

1 Identification of biopsychological trait markers in functional 2 neurological disorders

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5 Abstract

6 Stress is a well-known risk factor to develop a functional neurological disorder, a frequent
7 neuropsychiatric medical condition in which patients experience a variety of disabling
8 neurological symptoms. Only little is known about biological stress regulation, and how it
9 interacts with predisposing biological and psychosocial risk factors. Dysregulation of the
10 hypothalamic-pituitary-adrenal axis in patients with functional neurological disorders has been
11 postulated but its relationship to preceding psychological trauma and brain anatomical changes
12 remains to be elucidated. We set out to study the hypothalamic-pituitary-adrenal axis analysing
13 the cortisol awakening response and diurnal baseline cortisol in 86 patients with mixed functional
14 neurological symptoms compared to 76 healthy controls. We then examined the association
15 between cortisol regulation and the severity and duration of traumatic life events. Finally, we
16 analysed volumetric brain alterations in brain regions particularly sensitive to psychosocial stress,
17 acting on the assumption of the neurotoxic effect of prolonged cortisol exposure. Overall, patients
18 had a significantly flatter cortisol awakening response ($P < 0.001$) and reported longer ($P = 0.01$)
19 and more severe ($P < 0.001$) emotional neglect as compared to healthy controls. Moreover,
20 volumes of the bilateral amygdala and hippocampus were found to be reduced in patients. Using
21 a partial least squares correlation, we found that in patients, emotional neglect plays a role in the
22 multivariate pattern between trauma history and hypothalamic-pituitary-adrenal axis dysfunction,
23 whilst cortisol did not relate to reduced brain volumes. This suggests that psychological stress
24 acts as a precipitating psychosocial risk factor, whereas a reduced brain volume rather represents
25 a biological predisposing trait marker for the disorder. Contrarily, an inverse relationship between
26 brain volume and cortisol was found in healthy controls, representing a potential neurotoxic
27 effect of cortisol. These findings support the theory of reduced subcortical volumes representing
28 a predisposing trait factor in functional neurological disorders, rather than a state effect of the

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1 illness. In summary, this study supports a stress-diathesis model for functional neurological
2 disorders and showed an association between different attributes of trauma history and
3 abnormalities in hypothalamus-pituitary-adrenal axis function. Moreover, we suggest that
4 reduced hippocampal- and amygdalar volumes represent a biological ‘trait marker’ for functional
5 neurological disorder patients, which might contribute to a reduced resilience to stress.

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25 **Running title:** Stress-diathesis in FND

26 **Keywords:** conversion disorders; emotional neglect; cortisol; hypothalamic-pituitary-adrenal
27 axis; voxel-based morphometry; partial least squares correlation

1 **Abbreviations:** AAL = Automatic anatomic labelling (atlas); AUC = Area-under-the-curve; BDI
2 = Beck's depression inventory; CAR = Cortisol awakening response; CTQ = Childhood trauma
3 questionnaire; DBC = Diurnal baseline cortisol; DBCC = Diurnal baseline cortisol concentration;
4 FDR = False-discovery rate; FEW = Family-wise error; FND = Functional Neurological
5 Disorders; HC = Healthy controls; HPA = hypothalamus-pituitary-adrenal (axis); PACC = Post-
6 awakening cortisol concentration; PLSC = Partial least squares correlation; ROI = Region-of-
7 interest; STAI = State-trait anxiety inventory; TEC = Traumatic experiences checklist; TIV =
8 Total intracranial volume; SVD = Single value decomposition

10 Introduction

11 Functional neurological disorders (FNDs) represent a frequent medical condition¹⁻³ in which
12 typical symptom presentation,^{4,5} diagnostic criteria,⁶ and multimodal treatment options^{1,3,7} are
13 well established, but only little is known about the underlying neuropathophysiological
14 mechanisms causing the diverse symptoms.⁸ Recent pathophysiological models focus on a
15 multifactorial origin of FND in the framework of a stress-diathesis model^{9,10} (from the ancient
16 Greek term “diathesis” = predisposition) integrating predisposing, precipitating and preceding
17 risk factors,^{3,11,12} and evaluate state versus trait markers of the disorder.^{13,14} Studying
18 biopsychosocial vulnerability factors is thus of utmost importance and could further explain the
19 development of FND symptoms in a subgroup of (biologically) vulnerable individuals with
20 certain psychosocial risk factors.^{11,15}

21 Negative life events have recurrently been reported in FND,^{12,16-18} traditionally highlighting the
22 role of sexual and physical abuse during childhood as preceding risk factor.^{12,18,19} Moreover,
23 severity and frequency of childhood abuse could be linked to symptom severity.²⁰ Similarly,
24 symptom onset and severity could be connected to recent adverse social-occupational life events
25 with a partial link to early childhood physical and sexual abuse,¹⁹ highlighting the importance of
26 type but also timing of trauma. In this regard, a recent meta-analysis confirmed an increased
27 frequency of childhood and adult adverse life events and abuse in FND patients compared to
28 healthy controls (HC) and psychiatric control patients.²¹ Additionally, emotional neglect was
29 identified to be much stronger associated with the symptom development, and thus weakened the
30 dominating role of sexual abuse in the suspected aetiology of FND.²¹

1 Neuroimaging studies intensively investigated the relationship between traumatic life events,
2 symptom presentation and brain functional- and structural abnormalities in FND. As such,
3 structural alterations in limbic and motor regions could be associated to childhood abuse and
4 symptom severity,^{22–24} whose effect was even more pronounced in women.²⁵ Similarly, an
5 aversive emotional-stimulus dependent alteration of cortico-limbic and limbic-motor brain
6 networks, involving regions such as the hippocampus,^{26–28} the amygdala,^{28,29} the supplementary
7 motor area (SMA²⁶) and the prefrontal cortex (PFC^{26,27}) have been identified in FND.
8 Noteworthy, hippocampal deactivation is suggested to disinhibit the hypothalamus-pituitary-
9 adrenal (HPA) axis, triggering a stress response,^{30,31} resulting in the release of stress hormones
10 such as cortisol.³² HPA-axis alterations – as for example observed under chronic stress – have
11 been associated with neuroanatomical changes, particularly in the hippocampus, the amygdala, or
12 the PFC^{33,34} which was attributed to a potential neurotoxic effect of glucocorticoids.^{33,35}

13 In FND, some studies suggested that patients have prominent hyperarousal, as stress markers of
14 the autonomic nervous system were found to be increased.^{36–38} Only few studies, however,
15 analysed cortisol in FND,^{36,39–43} – as a measure of the adaptive (slow) stress response³² – and the
16 results were inconsistent. As such, decreased morning⁴¹ and basal diurnal⁴³ cortisol were
17 reported, in contrast to no differences⁴² or increased basal diurnal cortisol compared to levels in
18 HC.^{39,40} This is explained essentially by methodological issues: studies were conducted using
19 small sample sizes, focusing on only one particular symptom type, or within different test
20 settings, potentially biasing the results.⁴⁴ This highlights the need to study the role of biological
21 stress in relation to its neurological-, and psychological correlates, which could advance the
22 understanding of pathophysiological mechanisms in FND and could generalize previous findings.

23 We set out to study alterations in the HPA-axis in a transdiagnostic approach across a large
24 cohort of FND patients with mixed symptoms in a standardized domestic setting, to minimize
25 biases of experimental setting. We adapted a transdiagnostic approach, as this efficiently targets
26 the commonalities across the different symptom types. The primary aim was to assess the cortisol
27 awakening response in FND compared to HC. The secondary aim was to evaluate the relationship
28 between HPA-axis dysfunction, volumetric brain alterations and preceding trauma, and to discuss
29 their potential role as predisposing (trait) versus precipitating factors.

30

1 **Materials and methods**

2 **Participants**

3 The study was conducted at the University Hospital Inselspital Bern, Switzerland. We included
4 data of 86 FND patients with motor (F44.4) and sensory symptoms (F44.6), with functional
5 seizures (F44.5), mixed symptom type (F44.7), and persistent postural-perceptual dizziness
6 (PPPD). Board-certified neurologists confirmed the diagnosis of FND according to DSM-5⁶ and
7 using positive signs.⁴⁵ We included 76 age- and sex-matched HC. Due to COVID-19 pandemic
8 regulations in the hospital, no HC older than 65 years were allowed to be invited, and thus FND
9 patients older than 65 years were not matched. Exclusion criteria were: 1) major neurological
10 comorbidities, 2) a current severe psychiatric condition (acute suicidality, active psychotic
11 symptoms), 3) alcohol or drug abuse, 4) pregnancy or breast-feeding, 5) contraindications for
12 MRI and 6) insufficient language skills. The study was approved by the Competent Ethics
13 Committee of the Canton Bern (SNCTP000002289) and conducted according to the Declaration
14 of Helsinki. All subjects provided written informed consent.

15 **Saliva samples**

16 Saliva samples were collected according to the consensus guidelines of Stalder,⁴⁴ concerning
17 design and strategies to control for adherence, and to account for covariates. All participants were
18 instructed in an initial face-to-face appointment and received written take-home instructions and
19 a self-reported diary. We assessed smoking habits, and for female participants information about
20 their menstrual cycle and intake of hormonal contraceptives, as they represent potentially
21 confounding factors of cortisol secretion.^{44,46,47} Saliva was collected within a domestic setting,
22 and a sampling date convenient for the participant was set. A reminder was sent by e-mail the
23 evening prior to the sampling date. Participants were asked to collect nine saliva samples
24 throughout the day by chewing for 2 minutes on a cotton swab (Salivette collection devices,
25 Sarstedt, Rommelsdorf, Germany). Samples were taken directly upon awakening, 15-, 30-, 45-
26 and 60 minutes post-awakening and further at 2-, 3-, 4- and 5 p.m. Participants were instructed to
27 complete the five samples before breakfast and to refrain from heavy meals, fruits or fruit juices,
28 coffee, carbonated soft drinks, chewing gum, smoking, teeth brushing or strenuous physical
29 activities during the sampling in the morning and 45-60 minutes prior to sampling in the
30 afternoon. Participants were instructed to note their wake-up time, any deviations from the

1 sampling time and potential confounds in their self-reported diary. Participants were free to
2 wake-up naturally or using an alarm clock and to follow their daily routine as usual. Saliva
3 samples were collected the next day, centrifuged (10 min at 3900 rpm and room temperature) and
4 frozen at -20 °C.

5 **Demographic, behavioural, and clinical characteristics**

6 Symptom severity was evaluated using the Clinical Global Impression (CGI) score (zero = no
7 symptoms to seven = among the most extremely ill patients) and the Simplified Version of the
8 Functional Movement Disorder Rating Scale (S-FMDRS⁴⁸). Duration of symptoms was
9 calculated from onset of symptoms to date of the study inclusion (in months). Use of
10 psychotropic medication (i.e., benzodiazepines, opioids, antidepressants, neuroleptics, and
11 antiepileptics), as well as corticosteroid medication were recorded. Mood was assessed using the
12 Spielberg State-Trait Anxiety Inventory (STAI⁴⁹) and the Beck's Depression Inventory (BDI⁵⁰).
13 Sleep quality of the night prior to saliva sampling was assessed using item four and five of the
14 Leeds Sleep Evaluation Questionnaire (LSEQ⁵¹).

15 **Traumatic life events**

16 Traumatic life experiences were measured using the Traumatic Experiences Checklist (TEC⁵²).
17 The TEC is a 29-item self-reported questionnaire which assesses the presence of diverse physical,
18 emotional, and sexual traumata including age, relationship to the perpetrator, and the self-
19 reported impact of the respective trauma. The TEC was scored using the syntax available at
20 <http://www.enjehuis.nl/tec>. Based on the syntax we computed 1) the overall number of
21 experienced traumata (sum of all items), 2) six individual trauma severity subscores (determined
22 by subjective impact and age of trauma for emotional neglect, emotional abuse, physical abuse,
23 sexual harassment, sexual abuse, and bodily threat), and 3) developmental composite scores
24 calculating experienced trauma according to the age ranges of 0 to 6 years, 7 to 12 years, 13 to 18
25 years and > 19 years. Additionally, we computed duration and relationship to the perpetrator for
26 each trauma subscore. The duration of trauma was calculated using the maximum duration within
27 those questions belonging to each trauma subscore. The relationship to the perpetrator was coded
28 into categorical variables being one: inner-family circle (parents, siblings, partner), two: outer-
29 family circle (relatives), three: friends and acquaintances, four: strangers. Additionally, to focus
30 on trauma occurring only during childhood, we used the Childhood Trauma Questionnaire

1 (CTQ⁵³); a 25-item self-reported questionnaire which assesses childhood trauma across five
2 domains including emotional- and physical abuse and neglect, and sexual abuse.

3 **Saliva samples analysis**

4 Salivary cortisol was analysed by a commercial saliva-specific competitive enzyme immunoassay
5 (cELISA, Salimetrics, Newmarket, United Kingdom). The manufacturer states a functional
6 sensitivity of 0.28 ng/mL, and cross-reactivity for 14 endogenous and synthetic steroids is
7 reported to be <1% each. The assay had been used according to the manufacturer's protocol.
8 Intra- and inter-assay coefficients of variation were 4.5% and 4.8%, respectively.

9 **Neuroimaging data acquisition and pre-processing**

10 To investigate neuroanatomical differences between patients and controls, we used a voxel-based
11 morphometry approach. Anatomical images were acquired for all subjects except of three FND
12 patients and three HC. MRI sequence and pre-processing is detailed in the Supplementary
13 Material.

14

15 **Statistical analysis**

16 **Behavioural data**

17 Statistical analyses were performed using *R* software (version 4.1.2.) and MATLAB (R2017b,
18 MathWorks Inc., Natick, USA). Questionnaire data were tested for normality using Shapiro-
19 Wilk's test. Normally distributed data were analysed using two-sample t-test, highly skewed data
20 using Wilcoxon rank sum test. Questionnaires with subscores were corrected for multiple
21 comparisons using false discovery rate (FDR). Categorical data were analysed using Chi-squared
22 test (sex) and Fisher's exact test (menstrual cycle and relationship to perpetrator (TEC)). To
23 determine significance, alpha-level was set at $P < 0.05$.

24 **Biological data**

25 We analysed two metrics to assess cortisol levels: the cortisol awakening response (CAR) and the
26 diurnal baseline cortisol (DBC).

1 The CAR describes the rapid increase in cortisol secretion across the first 30 to 45 minutes upon
2 awakening and thus, represents the dynamic changes of cortisol secretion occurring upon
3 awakening.^{44,54} It has been shown that the intraindividual stability is relatively high and subtle
4 changes in HPA-axis function regarding environmental noise can be detected with high
5 accuracy.⁴⁷ To assess group cortisol differences in the CAR, a repeated measures ANOVA was
6 used on the fitted data of the five morning samples (wake-up until 60 min post-awakening) using
7 a linear mixed model with fixed effects of factor group and timepoint, and using age, sex,
8 smoking, wake-up time, BDI, STAI, hormonal contraception, corticosteroid medication,
9 psychotropic medication, menstrual cycle, menopause, and sleep quality as covariates of no
10 interest.⁴⁶

11 The DBC represents the dynamic changes of cortisol throughout the afternoon (from 2 p.m. to 5
12 p.m.). To analyse the DBC, the same analysis was performed as in the CAR using the four
13 samples in the afternoon. For the analyses of the CAR and the DBC, we excluded data from eight
14 FND patients and nine HC as they did not properly adhere to the saliva sampling protocol with
15 either missing samples ($N = 3$) and/or delays ($N = 16$) (strict sampling accuracy margin of $\Delta t > 5$
16 min for post-awakening samples and $\Delta t > 15$ min for afternoon samples⁴⁴).

17 As we were interested in examining the multivariate pattern of correlation between cortisol and
18 other variables (see below), single estimates of the CAR and the DBC were calculated using area-
19 under-the-curve (AUC) based measures, as recommended in methodological consensus
20 guidelines.^{44,55} As such, the post-awakening cortisol concentration (PACC) and the diurnal
21 baseline cortisol concentration (DBCC) were computed. The PACC describes the summed
22 cortisol concentration across the first five samples in the morning. The DBCC represents the
23 cumulated cortisol concentration of the four afternoon samples. As a measure for the PACC and
24 DBCC, the AUC with respect to ground (AUC_G) was calculated. Additionally, as a (static)
25 measure for the CAR, the AUC with respect to increase (AUC_I) was calculated on the five
26 morning samples (CAR_i).⁴⁴ AUC-based measures were calculated according to Pruessner.⁵⁴ Three
27 subjects were excluded for calculating the AUC-based measures due to missing samples. Subjects
28 reporting delays were included, as the AUC formula can account for sampling delays (see
29 Supplementary Material and Supplementary Fig. 1 for more details). All analyses were repeated
30 in females only Supplementary Fig. 9.

1 **Imaging data**

2 To analyse between group differences of cortical volumes, we firstly applied a general linear
3 model on the smoothed whole-brain anatomical images within SPM12. Second, given the *a priori*
4 hypothesis of the hippocampus and the amygdala being particularly vulnerable to anatomical
5 changes in the context of chronic stress,^{33,34} we analysed volumetric differences in those two
6 regions. As such, we performed two region-of-interest (ROI) analyses using the corresponding
7 ROI masks, derived from the automatic anatomic labelling atlas 3 (AAL3⁵⁶). Whole-brain, as
8 well as ROI analyses were corrected for multiple comparisons using a family-wise error (FWE)
9 rate at $P < 0.05$, and total intracranial volume (TIV), age, sex, depression, and anxiety were
10 added to the analysis as covariates of no-interest. Lastly, we extracted subject-wise estimates of
11 the mean ROI volumes for external analyses. All analyses were repeated in females only
12 Supplementary Fig. 10, Supplementary Table 6.

13 **Multivariate pattern of correlation**

14 In a last step, we applied partial least squares correlation (PLSC^{57,58}) to evaluate multivariate
15 patterns of correlation between behavioural data (trauma scores), cortisol AUC_G and AUC_I
16 measures (CAR_i, PACC, DBCC), and volumetric data (mean ROI volume) in FND patients and
17 healthy controls. For the PLSC analysis, only those subjects were included of which salivary
18 cortisol (FND = 84, HC = 75) and imaging data (FND = 83, HC = 73) were complete. Data was
19 standardized and a correlation matrix was calculated between the two sets of variables. To find
20 individual weights of the corresponding data tables (cortisol data, volumetric data, trauma
21 scores), a single value decomposition (SVD) was applied on the correlation matrix. The SVD
22 leads to different correlation components consisting of a set of design weights and outcome
23 weights (salience), indicating the strength of contribution of each weight to the multivariate
24 pattern. The weights were used to calculate two sets of latent variables as such that the covariance
25 was maximized. Significance was evaluated by permutation testing (5000 permutations). Stability
26 of the weights was assessed using bootstrapping (200 bootstrapping samples). PLSC allows for
27 examining the relationship between multiple variables with different attributes. We used the
28 publicly available PLS toolbox for MATLAB ([https://github.com/FND-
29 ResearchGroup/myPLS_SL.git](https://github.com/FND-ResearchGroup/myPLS_SL.git)), the use of which has already been described in other studies.^{59,60}

1 We conducted three individual PLSC analyses; First, we used the cortisol values as design
2 variables, and TEC severity scores, developmental scores, duration of trauma, and relationship to
3 the perpetrator as outcome variables to evaluate multivariate pattern of correlation of trauma
4 history and HPA-axis dysfunction. Second, we used the volumetric data of the whole-brain, as
5 well as hippocampus and the amygdala alone (normalized for TIVs) as design variables, and age,
6 sex, and cortisol values as outcome variables to evaluate the multivariate pattern of correlation
7 between cortisol and changes in brain volume. Lastly, we evaluated in patients only the
8 relationship of the aforementioned factors with clinical data (i.e., symptom severity, and duration
9 of symptoms), Supplementary Figures 6 – 8.

10 **Data availability**

11 The data are not publicly available due to restrictions demanded by the administering institution
12 to guarantee the privacy of the participants. The data can be shared upon request.

13

14 **Results**

15 **Clinical, behavioural, and demographic characteristics**

16 Data from 86 FND patients and 76 age- and sex matched HC were included in this study.
17 Demographic, behavioural, and clinical data are presented in Table 1. The most common
18 symptom types were sensorimotor deficit (38.7%), gait disorder (21.5%), and/or tremor (14.6%).
19 Level of diagnostic certainty for functional seizure patients were: seven probable, three clinically
20 established, and four documented, according to diagnostic criteria of LaFrance.⁶¹ Five patients
21 were currently under corticosteroid medication, four of them only in a topical form (nasal spray)
22 used irregularly on demand, and one patient was under oral prednisone medication. Patients using
23 sprays resigned from using them on the day of saliva collection. FND patients and HC
24 significantly differed in their smoking habits (more smokers in FND), their BDI, and STAI scores
25 (more depression and anxiety in FND).

26

1 **Trauma**

2 **Traumatic life events**

- 3 (1) Overall number of experienced traumata (TEC): FND patients experienced significantly
 4 more total traumatic events compared to HC (reported as mean \pm SD: FND 6.78 ± 4.37 ,
 5 HC 4.21 ± 4.22 , $Z = 4541$, $P < 0.001$), Fig. 1A.
- 6 (2) Trauma severity scores (TEC): FND patients reported significantly more emotional
 7 neglect (FND 5.26 ± 6.32 vs. HC 2.4 ± 4.68 , $Z = 4247$, $P = 0.002$), Fig. 1B.
- 8 (3) Developmental composite scores (TEC): FND patients reported significantly more
 9 traumata occurring in the age range from 0 to 6 (FND 3.43 ± 4.87 vs. HC 2.08 ± 3.93 , $Z =$
 10 3810 , $P = 0.43$) from 7 to 12, (FND 4.71 ± 4.81 vs. HC 3.07 ± 4.17 , $Z = 3962$, $P = 0.043$)
 11 and > 19 years old (FND 2.9 ± 4.03 vs. HC 1.26 ± 2.24 , $Z = 3840$, $P = 0.01$), Fig. 1C.
- 12 (4) Duration of trauma (TEC): FND patients reported a longer duration of emotional neglect
 13 as compared to HC, i.e., 4.5 years longer (FND 6.95 ± 1.2 years vs. HC 2.36 ± 0.6 years,
 14 $Z = 3984$, $P = 0.01$), Fig. 1D. No significant differences were found with respect to
 15 duration of trauma for the other subscores.
- 16 (5) Relationship to the perpetrator (TEC): In FND patients, emotional neglect occurred more
 17 often through members of the inner-family circle (two-sided, $P = 0.006$). No significant
 18 differences were found in the other subscores.

19 **Childhood trauma**

20 FND patients reported significantly more childhood emotional abuse (CTQ scale reported as
 21 mean \pm SD: FND 10.1 ± 5.1 , HC 8.2 ± 4.2 , $Z = 4028$, $P = 0.02$), emotional neglect (FND $11.1 \pm$
 22 5.1 , HC 8.8 ± 4.2 , $Z = 4194$, $P = 0.009$), physical abuse (FND 7.3 ± 4.0 , HC 5.9 ± 2.0 , $Z = 3875$,
 23 $P = 0.03$), and physical neglect (FND 7.7 ± 3.1 , HC 6.79 ± 2.83 , $Z = 3935$, $P = 0.03$),
 24 Supplementary Fig. 2.

25 **Salivary cortisol**

26 A significant main effect of group was found for the CAR ($F(1,680) = 28.81$, $P < 0.0001$) with
 27 lower levels in FND than HC. Post-hoc multiple comparisons between group and timepoints,
 28 showed that FND patients and HC significantly different in their cortisol levels at timepoints 30'

1 upon awakening, and almost reached significance at timepoint 15', 45', and 60' upon
2 awakening ($P = 0.052$), Fig. 2. No significant differences were found in the DBC.

3 **Volumetric brain alterations in FND patients**

4 On a whole-brain level, significant group differences were found between FND patients and HC
5 in five clusters at thresholds of $P_{FWE} = 0.05$, Fig. 3A and Table 2. These clusters included the
6 following regions with decreased volumes in FND compared to controls: Left superior temporal
7 gyrus, left gyrus rectus, bilateral amygdala, hippocampal- and parahippocampal gyri, as well as
8 dorsolateral prefrontal gyri.

9 In line with the results on a whole-brain level, we confirmed our *a priori* hypothesis of a reduced
10 hippocampal- and amygdalar volume in FND patients using an inclusive brain mask at thresholds
11 of $P_{FWE} = 0.05$, Fig. 3B, Supplementary Table 1,2. Upon extraction of ROI volumes for external
12 analyses, we found that the hippocampus, as well as amygdala volume were significantly smaller
13 in FND patients compared to HC ($F(1,614) = 102$, $P < 0.001$). Post-hoc Tukey's HSD test
14 revealed a significant difference between FND patients and HC in 1) the left hippocampus ($P <$
15 0.001), 2) the right hippocampus ($P < 0.001$) (Fig. 3A, upper panel), 3) the left amygdala ($P =$
16 0.016), and 4) the right amygdala ($P = 0.025$) (Fig. 3B, lower panel).

17 **Relationship between trauma and cortisol**

18 To evaluate relevance of experienced trauma on the single estimates of the cortisol measures
19 (CAR_i, PACC and DBCC) in FND patients and HC, we first conducted a behavioural PLSC
20 including TEC severity scores, developmental scores, duration of trauma, and relationship to the
21 perpetrator as outcome variables. One PLSC component was found to be statistically significant
22 based on the permutation testing ($P = 0.033$). The outcome and cortisol saliences of the
23 previously mentioned component are shown in Fig. 4. Yellow highlighted weights indicate that
24 they were found to be robust (with the green dots representing the cortisol salience weights) and
25 can be interpreted similarly to correlation coefficients as the data was standardized. Based on the
26 PLSC results, a significant positive correlation was found in patients between the morning
27 cortisol values (CAR_i, PACC) and the relationship to the perpetrator of physical abuse – meaning
28 that the more familiar (inner-family circle) the perpetrator was, the higher the cortisol values. A
29 significant negative correlation was found in patients between the morning cortisol values (CAR_i,
30 PACC) and 1) the duration, and 2) severity of emotional neglect – meaning that the longer and

1 more severe the emotional neglect, the lower the cortisol values. In HC, a positive correlation
2 was found between cortisol values and 1) trauma occurring during late adolescence and 2)
3 adulthood – meaning that the more trauma happened during late adolescence and adulthood, the
4 higher the cortisol levels.

5 **Relationship between cortisol and brain volume**

6 To examine the potential relationship between single estimates of the cortisol measures (CAR_i ,
7 PACC and DBCC) and changes in whole-brain, respectively hippocampal- and amygdalar
8 volumes in FND patients and HC, we conducted a PLSC including cortisol values as outcome
9 variables and imaging data as design variables. No significant PLSC components were found
10 when using the mean cluster volumes from the whole-brain analysis as design variables. When
11 using the results from our ROI analysis (i.e., hippocampal and amygdalar volume), one PLSC
12 component was found to be statistically significant (permutation testing, $P = 0.021$). The outcome
13 and imaging saliences are shown in Fig. 5.

14 Based on this PLSC analysis, a significant negative correlation was found only in HC between
15 the brain volumes of the bilateral hippocampus and the bilateral amygdala and 1) the age –
16 meaning that the older the subject, the smaller the brain volume – and 2) CAR_i – meaning the
17 smaller the brain volume, the higher the cortisol levels. No multivariate pattern of correlation
18 between brain volumes and cortisol data was found in FND patients.

19 **Relationship with symptom severity in FND**

20 No significant multivariate correlation was identified in patients, when using symptom severity as
21 outcome variable, and trauma scores, single estimates of cortisol measures, or brain volumes,
22 independently, as design variables, Supplementary Fig. 6-8.

23 **Discussion**

24 Our findings provide biopsychological evidence for the stress-diathesis model in FND (state
25 versus trait). We identified a reduced cortisol awakening response in a transdiagnostic approach
26 in FND patients. Moreover, we linked the potential HPA-axis dysregulation to prolonged
27 preceding emotional neglect, pointing towards a long-term process resulting in a maladaptive
28 HPA-axis sensitization. Lastly, we identified anatomical changes in the superior frontal gyrus, the
29 superior temporal gyrus, the hippocampus, and the amygdala. In FND, however, reduced cortical

1 volumes were not associated with cortisol – what would have pointed towards a potential
2 neurotoxic effect, nor with symptom severity – what could have explained a state related change.
3 These findings put in question whether the here found results represent a direct state effect of
4 FND, a biological trait factor, or a combination of both as will be further discussed below. A
5 schematic representation of the here discussed results are displayed in Fig. 6.

6 Only few studies investigated cortisol levels and the stress response in FND patients. Consistent
7 with our results, Chung⁴¹ detected a blunted CAR in 32 children with FND (mixed symptoms)
8 assessed using two saliva samples in the morning (at wake-up and 30 min later), which were
9 partially collected in a domestic setting. Likewise, a study in 15 female functional seizure
10 patients identified lower serum cortisol levels in the morning as compared to HC with a history of
11 abuse.⁴³ Contradictorily, a study in which 33 motor FND patients and 33 HC were hospitalized
12 overnight, no difference in morning cortisol levels were found.⁴² This discordance might be
13 explained by the testing conditions: a non-familiar environment (e.g., hospitalization⁴²) might
14 introduce alterations in cortisol levels that covary with psychosocial factors and might not
15 represent the clinical status of patients.^{44,62} Consistent with our results, no group differences in
16 the basal diurnal cortisol levels were found in 19 functional seizure patients,³⁶ nor in motor FND
17 patients ($N = 16$ ³⁹, $N = 33$ ⁴²). Contrarily, a group effect with higher basal diurnal cortisol levels in
18 the afternoon was found in motor FND,³⁹ mainly driven by stress, as well as in functional seizure
19 patients,⁴⁰ mainly driven by experienced sexual abuse. Lastly, cortisol secretion was studied in
20 response to stress. Using the Trier Social Stress Test, two studies reported a comparable stress
21 response in FND patients as to HC indicating a normal adaptation to social stress situations.^{36,39}
22 In summary, previous results on cortisol in FND show a large heterogeneity, mainly explained by
23 methodological issues: each of the studies was conducted in a different setting (stress test^{36,39,40}
24 versus no stress test and domestic setting versus hospitalized⁴¹⁻⁴³), assessing different measures
25 of cortisol (i.e., morning versus basal versus stress response), which in most cases prevents a
26 direct comparison between results. Our transdiagnostic approach has the advantage of having a
27 large sample with mixed symptoms, which ensures a better generalizability in comparison to
28 previous studies focused on small subgroups of FND patients.

29 Additionally – and firstly in FND, we identified an inverse relationship between cortisol
30 measures and various dimensions of emotional neglect (assessed using the TEC), whereas no
31 association with symptom severity or duration of symptoms was detected. As such, a significant

1 multivariate pattern of correlation was found in patients but not in controls, between lower
2 morning cortisol levels and higher duration and severity scores of emotional neglect (measured
3 by the TEC). Specifically for emotional neglect, exposure was in average 4.5 years longer in
4 FND as compared to HC. In general, adverse experiences occurred more frequent in early
5 childhood in FND than in HC, even though this effect was not specific to emotional neglect but
6 was found across all traumatic experiences. This result is consistent with the findings on the
7 CTQ, in which increased neglect and abuse was found in FND across all trauma subscores except
8 for sexual abuse. Particularly, the role of neglect as predisposing factor of FND has been
9 highlighted by the results of a meta-analysis of 34 case-control studies including 1405 patients
10 showing odd ratios (OR) of 5.6 for FND patients compared to control populations, which was
11 higher than for sexual and physical abuse (OR 3.3 and 3.9 respectively).²¹ Our results go further
12 than confirming an association between emotional neglect and FND in demonstrating that both
13 the severity and duration of emotional neglect are more pronounced in FND. The effect of
14 maltreatment on different expressions of psychopathology has been shown to depend on the
15 developmental period, severity, and frequency of trauma exposure.^{63,64} In FND, no clear
16 consensus on the role of trauma type, timing and number of traumatic events is known, with the
17 exception that early-onset FND was rather associated to childhood sexual abuse⁶⁵ when late-onset
18 was associated to physical trauma.⁶⁶ In sum, our results add to previous knowledge that trauma
19 predisposes to FND, highlighting the importance of emotional neglect. Additionally, we first
20 showed that in FND exposure to early and long-lasting emotional neglect might contribute to
21 disrupting the biological regulation of stress, as reflected by the association with blunted CAR.
22 This is further supported by the absence of an association between CAR and symptom severity,
23 as an association between CAR and symptom severity would rather indicate a (subacute) disease-
24 related ('state') change of the HPA-axis.

25 Thereby, dysregulation of morning cortisol secretion might represent a downregulation of the
26 HPA-axis following initial high levels of cortisol in response to long-term stress.⁶⁷ A proposed
27 mechanism of action is the suppression of the negative feedback inhibition of cortisol.^{33,34} Under
28 normal health conditions, an acute stressor would activate the HPA-axis and subsequent cortisol
29 secretion through the amygdala. The amygdala is strongly regulated by the PFC and the
30 hippocampus, which are responsible for the integration of information on threat stimuli. When
31 the stressor is removed, a negative feedback inhibition is induced through the hippocampus and
32 the HPA-axis itself, reducing the cortisol secretion. In a chronic state of hypervigilance to

1 stressors, the HPA-axis is tonically inhibited through the hippocampus, as a result of suppressed
2 negative feedback inhibition due to HPA-axis sensitization (maladaptive habituation) to the
3 stressor. Correspondingly, an overreactive HPA-axis has been observed in early phases of
4 chronic stress, whereas a downregulation corresponds to subsequent, sustained phases of chronic
5 stress.⁶⁸ Hence, the prolonged exposure to emotional neglect in FND patients might reflect a
6 long-term process resulting in the downregulation of the HPA-axis, as represented in the flattened
7 CAR. At the same time, it is suspected that glucocorticoid receptors become more sensitive to
8 enhanced cortisol levels during early phases of chronic stress, and consequently to the increased
9 neurotoxic effects of cortisol.^{69–71} Chronic stress indeed has been repeatedly associated with
10 neuroanatomic alterations in regions expressing a high glucocorticoid receptors density i.e.,
11 hippocampus, PFC, and amygdala (for review^{33,34}). In FND, a volume reduction of the
12 hippocampus has previously been found to inversely relate to trauma history.²⁵ No data on
13 cortisol was available in this study but it was hypothesized that the hippocampal atrophy might be
14 mediated by changes in stress biomarkers such as cortisol. However, large variation in
15 hippocampal volumes has also been described in healthy populations, irrespective of chronic
16 stress or trauma history, suggesting that reduced hippocampal volume may represent a trait
17 factor rather than a disease-related feature (state).⁷² In line with these findings, our results on
18 smaller hippocampal and amygdalar volumes compared to HC, and the absence of a correlation
19 with cortisol measures nor with symptom severity suggest that these anatomical variations rather
20 represent a trait factor for FND, in terms of a biological predisposition. Interestingly, while some
21 studies neither identified a relationship between cortical volumes and symptom severity,^{23,73,74}
22 recent studies inversely correlated symptom severity to lower volumes in regions other than the
23 hippocampus, such as the left insula,^{22,25,75} precentral gyrus,⁷⁵ as well as the temporo-parietal
24 junction.⁷⁶ Therefore, regional differences in cortical volume might be linked to trait-
25 vulnerability (e.g., hippocampus) while others might be linked to disorder-related
26 pathophysiological changes (state). However, additional research is needed to disentangle the role
27 of regional structural abnormalities in the pathophysiology of FND. On the contrary in HC, the
28 inverse relationship between subcortical volume and cortisol measures may represent a plasticity
29 phenomenon in response to recent stress. In summary, a disease model including HPA-axis
30 sensitization might contribute to the development of FND in terms of maladapting to long-term
31 emotional neglect. Moreover, the here found reduced hippocampal and amygdalar volumes in

1 FND point towards a ‘trait’ biomarker for FND, which potentially decreases the resilience to
2 stress.

3 Psychosocial stressors, HPA-axis sensitization and biological predisposition might represent
4 transdiagnostic risk factors⁷⁷ which conjointly contribute to general psychopathology and
5 symptom overlaps in neuropsychiatric disorders.⁷⁸ However, by way of example, about 15% of
6 childhood maltreatment survivors do not develop mental health problems,⁷⁹ and further variations
7 in psychopathology have been explained by individual resilience to stress.⁷⁸ Similarly, FND
8 represents a disorder of multifactorial origin.³ Biopsychological risk factors might interplay with
9 other, yet unknown factors which might explain why a subgroup of vulnerable individuals
10 develop FND and not any other psychopathology. Recently, research on resilience focuses not
11 only on the exploration of eco-phenotypes (i.e., environmental factors), but also genetics and
12 their interplay (endo-phenotypes, i.e., gene \times environment interactions). As such, early life
13 adversities may influence brain development and mental health outcome by means of (epi-)
14 genetic mechanisms. The first two years of development is the critical window for emotional
15 development and has been associated with increased risk for mental disorders and negative
16 impact on the brain structure and function.^{80,81} Emotional neglect during early childhood is often
17 accompanied by social disentanglement and rejection, which prevents children to learn how to
18 properly process emotions,^{82–84} as found in FND populations.^{26,85–87} In terms of gene \times
19 environment interactions, a genetic variation in the oxytocin receptor (*OXTR*) in subjects with a
20 history of childhood emotional neglect was associated with reduced amygdalar and hippocampal
21 brain volumes.⁸⁸ The role of oxytocin in emotion processing has been studied in infants (5-7
22 months old): infants with increased *OXTR* methylation rates showed enhanced response to
23 aversive faces in a functional neuroimaging paradigm.⁸⁹ Epigenetic changes in the oxytocin
24 pathway are as well of particular interest in FND, as increased *OXTR* methylation was
25 demonstrated in a cohort of 16 FND patients compared to 15 HC.⁹⁰ Other genetic/epigenetic
26 changes in FND have been very recently studied: Diez²⁸ linked history of childhood physical
27 abuse to cortico-limbic brain network dysfunction in regions which *in situ* showed an overlap
28 with high expression of genes involved in neuronal morphogenesis. Those findings firstly linked
29 childhood trauma and its potential effects on brain function to a trauma-related functional brain
30 reorganization in the context of a gene \times environment interaction in FND. In the same line of
31 research, tryptophan-hydroxylase 2 (*THP2*) polymorphism was associated with childhood
32 trauma, symptom onset and severity, as well as amygdalar functional connectivity in FND.⁹¹ In

1 summary, individual resilience factors might explain how early childhood emotional neglect
2 potentially induce (epigenetically mediated) neurodevelopmental delays in individuals who later
3 develop FND affecting brain structure and function of regions involved in emotion regulation
4 which is reflected in a dysfunctional HPA-axis. Further research must be conducted to identify
5 risk factors specific for FND.

6 Our study has several limitations. First, the measure of cortisol awakening response relies on self-
7 reported diaries and deviations from the protocol cannot be fully controlled. To verify accurate
8 execution of cortisol sampling, objective verification of awakening and sampling times are
9 required,⁹² e.g., using objective electronic monitoring systems, such as polysomnography or wrist
10 actigraphy.⁹³ We did not use such objective tools but minimized the risk of error of self-report
11 data by thoroughly instructing our participants, agreeing on an appropriate day for the sampling,
12 and explaining them the importance of properly adhering to the protocol and/or reporting
13 deviations from the protocol. Second, we collected saliva samples on only one day, thus cortisol
14 alterations might represent fluctuations due to situational aspects rather than a long-term trait.⁴⁴
15 Thirdly, salivary cortisol only indirectly measures HPA-axis activity, as it depends on levels of
16 other biological factors such as corticotropin releasing factor, adrenocorticotrophic hormone, or
17 estrogens.⁹⁴ Nonetheless, salivary cortisol is considered to be a good measure of allostatic load,
18 and a useful biomarker in stress research.^{47,94} Another limitation in studying the role of trauma
19 lies in methodological issues as self-report questionnaires can have recall bias.²¹ Detailed
20 interview technique,⁹⁵ are less prone to recall bias but are time-consuming and requires
21 appropriate training of study personnel, which limits its feasibility in larger cohorts of
22 participants. Lastly, our patient cohort has only been compared to HC, which prevents making
23 conclusions on the specificity of the findings to FND in comparison to other stress-related
24 disorders. We, however, corrected for depression and anxiety and excluded severe psychiatric
25 conditions, therefore, we do not expect that the results are biased due to mood disorder
26 comorbidities. The lack of systematic psychiatric evaluation – such as the psychiatric interview
27 (SCID) – does not allow to check if the data could be confounded by a psychiatric co-morbidity
28 (e.g., post-traumatic stress disorder), which is common in FND.^{2,25}

29 **Conclusion**

30 Our findings point towards a multifactorial stress-diathesis model for FND. A flattened CAR
31 might represent a long-term process in direct relation to severity and duration of emotional

1 neglect (state). Reduced subcortical volumes in FND did not relate to HPA-axis dysfunction and
2 rather delineate a predisposing biological vulnerability, than a disease-related feature, thus
3 potentially representing a trait marker for FND. In line with a stress-diathesis model,
4 phenotypical variations in clinical presentation of symptoms must potentially be attributed to
5 different contributions of a variety of diverse eco-phenotypes (e.g., trauma history) and endo-
6 phenotypes (e.g., biological predisposition or trait markers). However, a causal relationship
7 between HPA-axis dysfunction, trauma, and brain functional- and structural stress adaptation
8 remains to be discovered. Longitudinal data would need to be assessed including the collection of
9 behavioural, neuroendocrine, genetic, and neuroimaging data already in early childhood.

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16 **Competing interests**

17 The authors report no competing interests.

18 **Supplementary material**

19 Supplementary material is available at *Brain* online.

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9 **Figure legends**

10

11 **Figure 1 Traumatic Life Events.** (A) For visualization purposes, means and confidence
12 intervals of overall number of experienced traumata (ranging from 0 to 29). (B) Means and
13 confidence intervals of six trauma severity scores (determined by subjective impact and age of
14 trauma, ranging from 0 to 13 for emotional neglect, emotional abuse, physical abuse, sexual
15 harassment, and sexual abuse or from 0 to 24 for bodily threat). (C) Means and confidence
16 intervals of developmental composite scores (across trauma subscores). (D) Means and
17 confidence intervals of duration of trauma. Significance codes: $P^{***} < 0.001$, $P^{**} < 0.01$, $P^{*} <$
18 0.05. Results are FDR-corrected.

19

20 **Figure 2 Cortisol Profile of FND patients and healthy.** Mean and confidence intervals of
21 daytime cortisol profile in FND patients and HC. Significance code: $P^{*} < 0.05$.

22

23 **Figure 3 Results of voxel-based morphometry analysis.** (A) Differential effect of voxel-wise
24 comparison (HC > FND) with smaller grey-matter volume in FND in the hippocampus,
25 parahippocampal gyri, amygdala, and dorsolateral frontal gyri. (B) Differential effect of mean
26 ROI volume using a hippocampal mask (upper panel) and amygdala mask (lower panel) with
27 smaller grey matter volume in FND. For both analyses, total intracranial volume (TIV), age, sex,
28 depression (BDI), and anxiety (STAI) were added as covariates, thresholded on whole-brain level
29 at $P_{FWE} < 0.05$. Significance codes: $P^{***} < 0.001$, $P^{**} < 0.01$, $P^{*} < 0.05$. A model corrected only

1 for TIV, age, and sex can be found in the Supplementary Material, Supplementary Fig. 3,
2 Supplementary Table 3.

3
4 **Figure 4 Partial least squares correlation (PLSC) results of the different cortisol measures**
5 **(CARI, PACC, DBCC) in FND patients and healthy controls.** The outcome (A) and cortisol
6 saliences (B) of the significant PLSC component ($P = 0.033$) are presented. 5th to 95th percentiles
7 of bootstrapping are indicated in the error bars and yellow highlighted bars indicate robustness.
8 The height of the bar corresponds to the salience weight to the multivariate correlation pattern
9 and can be interpreted similarly to correlation coefficients as the data was standardized. The
10 permutation null distribution and the bootstrap mean percentiles are reported in Supplementary
11 Fig. 4, Supplementary Table 4. Abbreviations: EN = Emotional neglect; EA = Emotional abuse;
12 PA = Physical abuse; SH = Sexual harassment; SA = Sexual abuse; BT = Bodily threat.

13
14 **Figure 5 Partial least squares correlation (PLSC) results of the imaging data (hippocampal**
15 **and amygdalar volumes) in FND patients and healthy controls.** The outcome (A) and imaging
16 saliences (B) of the significant PLSC component ($P = 0.021$) are presented. 5th to 95th percentiles
17 of bootstrapping are indicated in the error bars and yellow highlighted bars indicate robustness.
18 The height of the bar corresponds to the salience weight to the multivariate correlation pattern
19 and can be interpreted similarly to correlation coefficients as the data was standardized. The
20 permutation null distribution and the bootstrap mean percentiles are reported in Supplementary
21 Fig. 5, Supplementary Table 5.

22
23 **Figure 6 The stress-diathesis model in functional neurological disorders.** The aetiology of
24 FND is multifactorial and depends on predisposing, precipitating, and perpetuating risk factors.
25 Long-term exposure to stress can exert neurotoxic effects on regions particularly sensitive to
26 cortisol. Moreover, it can alter the HPA-axis in terms of a maladaptive habituation. Distinct
27 predisposing factors, i.e., ‘trait’ markers might influence the individual resilience to stress and the
28 later development of psychopathology. Abbreviations: CRF = corticotropin-releasing factor,
29 ACTH = Adrenocorticotrophic hormone.

30

1 **Table 1 Demographic, behavioural, and clinical data**

	FND (N = 86)	HC (N = 76)	Statistics
Age, mean (SD), years, [range]	37.7 (14.2), [17–77]	33.1 (10.9), [18–62]	ns
Sex (females/males)	64/22	55/21	ns
Hormonal Contraception (yes/no)	27/37	18/37	ns
Menopause (yes/no)	14/50	10/45	ns
Menstrual Cycle ^a	15 anovulation 10 follicular 22 luteal 2 menstruation 7 ovulation	10 anovulation 3 follicular 33 luteal 1 menstruation 3 ovulation	Two-tailed $P = 0.05^*$
Smoker (yes/no)	33/53	8/68	$\chi^2(1) = 15.2, P < 0.0009^{***}$
Disease severity (CGI, median, quantile)	2 [1–4]	NA	
Disease severity (S-FMDRS, median, quantile)	6 [2–12.75]	NA	
Duration of illness (in months)	75 (166)		
Symptom type ^b	45 sensorimotor 25 gait disorder 17 tremor 12 myoclonus 14 seizures 8 dystonia 7 PPPD 5 speech disorder 2 functional deafness 1 functional vision loss	NA	
ICD-10 Classification ^c	63 F44.4 7 F44.5 30 F44.6 8 F44.7 6 PPPD	NA	
Psychotropic medication	14 benzodiazepines 29 antidepressants 6 neuroleptics 9 antiepileptics 6 opioids	0/76	
Corticosteroids (yes/no)	5/81	0/76	
BDI score, mean (SD)	14.4 (9.96)	4.59 (6.28)	$Z = -7.61, P < 0.0001^{***}$
STAI-S score, mean (SD)	37.2 (10.9)	32.1 (7.67)	$t(156.68) = 3.22, P = 0.002^{**}$
LSEQ, mean (SD)	0.422 (0.169)	0.455 (0.15)	ns

^aMenstrual cycle was indeterminable in 8 patients and 5 healthy controls (natural irregularity or continuous intake of hormonal contraception).

^bPatients can present with several symptom types.

^cDiagnosis of mixed FND (F44.7) was given when F44.4, F44.5, and F44.6 was present.

$P^{***} < 0.001, P^{**} < 0.01, P^* < 0.05$.

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1 **Table 2 Whole-brain voxel-based morphometric results with total intracranial volume (TIV), age, sex, depression (bdi), and**
 2 **anxiety (stai) as covariates of no interest**

Cluster-level			Peak-level			Peak coordinates in MNI Space {mm}			Cerebral regions
P_{FWE}	P_{FDR}	Cluster extent	P_{FWE}	P_{FDR}	Peak voxel Z-score	x	y	z	
0.001	0.084	255	0.002	0.506	5.248	- 54	- 27	14	Left superior temporal gyrus
0.000	0.004	633	0.004	0.506	5.122	- 15	3	- 24	Left parahippocampal
			0.006	0.667	4.996	- 23	- 1.5	- 18	Left amygdala
			0.017	0.875	4.783	- 29	- 17	- 14	Left hippocampus
0.006	0.553	82	0.004	0.506	5.117	0	62	- 26	Left gyrus rectus
0.008	0.553	69	0.014	0.875	4.831	15	3	- 24	Right parahippocampal
			0.035	0.917	4.607	17	- 6	- 15	Right amygdala
0.009	0.553	61	0.019	0.875	4.753	- 11	59	- 15	Left superior frontal gyrus
			0.026	0.897	4.680	- 6	59	- 7.5	Left dorsolateral prefrontal gyrus

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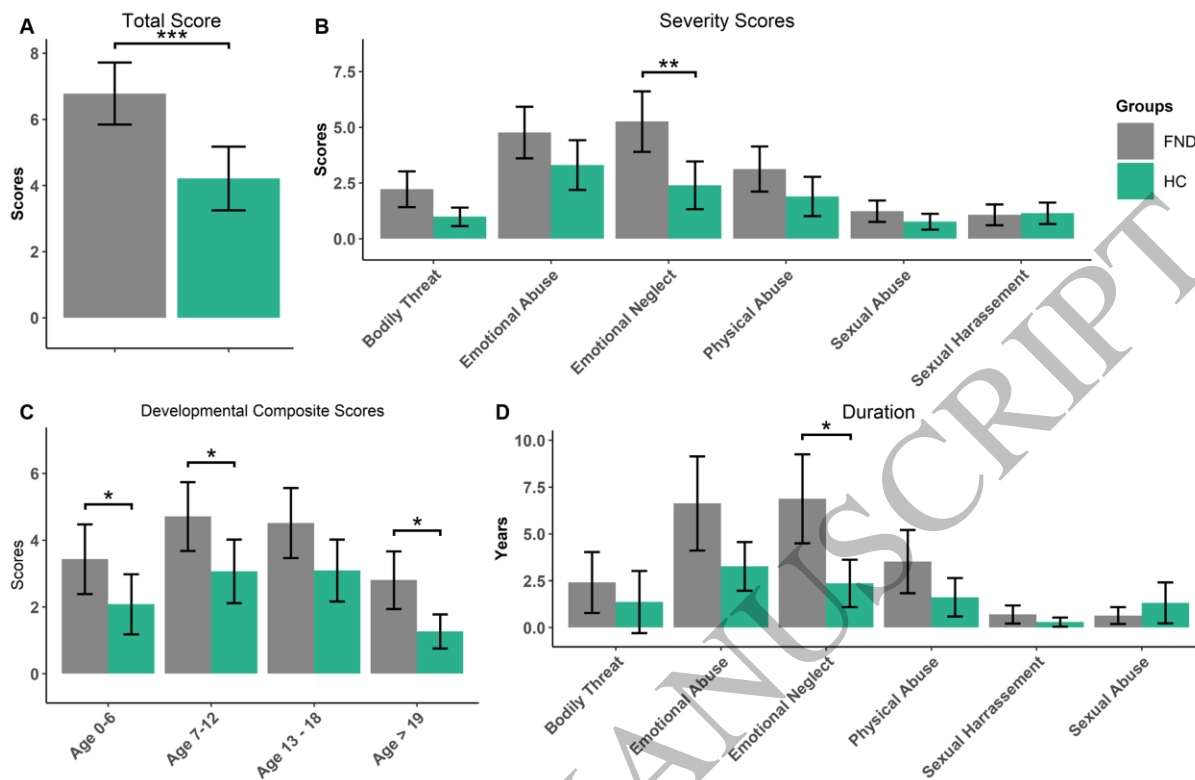


Figure 1
160x104 mm (.16 x DPI)

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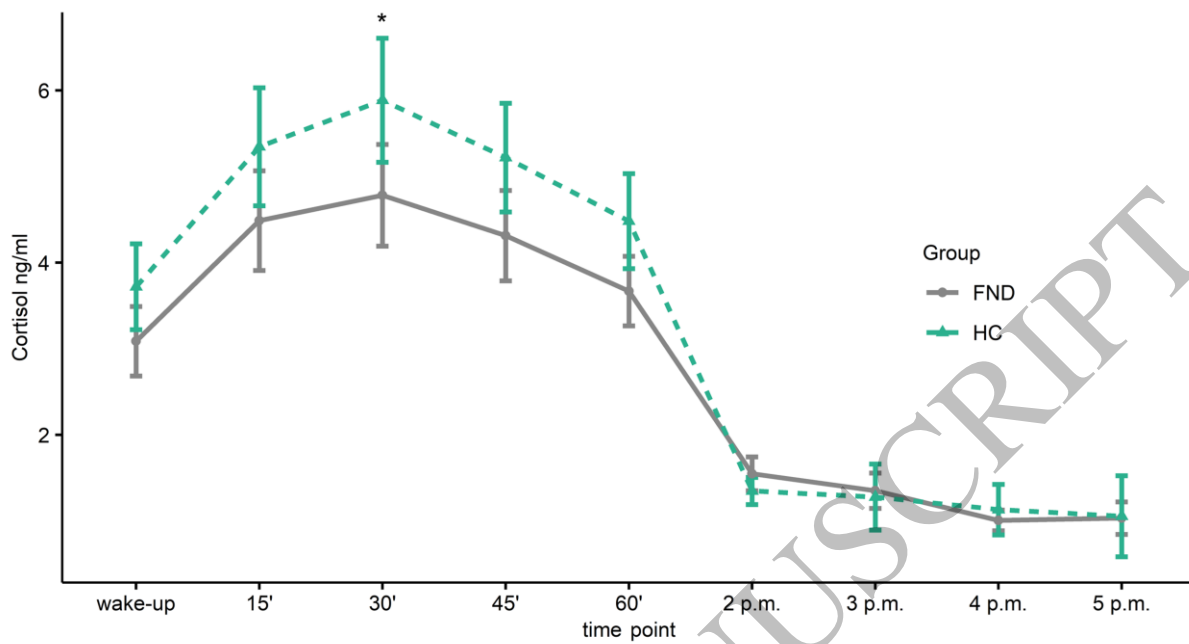


Figure 2
160x88 mm (.16 x DPI)

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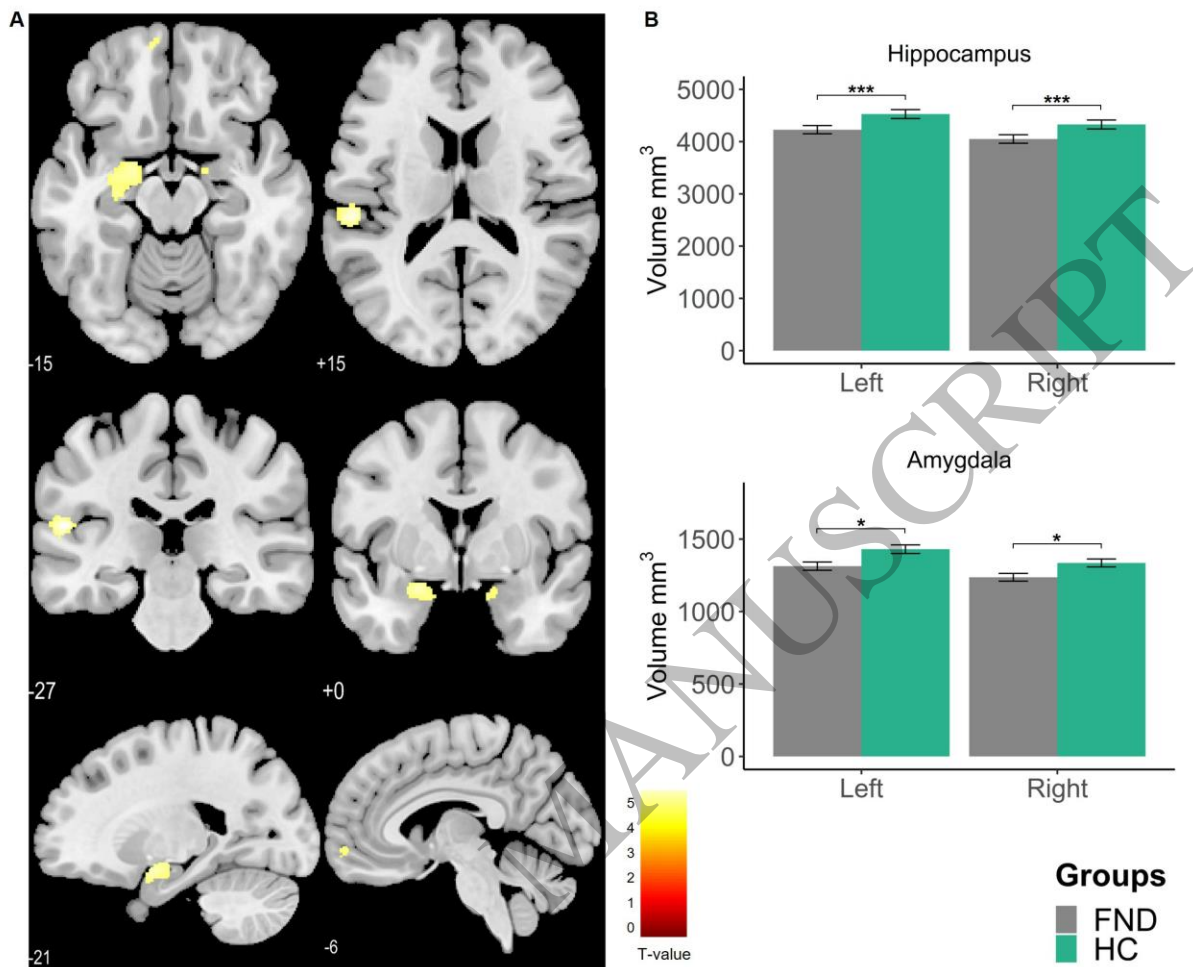


Figure 3
160x133 mm (.16 x DPI)

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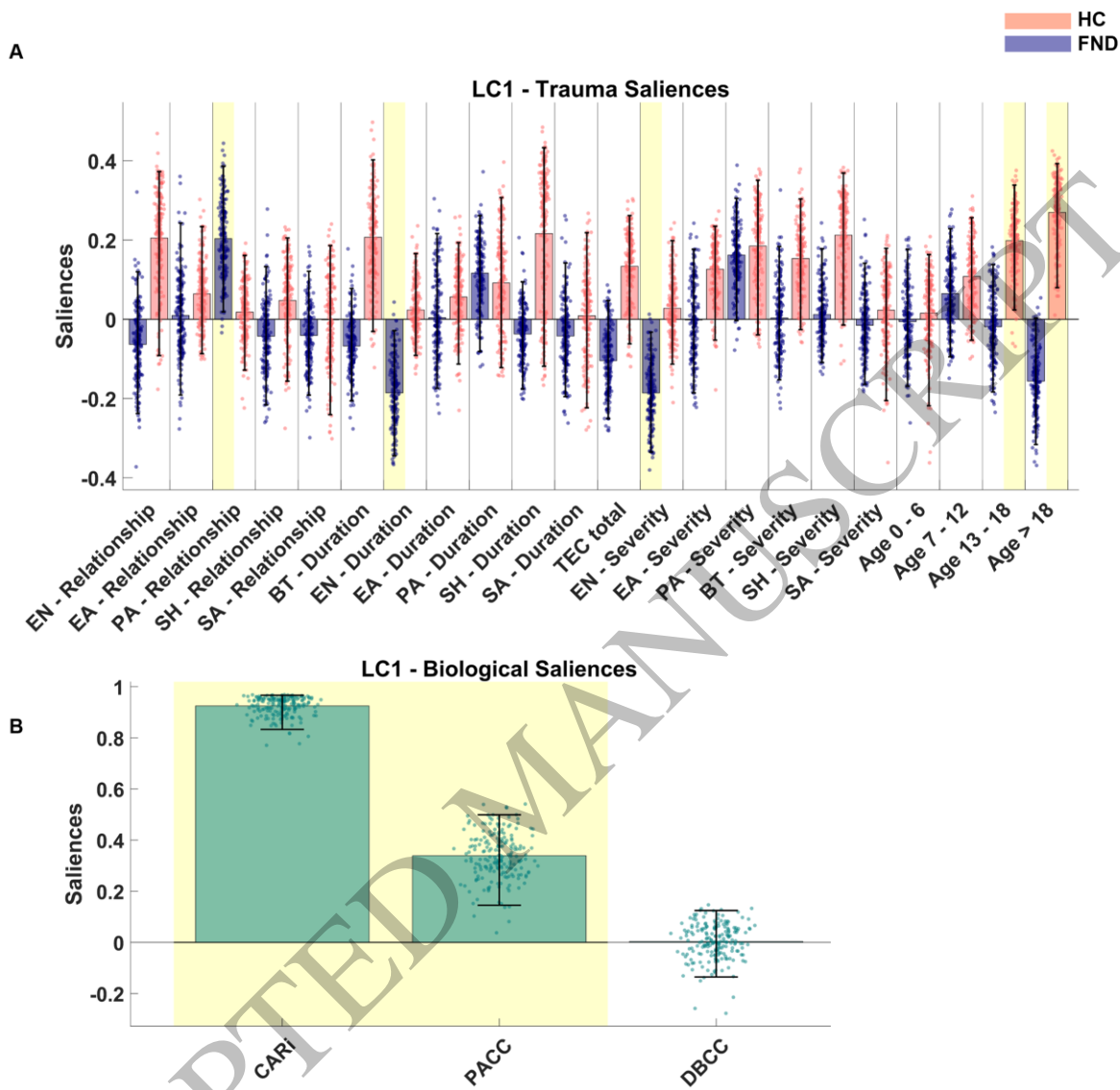


Figure 4
160x152 mm (.16 x DPI)

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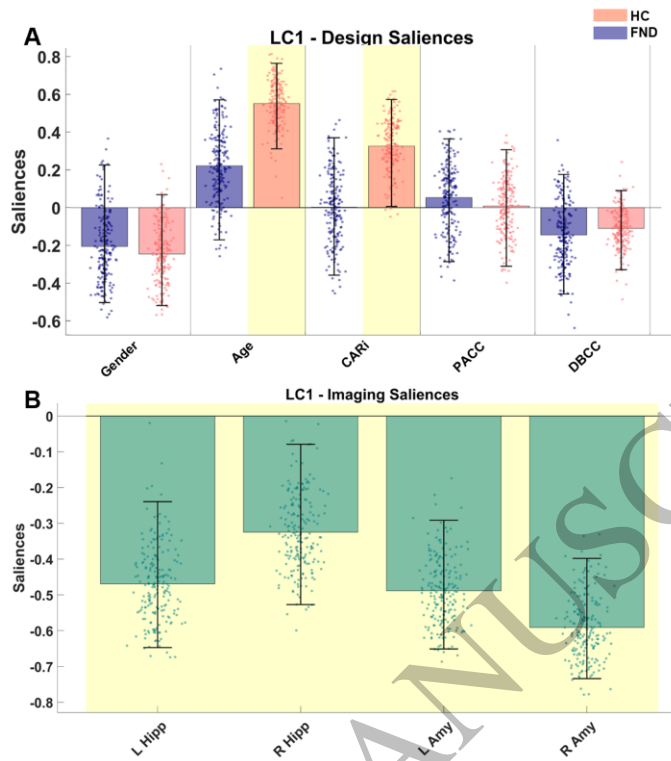


Figure 5
90x102 mm (.16 x DPI)

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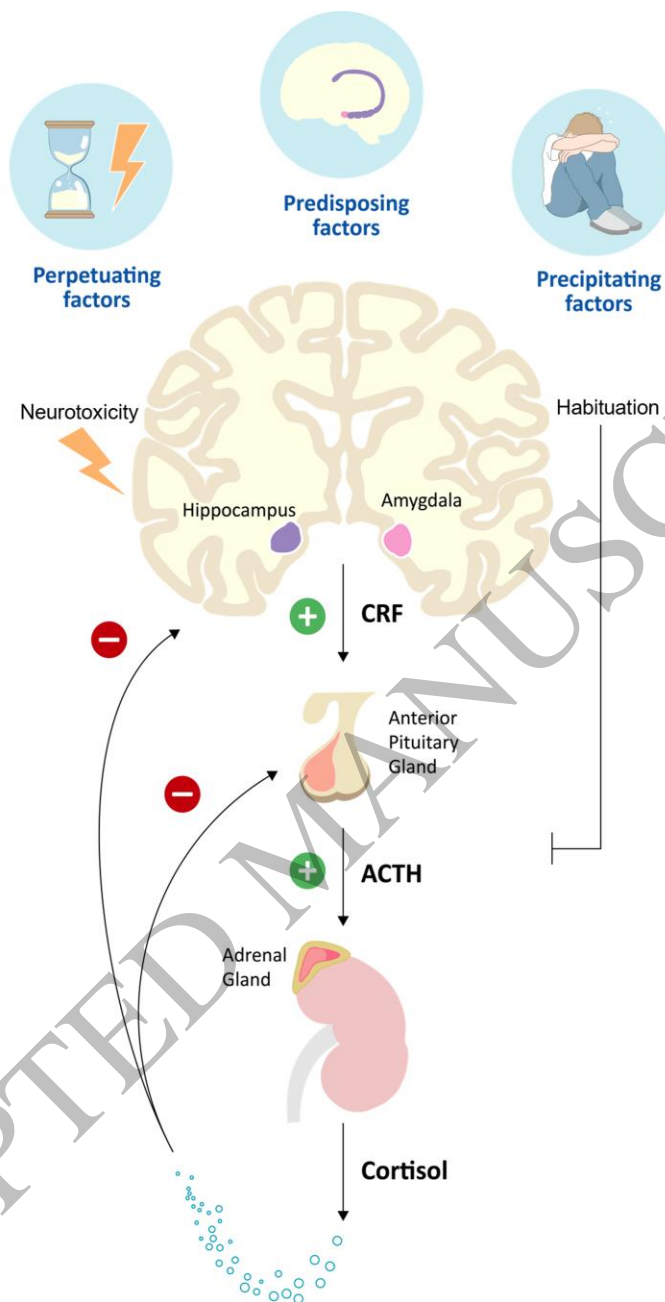


Figure 6
90x171 mm (.16 x DPI)

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