO production and thus the potential to form peroxynitrite (Pacher et al. 2007). Other composite scores, which are associated with physical neglect, indicate nitro-oxidative stress coupled with lipid peroxidation and/or protein oxidation, the latter reflecting increased peroxynitrite- and myeloperoxidase-induced HOCl production (Marsche et al. 2009). In addition, sexual abuse, but not the other ELT subtypes, predicts lowered levels of antioxidants, namely zinc, albumin and -SH groups.

Our findings extend those of do Prado et al. (2016) who reported that childhood adversity is associated with an imbalance between antioxidant defenses and increased oxidative stress. Thus, these authors detected that in individuals without

Table 7 Model-predicted marginal mean values of the total Childhood Trauma Questionnaire score (CTQ) and subscores

Variables	HC [A]	BD [B]	MDD [C]	F/χ^2	df	*p*
	$n = 67$	$n = 68$	$n = 37$			
CTQ total sum*	34.7 (2.0) [B,C]	51.2 (2.2) [A,C]	43.8 (2.9) [A,B]	16.58	2/166	< 0.001
Sexual Abuse score*	5.3 (0.4) [B]	7.9 (0.4) [A,C]	5.2 (0.6) [B]	13.20	2/166	< 0.001
Physical Abuse score*	7.0 (0.5) [B]	9.6 (0.5) [C]	8.3 (0.7)	6.39	2/166	0.002
Emotional Abuse score*	7.1 (0.6) [B,C]	12.2 (0.6) [A]	10.5 (0.9) [A]	18.70	2/166	< 0.001
Emotional Neglect score*	8.7 (0.7) [B,C]	12.7 (0.7) [A]	11.6 (1.0) [A]	9.26	2/166	< 0.001
Physical Neglect score*	6.7 (0.4) [B,C]	8.8 (0.5) [A]	8.2 (0.6) [A]	6.13	2/166	0.003

All results are shown as estimated marginal means (SE)

*obtained by multivariate GLM analysis with diagnosis and sex as independent variables

** obtained by multivariate GLM analysis with diagnosis, sex, metabolic syndrome and tobacco use disorder as independent variables

Table 8 Results of automatic stepwise multinomial logistic regression analyses with diagnosis of Bipolar Disorders (BD) and Major Depression (MDD) as dependent variables and emotional and sexual abuse and the composite score of general O&NS as explanatory variables (while controlling for severity of illness, tobacco use disorder, age and sex

Groups	Significant explanatory variables	Wald	df	*p*	Odds Ratio	95% CI
BD → HC	Emotional abuse	11.00	1	0.001	1.25	1.10–1.43
MDD → HC	zLOOH+SOD+ NOx + MDA + AOPP	5.35	1	0.021	1.33	1.04–1.69
BD → MDD	Emotional abuse	4.09	1	0.043	1.13	1.01–1.27
	Sexual abuse	4.15	1	0.042	1.61	1.02–2.53
	zLOOH+SOD+ NOx + MDA + AOPP	8.21	1	0.004	0.69	0.54–0.89

95% CI, 95% Confidence Interval; *HC*, Healthy Controls; *HAM-D*, Hamilton Depression Rating Scale score; *LOOH*, peroxides; *SOD*, superoxide dismutase; *NOx*, nitric oxide metabolites; *MDA*, malondaldehyde; *AOPP*, advanced oxidation protein products; *zLOOH+SOD+NOx + MDA + AOPP*, index of nitro-oxidative stress which caused damage to lipids and proteins

psychiatric problems, the CTQ was associated with higher SOD, protein carbonylation and reduced glutathione peroxidation, although no significant changes in -SH groups could be found. Nevertheless, our findings show that physical neglect and sexual abuse may induce long-lasting effects in ROS and RNS production and protein/lipid oxidation coupled with lower antioxidant defenses. Also, in mouse models, maternal separation with early weaning (an ELT model) activates superoxide production and increased expression of NADPH oxidase subunits in aortae (Ho et al. 2016). Future research should further examine the effects of physical neglect versus other ELT subtypes on O&NS biomarkers.

Our findings also extend previous reports that, in humans, psychosocial stressors may induce O&NS pathways, including a pro-oxidant state thereby causing lipid peroxidation (Aleksandrovskii et al. 1988; Pertsov et al. 1995; Sosnovskiii and Kozlov 1992). Sivonova et al. (2004) found that examination stress is accompanied by lowered antioxidant activities, increased sensitivity to lipid peroxidation and oxidation of DNA (Sivonova et al. 2004). In women, elevated perceived stress and inability to cope with stress are associated with increased oxidative damage to DNA (Irie et al. 2001). In animal studies, different stress or depression models (including chronic mild stress, swimming and restraint stress, chronic social isolation, olfactory bulbectomy) are accompanied by a) increased brain lipid peroxidation (TBARS/MDA) and damage to proteins (de Souza et al. 2006; Lucca et al. 2009a, b; Lucca et al. 2009a, b; Shao et al. 2015; Zhang et al. 2009); and b) lowered antioxidant defenses in the CNS, including glutathione, glutathione peroxidase, SOD, catalase and total antioxidant capacity (de Souza et al. 2006; Eren et al. 2007a, b; Gutteridge and Halliwell 1994; Pal and Dandiya 1994; Song et al. 1994; Zhang et al. 2009).

Another major finding of this study is that the O&NS biomarkers were associated with clinical characteristics of MAFD, which were also predicted by ELTs (especially emotional abuse), including severity of illness, clinical diagnosis and WHOQoL-BREF, but not with the number of depressive and manic episodes, substance use or suicidal behaviors. The results that ELTs are associated with these characteristics are consistent with previous studies, showing that ELT subtypes in BD and MDD are associated with more severe depressive symptoms, suicidal behaviors, alcohol use, disabilities and HRQoL (Daruy-Filho et al. 2011; Garno et al. 2005; Nanni et al. 2012; Sfoggia et al. 2008).

Our results on significant relationships between emotional abuse and severity of illness extend those of previous investigations showing that there is a greater risk of increased severity of anxiety and depressive symptoms in those who experienced sexual and emotional abuse (Etain et al. 2010). In our study, we found that ELTs together with O&NS had cumulative effects on severity of depression and anxiety, suggesting that ELT may influence O&NS pathways with consequent long-term and negative effects on severity of depression and anxiety. The significant associations between specific ELT subtypes and suicidal behaviors extend those of previous studies showing that childhood trauma may be independently associated with subsequent suicidal behaviors (Hadland et al. 2012; Roy and Janal 2005; Sfoggia et al. 2008). A previous study showed that, in BD, at least one subtype of childhood trauma was associated with increased numbers of depressive episodes (Etain et al. 2008). In

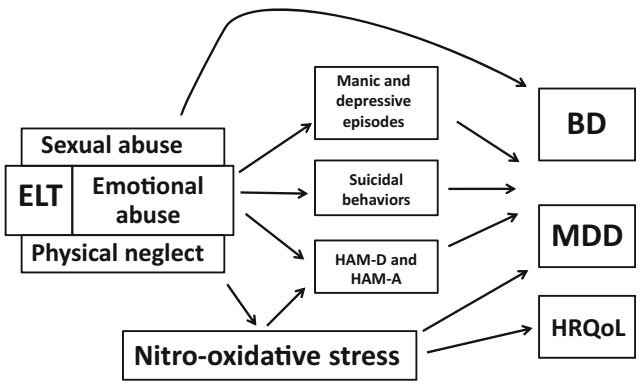

Fig. 1 A new hypothesis how early lifetime trauma (ELT) are associated with nitro-oxidative stress, major depression (MDD) and characteristics of mood disorders including bipolar disorder (BD).

our study, however, we could not find associations between number of depressive episodes or suicidal behaviors and the O&NS biomarkers, which were associated with ELTs. Nevertheless, previous research showed that individuals with a prior history of suicide attempts have higher serum LOOH and NOx levels and lowered total radical trapping antioxidant potential (TRAP) than those without suicidal attempts (Vargas et al. 2013). We found ELTs to be associated with poorer quality of life and higher degree of disability, findings which are in accordance with those of previous studies (Afifi et al. 2007; Chahine 2014; Simon et al. 2009). In our study, O&NS was significantly associated with HRQoL, although this relationship was no longer significant after entering ELT in the analysis.

We found that emotional abuse was the single best predictor of MAFD versus controls. This is consistent with previous studies showing that emotional abuse is the most frequently reported trauma by 37% of the patients, while 24% report physical abuse, 24% emotional neglect, 21% sexual abuse, and 12% physical neglect (Al-Fayez et al. 2012; Garno et al. 2005; Leverich and Post 2006). Moreover, we detected that BD was significantly discriminated from MDD by significant higher levels of sexual abuse. These findings add to the knowledge that ELTs are risk factors for MAFD and additionally show that different ELT subtypes may be differentially associated with BD and MDD.

All in all, our results show that ELT may cause activated O&NS pathways and damage to lipids and proteins thereby increasing the risk to develop MDD, but not BD. One possible factor that may explain the difference between MDD and BD is that some ELTs may have beneficial effects on resilience to stress in later life (Monaghan and Haussmann 2015) and that these protective effects could play a role in BD. Given these differences between MAFD subtypes, it is too early to generalize findings of animal models that ELT (e.g. early maternal separation) may cause increased oxidative stress in the brain and that this process enhances the risk to develop "psychiatric disorders" and "mental illnesses" (Mhillaj et al. 2015; Schiavone et al. 2015; Ventriglio et al. 2015).

The results of this study should be interpreted with regards to its strengths and limitations. Our study is a case control study and therefore no causal deductions can be made. We employed the CTQ, a self-report scale, to measure ELT and therefore this measurement may be modulated by memory and mood biases induced by the current psychopathological state. Nevertheless, analyses were adjusted for the effects of illness severity thereby minimizing the impact of the psychopathological state on our results. We included subjects between 18 and 65 years old and, therefore, we cannot generalize our findings to older or younger populations. One of the composite scores, namely zLOOH+SOD+NOx + AOPP, would be more complete if we had measured myeloperoxidase and hypochlorous acid. Future research should explore the association of ELT with O&NS and immune-inflammatory pathways in mediating the association of ELT subtypes with MAFD subtypes. The results suggest that many of the previous studies linking increases in such immune-inflammatory and oxidative stress biomarkers to MDD and BD, including in a number of meta-analyses, may have to be re-evaluated in association with more extensive investigation of early abusive events.

In summary, the ELT subtypes may have different effects on phenomenological and biological characteristics of MAFD. Therefore, it is necessary to examine the effects of separate ELT subtypes in addition to the total CTQ score. Fig. 1 provides a new hypothesis based on the major findings of this study. There was a strong association between early life trauma (ELT) and major affective disorders (MAFD) and clinical characteristics of MAFD, including course modifiers, severity of depression and anxiety, suicidal behaviors, lowered quality of live, increased disability, alcohol and hypnotics use and oxidative and nitrosative stress (O&NS) biomarkers. As such, a history of childhood maltreatment may aid in the identification of ecophenotypic variants of psychopathology as clinically and neurobiologically distinct subtypes of MAFD (Teicher and Samson 2013). Nevertheless, the ELT subtypes may have different effects: while physical neglect was associated with O&NS pathways, emotional abuse was related to MAFD characteristics including recurrence of episodes, suicidal behaviors and severity of depression (HAM-D) and anxiety (HAM-A) and lowered health-related quality of life (HRQoL) and greater disabilities. Increased O&NS, in turn, affects severity of illness, HRQol and major depression (MDD), suggesting that ELT may exert part of its effects on these characteristics via modulating O&NS pathways. While emotional abuse is the single best predictor of MAFD with an odds ratio of 3.62, sexual abuse predicts BD and not MDD. The findings suggest that the association between ELT and BD cannot be explained by activated O&NS pathways. Therefore, it is too early to conclude that ELT may enhance the risk to develop "psychiatric disorders" or "mental illnesses".

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