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Pretreatment cortisol predicts trauma-focused psychotherapy response in youth with (partial) posttraumatic stress disorder

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ABSTRACT

Background: Despite availability of effective trauma-focused psychotherapies, treatment non-response in youth with (partial) posttraumatic stress disorder remains substantial. Studies in adult PTSD have suggested that cortisol is associated with treatment outcome. Furthermore, cortisol prior to treatment could be used to predict treatment success. However, there is a lack of comparable studies in youth with (partial) PTSD. The objective of the current study was therefore to test whether cortisol prior to treatment would differ between treatment responders and non-responders and would positively predict the extent of clinical improvement in youth with (partial) PTSD.

Methods: Youth aged 8–18 with PTSD (79.2%) or partial PTSD (20.8%) were treated with 8 sessions of either trauma-focused cognitive behavioral therapy (TF-CBT) or eye movement desensitization and reprocessing (EMDR). Prior to treatment initiation, salivary cortisol was measured in treatment responders (n = 23) and treatment non-responders (n = 30) at 10 and 1 min before and 10, 20 and 30 min after personalized trauma script driven imagery (SDI). The cortisol stress response (> 1.5 nmol/L increase from baseline) and basal cortisol secretion was assessed during the SDI procedure. We hypothesized that treatment responders would display higher cortisol levels caused by increased cortisol reactivity prior to trauma-focused psychotherapy relative to psychotherapy non-responders and higher cortisol levels would positively predict the extent of clinical improvement.

Results: Script driven imagery did not induce a cortisol stress response in all but two participants. Prior to treatment responders showed significantly higher basal cortisol secretion during SDI compared to treatment non-responders. This effect remained significant after controlling for gender. Higher pre-treatment basal cortisol secretion further positively predicted the extent of clinical improvement during trauma-focused psychotherapy.

Conclusion: Because SDI failed to provoke a cortisol stress response in our sample, the question if cortisol reactivity differs between treatment responders and non-responders remains inconclusive. However, our results do suggest that higher pretreatment basal cortisol secretion forms a potential indicator of prospective trauma-focused psychotherapy response in youth with (partial) PTSD. Although, the amount of uniquely explained variance in clinical improvement by pre-treatment cortisol secretion is limited and still renders insufficient basis for clinical applicability, these findings do suggest directions for future studies to delineate the mechanisms of treatment success in youth with (partial) PTSD

1. Introduction

Posttraumatic stress disorder (PTSD) is a mental health disorder that develops in approximately 16% of youth exposed to traumatic events, which may include domestic violence, sexual abuse and accidents (Alisic et al., 2014). The daily lives of youth with PTSD are hampered

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by frequent re-experiencing of the traumatic event, persistent avoidance, hyperarousal and negative alterations in cognition and mood (AmericanPsychiatricAssociation, 2013). These symptoms can interfere with social functioning and school performance and have a deeply negative effect on the quality of life of the affected youth and those around them (Carrion et al., 2002). Moreover, they are a crucial factor in shaping the vulnerability to depression and suicidality later in life (Molnar et al., 2001). Furthermore, youth exposed to traumatic events with clinically important symptoms of PTSD but with subthreshold criteria for PTSD (partial PTSD) also demonstrate substantial functional impairment and distress which do not differ significantly from youth meeting full PTSD criteria (Carrion et al., 2002). Current practice parameters therefore recommend that in youth, patients with partial PTSD should also be provided with evidence-supported treatment options (National Institute for Health and Care Excellence, 2018). All of the above highlight the vital importance of effective treatment for youth with (partial) PTSD.

Although, multiple randomized controlled trials have shown efficacy of trauma-focused psychotherapies in youth with (partial) PTSD, treatment non-response remains a major clinical challenge (Gillies et al., 2012; Leenarts et al., 2013). Treatment non-response leads to persistent symptoms, prolonged suffering and longer treatment trajectories. Objective and reliable predictive markers of treatment response are needed to guide treatment selection and improve treatment efficacy. Investigation of biological factors associated with effective treatment may help to identify biomarkers of treatment response (Zantvoord et al., 2013a).

As the major neuroendocrine stress regulating system, the hypothalamic-pituitary-adrenal (HPA) axis has had considerable attention in PTSD research (Morris et al., 2012). Cortisol, the end product of HPA-axis activation, plays a central role in an individual's response to threat. Cortisol promotes survival by mobilizing energy resources contributing to a state of increased vigilance and arousal. Through a negative feedback system, cortisol terminates the stress response by inhibiting the HPA-axis through binding to the glucocorticoid receptors. Furthermore, cortisol is crucially involved in (emotional) memory consolidation, retrieval of information from long-term memory, memory reconsolidation and extinction learning. These learning and memory processes have been shown pivotal in PTSD and may be involved in trauma-focused psychotherapies (de Quervain et al., 2017d).

Findings regarding HPA function in adults with PTSD have been mixed. Meta-analyses of Morris and colleagues showed enhanced glucocorticoid receptor negative feedback, lower 24-h cortisol secretion and flattened (morning) cortisol diurnal rhythms in PTSD patients compared to (non-traumatized) controls (Morris et al., 2012). However, two other meta-analyses did not show differences in HPA function between PTSD patients and (traumatized) controls (Klaassens et al., 2012; Meewisse et al., 2007). Finding from these and other meta-analyses do highlight the importance of age, gender, comorbid depression, time since trauma, type of control group (trauma exposed or non-trauma exposed), differences in assessment method and timing of trauma exposure as moderators of HPA function in PTSD patients (Doom et al., 2013; Friedman et al., 2007; Klaassens et al., 2012; Kuhlman et al., 2015; Meewisse et al., 2007; Morris et al., 2012; Schumacher et al., 2019).

Studies on HPA function in youth suffering from posttraumatic stress symptoms are altogether scarce. They pose additional methodical challenges because of heterogeneity associated with ongoing developmental change in HPA function throughout childhood and adolescence (Lupien et al., 2009). Furthermore, clinical heterogeneity is increased, as some studies only include youth with a full PTSD diagnosis while others also include patients with (partial) PTSD. Findings on HPA function in youth with (partial) PTSD are therefore not necessarily in line with findings in adults (Kirsch et al., 2011). For instance, youth with (partial) PTSD have shown increased 24-h cortisol secretion and normal glucocorticoid receptor negative feedback (De Bellis et al., 1999; Duval et al., 2004; Lipschitz et al., 2003). Together, these findings suggest that results on HPA function obtained in adults with PTSD cannot be readily extrapolated to youth with (partial) PTSD. This emphasizes the need for studies on HPA function specifically performed in youth.

Interestingly, relatively few prospective studies have investigated the association between HPA function and the course of illness or treatment efficacy (Schumacher et al., 2018; Zantvoord et al., 2013a). Studies in adults with PTSD suggest lower cortisol levels in the acute aftermath of trauma exposure to be associated with an increased risk of developing PTSD over time (Walsh et al., 2013). Furthermore, lower hair cortisol concentrations and lower cortisol stress reactivity before deployment were predictive of a greater PTSD symptom increase in soldiers who had experienced new-onset traumatic events (Steudte-Schmiedgen et al., 2015). In youth, some studies have also found decreased afternoon cortisol in the aftermath of trauma to be associated with an increased risk of developing post-traumatic stress symptoms (Pfeffer et al., 2007), while others have indicated increased afternoon cortisol to be predictive of symptom development (Pervanidou et al., 2007). The association between cortisol and treatment outcome was examined in adults with PTSD, for a recent and comprehensive overview see Schumacher et al. (2018). Studies on basal cortisol secretion prior to treatment as a predictor of treatment outcome were mostly negative (Nijdam et al., 2015; Rauch et al., 2015; Yehuda et al., 2014). However, increased cortisol reactivity prior to treatment was shown to be predictive of PTSD symptom reduction, both in the form of the cortisol awakening response (*CAR*) (Pacella et al., 2014; Rapcencu et al., 2017), suppression of the *CAR* by dexamethasone challenge and activation by script-driven imagery (Nijdam et al., 2015; Rauch et al., 2015). Together these findings suggest that in adult PTSD, higher cortisol reactivity and not basal cortisol secretion is a predictive biomarker of treatment response. However, the number of studies is still small and heterogeneity in design considerable, precluding a strong synthesis of the current evidence.

Surprisingly however, no prior study has specifically examined the relationship between HPA function and treatment outcome in youth with (partial) PTSD. Thus, it is unknown whether HPA function in general and cortisol in particular prior to treatment is predictive of treatment response. Therefore, we examined the association between salivary cortisol prior to treatment and trauma-focused psychotherapy outcome in youth with (partial) PTSD, while accounting for relevant clinical and demographic confounders. First, we hypothesized that treatment responders would display higher cortisol levels caused by increased cortisol reactivity prior to trauma-focused psychotherapy relative to psychotherapy non-responders. Furthermore, we hypothesized that higher pretreatment cortisol levels would positively predict the extent of clinical improvement in youth with (partial) PTSD.

2. Methods

2.1. Participants

Participants were recruited between April 1, 2011 and June 1 2017 at the outpatient child psycho-trauma center of the department of child and adolescent psychiatry, de Bascule as part of a larger randomized controlled trial on efficacy of trauma-focused psychotherapies in youth with (partial) PTSD (Diehle et al., 2015). Youth were referred for assessment and treatment by child welfare services, physicians or their general practitioner. Youth were eligible when fulfilling the following inclusion criteria: age of 8 through 18 years, mastery of the Dutch language and a PTSD or partial PTSD diagnosis. PTSD was diagnosed by a clinician according to the DSM-IV criteria using both child reports on the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA) semi-structured interview and caregiver reports on the PTSD scale of the Anxiety Disorders Interview Schedule – Parent Version (ADIS-P). Partial PTSD was defined as either fulfilling two of the three

PTSD symptom clusters or one symptom present in each of the three symptom clusters (Stein et al., 1997). Exclusion criteria were acute suicidality, IQ < 70, pregnancy, meeting the criteria of one of the following diagnosis (assessed using the relevant screening questions of the ADIS child and parent versions): psychotic disorders, substance use disorder or pervasive developmental disorders, presence of an endocrine disorder or other significant medical illness potentially influencing HPA function, the use of oral glucocorticoid medication or other medication potentially influencing HPA function within the 2 weeks before study entry (Stalder et al., 2016). In accordance with procedures approved by the Institutional Review Board of the Amsterdam University Medical Center and the declaration of Helsinki, written informed consent was obtained from all parents or legal guardians and youth aged 12 years and over. For youth aged 11 and under assent from the youth was obtained. All participants received a monetary incentive for participation (€5).

2.2. Clinical assessment

After study-entry and after eight sessions of trauma-focused treatment, all participants were repeatedly assessed with a semi-structured clinical interview and self-report questionnaires. Semi-structured interviews were administered by trained psychologists.

PTSD diagnosis and PTSD severity were confirmed using the Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA) semi-structured interview (Nader et al., 1996). To complement PTSD diagnosis based on youth's reports, we administered the PTSD scale of the Anxiety Disorders Interview Schedule – Parent Version (ADIS-P) (Verlinden et al., 2014). Parents or caregivers rated every symptom of PTSD as either absent or present. The CAPS-CA assesses all possible symptoms of PTSD according to DSM-IV-TR and has become the gold standard for the assessment of pediatric PTSD. For every symptom, frequency of occurrence was rated from 0 to 4 (0 = never in the past month, 4 = four or more times a week in the past month). Intensity was also rated from 0 to 4 (0 = not a problem, 4 = extreme). A PTSD case was identified if participants met the requisite DSM-IV symptoms at least at a frequency of 1 and at an intensity of 2 (Weathers et al., 1999). Partial PTSD was identified with the same "frequency at least 1 and intensity at least 2" scoring rule by either fulfilling two of the three PTSD symptom clusters or one symptom present in each of the three symptom clusters (Stein et al., 1997). In addition, a suffering score of at least 4 on a 0-to-8 scale (0 = no impairment, 8 = a lot of impairment) was needed for a participant to fulfill a full or partial PTSD diagnosis. The overall PTSD severity score on the CAPS-CA was measured by adding the total frequency and intensity score and could range between minimal (< 20) and extreme (80–136). The Dutch version of the CAPS-CA has shown good psychometric properties in a sample overlapping the current sample (Cronbach's alpha's: 0.62-0,83; ICC for interrater reliability: 0.97-0.99) (Diehle et al., 2013, 2015). Both CAPS-CA and ADIS-P were administered by trained psychologists.

Depressive and anxiety symptoms were assessed using the subscales of the Dutch Revised Child Anxiety and Depression Scale (RCADS), a 47 item questionnaire that measures the reported frequency of various symptoms of social phobia (SP), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), panic disorder (PD), separation anxiety disorder (SAD) and depression (MDD) (Chorpita et al., 2000). Both youth (RCADS) and their caregiver (RCADS-P) filled out the questionnaires. Items were scored on a four-point Likert scale ranging from 0 (never) to 3 (always). Cronbach's alpha's for the Dutch RCADS (-P) were 0.93 for the pediatric version and 0.90 for the parent version.

2.3. Script driven imagery (SDI) and cortisol collection

All study participants performed a standardized protocol for script driven imagery (SDI) (Shalev et al., 1992) within two weeks before the start of trauma-focused psychotherapy. Youth were instructed to abstain from intensive physical exercise the day before and during the day of SDI. Also, youth were instructed to abstain from eating, drinking (except water) and smoking three hours before SDI and during the remaining sampling period. Compliance to the instructions was checked by the examiner before the start of the SDI procedure, in case of non-compliance the procedure was postponed. During the previous CAPS-CA interview all participants provided a detailed contextual description of their most disturbing traumatic event, including physical sensations that were experienced during the event. This information was used to compose and record a 30 s (range 29–31 sec) personalized trauma audio

Table 1
Subject characteristics.

	Responders (n = 23)	Non-responders (n = 30)	p-value[a]
Sociodemographic characteristics			
Female (%)	43.5	66.7	**.091**
Age (years; mean, SE)	12.3 (0.64)	12.6 (0.54)	.686
West European Ethnicity (%)	45.8	42.8	.509
Current educational level (%)			.614
Elementary school	56.2	43.3	
Middle/High school lower level	8.7	3.3	
Middle/High school middle level	21.7	40.0	
Middle/High school higher level	8.7	6.7	
Vocational school	4.3	6.7	
Weight (kg; mean, SE)	49.2 (5.19)	50.2 (2.27)	.863
Current psychotropic medication (%)	8.7	10	.911
Smoking (%)	5%	4%	.697
Alcohol > 1 consumption/day (%)	0%	0%	N/A
Time of cortisol assessment (hrs:min; mean, SE)	13:22 (0:28)	13:36 (0:27)	.712
Trauma characteristics			
Index trauma (%)			.178
Sexual abuse	34.7	20.0	
Domestic violence	21.7	13.3	
Community violence	13.0	33.3	
Accidents/Medical	17.4	6.7	
Other	13.0	26.7	
Repeated trauma exposure (%)	43.5	56.6	.341
Age at index trauma (years; mean, SE)	8.4 (0.97)	9.2 (0.73)	.525
Time since index trauma (years; mean, SE)	3.9 (0.81)	3.4 (0.62)	.669
Clinical characteristics			
CAPS-CA study entry (mean, SE)[b]			
Total	46.3 (4.26)	52.7 (4.73)	.322
Re-experiencing	13.9 (1.92)	18.1 (2.17)	.154
Avoidance	17.7 (1.83)	18.8 (2.13)	.707
Hyperarousal	14.9 (1.84)	17.2 (1.84)	.272
Full PTSD diagnosis (%)	78.3	80.0	.877
RCADS study entry (mean, SE)[b]			
MDD	10.1 (1.31)	12.0 (1.21)	.301
GAD	6.9 (1.02)	6.8 (0.75)	.936
OCD	5.4 (0.67)	6.7 (0.69)	.205
PD	6.7 (1.30)	8.4 (1.06)	.305
SAD	5.5 (0.90)	6.2 (0.89)	.589
SP	10.3 (1.44)	11.9 (1.52)	.452

Abbreviations: CAPS-CA, Clinician-Administered PTSD Scale for Children and Adolescents; RCADS, Revised Child Anxiety and Depression Scale; MDD, major depressive disorder; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PD, panic disorder; SAD, separation anxiety disorder; SP, social phobia; SE, standard error.

[a] p-values < 0.1 shown in bold. Independent samples *t*-test for continuous and x^2 tests for categorical variables.

[b] Ranges: CAPS-CA total, 0–139; RCADS MDD, 0–30; RCADS GAD, 0–18; RCADS OCD, 0–18; RCADS PD, 0–27; RCADS SAD, 0–21; RCADS SP.0–27.

script prior to the SDI procedure. A general 30 s neutral audio script describing tooth brushing was also composed and recorded. Both scripts were recorded in present tense by a member of the research team with corresponding sex as a given participant. The SDI procedure was performed on weekdays, at the end of morning or early afternoon (Table 1), in a room with constant temperature and light exposure. During the SDI procedure the neutral script always preceded the trauma script condition, both scripts were preceded by a three min movie clip depicting neutral landscapes. Participants were instructed to vividly imagine the events described in the scripts with their eyes closed during and 30 s after the scripts. For the remainder of the cortisol sampling period participants remained seated in the examination room together with the examiner while reading or engaging in neutral conversation with the examiner.

Five saliva samples were collected using Salivettes (Sarstedt Inc. Newton, NC, USA) 10 min and 1 min prior to trauma script imagery as well as 10 min, 20 min, and 30 min after trauma script imagery. Salivettes were stored at −20 °C at the Amsterdam University Medical Center until transport to Universitaet Trier for processing and analysis. After transport samples were centrifuged at 2000 g for 10 min. Duplicate analysis was executed using 100ul saliva. Salivary free cortisol concentrations were determined using a competitive solid phase time-resolved fluorescence immunoassay with fluorometric endpoint detection (DELFIA) (Dressendorfer et al., 1992). The intra-assay coefficient of variation was between 4.0% and 6.7%, and the corresponding inter-assay coefficients of variation were between 7.1%–9.0%.

2.4. Treatment

After study-entry all patients were randomized to receive either trauma-focused cognitive behavioral therapy (TF-CBT) or eye movement desensitization and reprocessing (EMDR). In a previous manuscript we showed that TF-CBT and EMDR are effective in youth with (partial) PTSD with no significant differences in efficacy between TF-CBT and EMDR (Diehle et al., 2015). Both TF-CBT and EMDR consisted of eight sessions with 60-min duration, which were given on a weekly basis. Treatment was delivered by experienced therapists who were all trained in TF-CBT and EMDR before the initiation of the study. Supervision by experts on TF-CBT and EMDR were provided throughout the study. In short, the EMDR treatment protocol consisted of the following components: psychoeducation and preparation, assessment, desensitization, installation, body scan, positive closure and enhancing future safety (Shapiro, 2001). TF-CBT consisted of psychoeducation and parenting skills, relaxation, affective modulation, cognitive coping and processing, trauma narrative, in vivo mastery of trauma reminders, conjoint child-parent sessions, enhancing future safety and development (Deblinger et al., 2011).

Pre- to posttreatment symptom change was calculated by subtracting the baseline from the posttreatment CAPS-CA total score (ΔCAPS-CA) for each participant. There is no established definition of a response criterion or a consensus definition of response terms in the child trauma treatment field. Based on the psychometric properties of the CAPS(-CA) and previous treatment outcome studies using the CAPS-CA, a tentative response criterion of > 50% reduction of CAPS-CA total score was a priori adopted as reflecting a substantial and clinically meaningful improvement (Diehle et al., 2013; Weathers et al., 2001). We chose not to employ presence of a PTSD diagnosis at posttreatment (e.g. remission) as an outcome measure, as patients with partial PTSD did not meet full PTSD diagnostic criteria at baseline which would make it impossible for these patients to 'improve'.

2.5. Data cleaning and handling of missing data

Cortisol data were positively skewed and therefore log-transformed to approximate a normal distribution. Extreme outlying cortisol values were identified as log-transformed values that were located more than three standard deviations from the mean (Stalder et al., 2016). No outlying cortisol values were identified.

Data for missing cortisol concentrations was interpolated by using the mean value of the preceding and following sample concentrations (Yehuda et al., 2005). In the case that the first or last sample was missing, the second and fourth samples were used respectively. In total 15 out of 265 (5,7%) cortisol concentrations were missing and interpolated. The number of missing cortisol concentrations did not differ between responders and non-responders ($p > 0.10$).

2.6. Statistical analyses

Statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago IL, USA). In order to detect potential confounders, the distribution of characteristics at study entry across responders and non-responders was examined using two-tailed X^2-tests for categorical variables, independent sample *t*-tests for normally distributed continuous variables and Mann-Whitney test for non-normally distributed continuous variables. In case of significant group differences, variables were subsequently included as covariates.

The cortisol stress response was defined as an increase of at least 1.5 nmol/l compared to baseline levels. For each participant we determined if SDI induced a cortisol stress response (Miller et al., 2013). Area under the curve with respect to ground (AUCg) and increase (AUCi) were derived using the trapezoidal formulas (Pruessner et al., 2003). As the SDI failed to induce a cortisol stress response in all but two participants, we did not use the AUCi as measure of cortisol responsivity in further analyses. The AUCg was used as a measure of total cortisol output which captures basal cortisol secretion as opposed to stressor reactivity. We therefore excluded the two participants who did have a cortisol stress response during SDI from further analysis. AUCg was examined for normality of distribution within each group. Non normally distributed data were log-transformed.

To test our first hypothesis, a ANCOVA was conducted to determine group differences between responders and non-responders on log-transformed AUCg, gender was added as an additional covariate. To test the robustness of findings a sensitivity analysis was performed with a more lenient response criterion (> 30% instead of > 50% reduction in CAPS-CA total scores).

Furthermore, a sequential multiple regression analysis was performed in order to test the second hypothesis that cortisol can uniquely predict treatment response. First, we examined zero-order correlations of the treatment outcome variable (posttreatment CAPS-CA), with the log-transformed cortisol AUCg as well as with a priori selected putative confounders of treatment outcome (baseline CAPS-CA score, baseline RCADS-MDD scores, age, gender and type of index trauma) to test for (multi)collinearity using Pearson's r (Deblinger et al., 2006; Goldbeck et al., 2016). There was an intercorrelation between baseline CAPS-CA and RCADS-MDD scores ($r(48) = 0.71$ $p < .001$). To prevent multicollinearity RCADS-MDD score was excluded as a covariate in the subsequent regression analysis. Among the possible confounders pretreatment CAPS-CA total scores, age and gender were selected as most relevant. A sequential multiple linear regression model was constructed with posttreatment CAPS-CA as outcome measure, with gender, age and pretreatment CAPS-CA at the initial step and with log-transformed cortisol AUCg as predictor at the second step. Finally, because we included youth with a broad age range (8–18 years), we tested if age moderated the relationship between log-transformed cortisol AUCg and treatment outcome by adding the interaction term age x log-transformed cortisol AUCg in the final step (Aiken et al., 1991; Lupien et al., 2009).

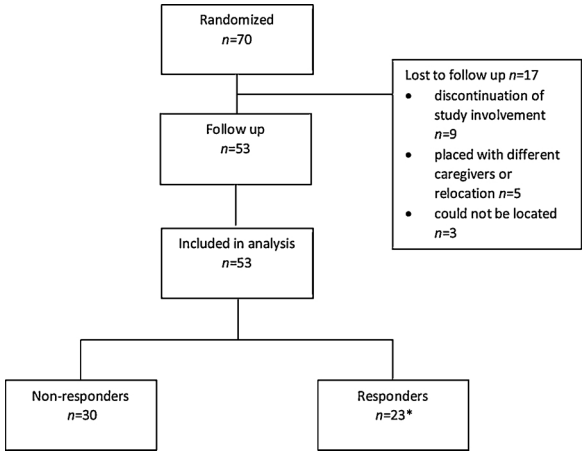

Fig. 1. Flow diagram of included patients.
* Response = > 50% reduction in CAPS-CA total score

3. Results

3.1. Participant characteristics

A summary of participant characteristics is shown in Table 1. Responders and non-responders did not differ in baseline sociodemographic, trauma or clinical characteristics apart from female to male ratio ($p < 0.10$), for which was controlled in further analyses. The time of cortisol assessment did not differ between responders and non-responders. At baseline 79.2% of participants met the full DSM-IV diagnostic criteria for PTSD, the remaining 20.8% met criteria for partial PTSD. The average baseline CAPS-CA score was $M = 49.9$ points, $SD = 23.7$, which is indicative of moderately severe PTSD. The most common index trauma was sexual abuse, followed by community violence and witnessing domestic violence.

3.2. Treatment outcome

Fig. 1 shows a flow diagram of participants. Of 70 patients randomized to EMDR or TF-CBT, 17 (24%) were lost to follow-up (reasons described in Fig. 1). Treatment completers and non-completers did not differ in baseline sociodemographic, trauma or clinical characteristics and cortisol measures apart from age, in which treatment completers' mean age was lower ($M = 12.5$, $SD = 2.97$) compared to non-completers ($M = 14.8$, $SD = 2.80$); $t(69) = 2.90$, $p = 0.005$. Setting a cutoff of 50% reduction of CAPS-CA total score as the response criterion, overall treatment response rate was 43.4%. 23 participants were responders and 30 were non-responders. Using a 30% CAPS-CA reduction response criterion, overall response rate increased to 62.3%. Posttreatment mean total CAPS-CA scores improved ($M = 19.8$ points, $SD = 21.9$ $t(52) = 9.8$, $p < .001$).

3.3. Salivary cortisol response during script driven imagery

Fig. 2 shows mean levels of cortisol measured 10 min and 1 min prior to trauma script imagery as well as 10 min, 20 min, and 30 min after trauma script imagery for both treatment responders and non-responders. All but two participants (one treatment responder and one treatment non-responder) failed to show a cortisol stress response (> 1.5 nm/L salivary cortisol increase from baseline) during SDI. Both cortisol stress responders were excluded from further analyses.

3.4. Differences between treatment responders and non-responders in pretreatment salivary cortisol

An ANCOVA with log-transformed AUCg showed a significant effect of treatment response group after controlling for gender $F(1, 48) = 4.46$, $p = .040$, partial $\eta^2 = .085$, showing a higher pre-treatment log-transformed cortisol AUCg in responders ($M = 1.0$, $SD = 0.27$) compared to non-responders ($M = 0.85$, $SD = 0.25$).

A sensitivity analysis, using a more lenient response criterion (> 30% CAPS reduction), also showed a significant effect of treatment response group $F(1, 48) = 5.50$, $p = .023$, partial $\eta^2 = .10$, showing a higher pre-treatment log-transformed cortisol AUCg in responders ($n = 31$, $M = 0.98$, $SD = 0.29$) compared to non-responders ($n = 20$, $M = 0.81$, $SD = 0.19$).

3.5. Regression analysis

In Table 2, the results of the sequential multiple regression analysis are presented. Among the possible confounders gender, age and baseline CAPS-CA scores were selected as most relevant. At the first step of the model gender, age together with baseline CAPS-CA scores explained 35.5% of the variance in posttreatment PTSD severity (posttreatment CAPS-CA) (Adjusted $R^2 = 0.31$, $F(3\ 47) = 8.61$, $p < .001$). At the second step, there was a positive significant contribution of the log-transformed AUCg in explaining variance in posttreatment PTSD severity. Log-transformed cortisol AUCg prior to treatment significantly explained 5.70% of the variance in PTSD severity after treatment above and beyond gender, age and baseline CAPS-CA scores (R^2 change = 0.073 F change(1, 46) = 4.45 Sig F change = .040. At the final step the interaction term age x log-transformed cortisol AUCg did not make a significant contribution to R^2 (R^2 change = 0.009 F change (1, 45) = 0.731, Sig F change = .397). A final model containing gender, age, baseline CAPS-CA and log-transformed AUCg was chosen. The final model explained 41.2% of the variance in posttreatment CAPS-CA scores (Adjusted $R^2 = 0.36$, $F(4, 46) = 8.05$, $p < .001$). The log-transformed AUCg ($\beta = -.266$, $p = .040$), gender ($\beta = -.316$, $p = .021$) and baseline CAPS-CA scores ($\beta = .336$, p .016) showed a positive independent contribution to the final model.

There were no violations of regression assumptions in this analysis. In Fig. 3, a scatterplot is given to show that the pretreatment log-transformed AUCg was linearly related to posttreatment PTSD severity.

4. Discussion

We examined the association between salivary cortisol prior to treatment and trauma-focused psychotherapy outcome in youth with (partial) PTSD. We hypothesized that treatment responders would display higher pretreatment cortisol levels caused by increased cortisol responsivity to trauma script driven imagery relative to psychotherapy non-responders. Contrary to our expectations, we found that trauma script driven imagery did not induce a cortisol stress response in the vast majority of youth in our sample. Therefore, we cannot conclude if cortisol responsivity prior to treatment differs between treatment responders and non-responders. However, we did find that basal cortisol secretion prior to treatment, as measured with the total cortisol AUCg during the SDI procedure, did differ between responders and non-responders. Consistent with our hypothesis, our study revealed higher cortisol levels in treatment responders relative to non-responders. Higher pre-treatment cortisol levels further positively predicted the extent of clinical improvement during trauma-focused psychotherapy. Although we included patients with a broad age range (8–18 years), age did not moderate the relationship between pretreatment cortisol and treatment outcome. Together, these novel findings suggest cortisol prior to treatment is associated with and may predict the efficacy of trauma-focused psychotherapy in youth with (partial) PTSD.

There are several possible explanations why trauma script driven imagery did not elicit a cortisol stress response in most youth in our sample. First, effectiveness of stressor paradigm to elicit a stress response is subjective to developmental change. Throughout childhood and adolescence, marked changes are found in the ability of the same

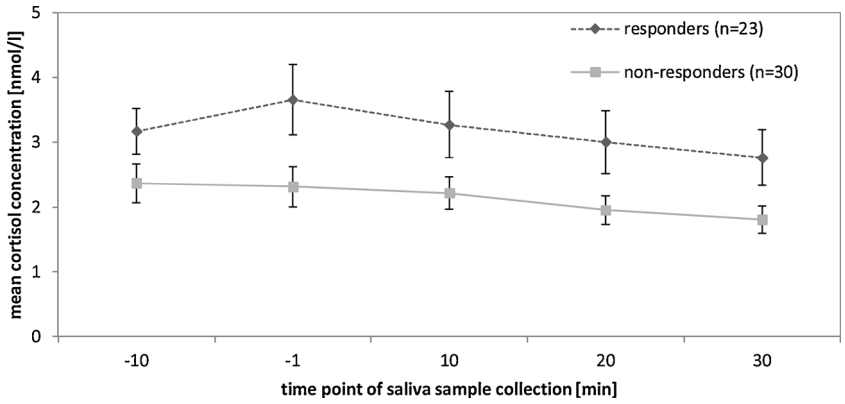

Fig. 2. Mean (± SE) saliva cortisol concentrations (original units) of pediatric posttraumatic stress disorder treatment responders and non-responders.

Table 2
Results of regression analysis ($N = 51$) with outcome variable posttreatment CAPS-CA total score.

	B [95% CI]	*SE B*	Beta	ρ
Step 1				
Constant	6.59 [−16.5, 29.6]	11.44		.569
Gender	15.0 [2.72, 27.3]	6.10	.34	**.018**
Pretreatment CAPS-CA	0.36 [0.08, 0.63]	0.14	.36	**.012**
Age	−0.23 [−2.14, 1.69]	0.95	−.030	.813
Step 2				
Constant	17.0 [−7.4, 41.4]	12.1		.167
Gender	14.1 [2.21, 26.0]	5.91	.316	**.021**
Pretreatment CAPS-CA	0.33 [0.06, 0.59]	0.13	.336	**.016**
Age	0.72 [−1.34, 2.75]	1.02	.096	.485
Log transformed AUCg	−22.1 [−43.2, −1.02]	10.48	−.266	**.040**
Step 3				
Constant	16.5 [−7.9, 41.00]	12.15		.180
Gender	16.0 [3.25, 28.7]	6.31	.358	**.015**
Pretreatment CAPS-CA	0.33 [0.07, 0.60]	0.13	.340	**.016**
Age	0.64 [−1,43, 2.71]	1.03	.085	.535
Log transformed AUCg	−20.8 [−42.2, 0.57]	10.6	−.250	.056
Age x Log transformed AUCg	−3.27 [−10.8, 4.3]	3,78	-.106	.397

Significant independent contributors to the model shown in bold.

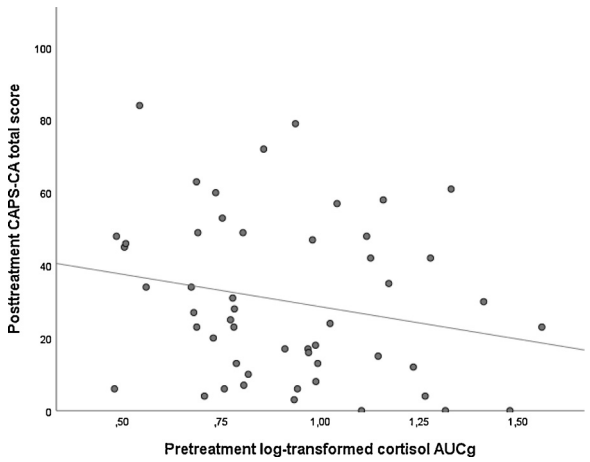

Fig. 3. Association of posttreatment PTSD symptoms (CAPS-CA total) with pretreatment log-transformed cortisol area under the curve with respect to ground (AUCg).

stressor paradigm to provoke elevations in cortisol. These changes in stressor paradigm effectiveness may be related to (neuro)developmental and psychological changes during childhood and adolescence. Gunnar et al. (2009) showed that threat to the social self is a critical psychological factor in determining the ability of a stressor paradigm to elicit cortisol elevation in youth, especially in older children and adolescents (Gunnar et al., 2009). Although the SDI contains a detailed contextual description of the patients' most disturbing traumatic event, it does not necessarily contain a threat to the social self. Furthermore, the examiner was present with the participants during the whole SDI period, which could have been perceived as social support. This is further supported by findings from a study by Dieleman et al. (2016) in youth with anxiety disorders treated with CBT. They did find pretreatment cortisol responsivity during a social stress task, which contains potential threat to the social self, to be associated with symptom improvement at one year follow-up (Dieleman et al., 2016). A second possible explanation of the absence of a cortisol stress response in our sample is that participants knew they would be exposed to a personalized trauma script during the procedure before the start of the SDI procedure. This could have induced high anticipatory anxiety which may have led to a ceiling effect in cortisol levels. Our findings emphasize the complex challenges in studying cortisol reactivity during development in youth with anxiety and trauma related disorders. Future research in youth should therefore also include stress paradigms with a social stress component.

There are several possible explanations how higher basal cortisol secretion might be associated with better psychotherapy outcome. First, trauma-focused psychotherapies require that patients confront, rather than avoid, traumatic memories (Foa et al., 2008; Shapiro, 2001). By confronting traumatic memories and associated distress in a safe therapeutic environment, a gradual decrease of the patients' distress to the traumatic memory can begin through habituation. However, patients may engage in avoidance before habituation can commence which hampers treatment success. Cortisol has been shown to have anxiolytic effects, increasing tolerance for distressing recollection of the traumatic memory (de Quervain et al., 2017d). It might thus minimize avoidance and promote engagement during treatment sessions (Yehuda et al., 2009). Second, cortisol has been demonstrated to directly enhance memory reconsolidation of emotionally arousing experiences and extinction learning (de Quervain et al., 2017d). This is relevant for trauma-focused treatments as emotionally arousing experiences are discussed to provide corrective information through cognitive restructuring and support extinction learning (Foa et al., 2008). Higher cortisol levels during treatment could thus improve treatment outcome by contributing to reduce avoidance and by promoting memory reconsolidation and extinction learning.

The results presented here show partial overlap with the few existing prospective studies on the relationship between cortisol and treatment efficacy in adults with PTSD. Studies in adult PTSD so far provide preliminary evidence that higher cortisol levels are related to increased treatment gains (Pacella et al., 2014; Rapcencu et al., 2017; Rauch et al., 2015; Yehuda et al., 2014). However, studies in adults suggest that higher cortisol levels are mainly driven by higher cortisol reactivity and not basal cortisol secretion. Higher reactivity, as

measured through the cortisol awakening response (CAR) and suppression of the CAR by dexamethasone challenge, was found in responders (Nijdam et al., 2015; Pacella et al., 2014; Rapcencu et al., 2017). Furthermore, the only prospective study using script driven imagery to assess cortisol reactivity in adult PTSD showed increased post script cortisol levels in treatment responders prior to treatment (Rauch et al., 2015). Contrary to our findings however, in adults with PTSD basal cortisol secretion was not associated with treatment outcome (Nijdam et al., 2015; Rauch et al., 2015; Yehuda et al., 2014). Together these findings again emphasize that findings on HPA function in adults with PTSD are not readily translated to youth with (partial) PTSD.

Our findings indicate pretreatment cortisol AUCg explained 5.70% of the variance in posttreatment symptom severity. The unique predicting value of cortisol in our study can be considered as rather small when compared to the predicting value of clinical and demographic variables in our study. Baseline symptom severity, age and gender accounted for 35.5% of the explained variance in posttreatment PTSD symptom severity, contributing considerately more to the final prediction model. The predictive value of cortisol measures in the current study is also limited compared to cortisol biomarkers in adult PTSD studies. Previous studies in adults reported effect sizes for treatment biomarkers ranging from 10.7% for CAR and 35% for CAR response following dexamethasone administration (Nijdam et al., 2015; Rapcencu et al., 2017). The limited amount of explained variance could reflect increased complexity in treating youth with (partial) PTSD in which treatment outcome is dependent on a more extensive and heterogeneous set of (developmental) factors. Indeed, youth with (partial) PTSD have shown increased heterogeneity in both clinical expression and biological characteristics, reflecting developmental differences across age groups (Scheeringa et al., 2011; Zantvoord et al., 2013b).

In the current study the average total CAPS-CA reduction from pre- to post treatment was 20 points. Previous trials using CAPS-CA as an outcome measure have shown comparable (Diehle et al., 2015; Ertl et al., 2011) and higher (Goldbeck et al., 2016; Smith et al., 2007) CAPS-CA reductions after trauma-focused psychotherapy in youth with (partial) PTSD. With a 50% reduction of CAPS-CA total score as response criterion, overall treatment response rate was 43.4%. Several factors could have contributed to the relative low response in the current study. First, our sample had a relative underrepresentation of youth exposed to single non-interpersonal traumatic events compared to previous trials (Gillies et al., 2012). Youth were predominantly exposed to repeated interpersonal trauma in which first trauma exposure often was at a young age and in a domestic setting. Furthermore, some participants were exposed to ongoing stressful life events such as ongoing third custody cases and out-of-home placement during the course of treatment. These trauma characteristics are associated with a poorer treatment response compared to single non-interpersonal trauma (Ertl et al., 2011; Smith et al., 2007). Second, although at pretreatment the majority (79.2%) of included youth had a full PTSD diagnosis, the remaining 20.8% had a partial PTSD diagnosis. Patients with partial PTSD show a more diffuse pattern of symptoms across different disorders and higher rates of comorbidity with depression, anxiety and externalizing disorders. In these patients treatment gains are not necessarily reflected in a reduction of CAPS-CA scores, treatment gains could be defined as a reduction of symptoms and problems in multiple domains beyond PTSD diagnostic criteria (Carrion et al., 2002). Furthermore, change scores in the partial PTSD group could have been relatively low due to a floor effect. Including youth with partial PTSD in our sample thus increased clinical heterogeneity and might have lowered overall reduction of CAPS-CA total score during treatment. On the other hand, by including youth with partial PTSD our sample better reflects the real-life clinical setting, which adds to the ecological validity of our findings. Finally, our sample received a limited number of treatment sessions compared to most previous trials and had a short posttreatment follow-up period. In the current study both the EMDR and TF-CBT protocols consisted of eight weekly treatment sessions. Both protocols have shown efficacy in previous trials, however, conventional treatment protocols tent to contain more sessions. Furthermore, a previous trial using an eight session protocol has shown that symptom reduction continues even in the period after treatment sessions have stopped (Ertl et al., 2011). Youth included in our study thus had fewer sessions and less time to respond compared to most previous trials. Therefore, it cannot be ruled out that some non-responders would have shown response if they received more treatment sessions or had a longer posttreatment follow-up period. We have tried to account for this possibility by performing a sensitivity analysis with a more lenient response criterion (30% CAPS-CA reduction) which confirmed our finding of higher pre-treatment cortisol levels in treatment responders. Nevertheless, future studies using more treatment sessions are warranted to compare cortisol levels in short term treatment responders and delayed responders.

The present study details novel findings regarding the relationship between salivary cortisol and treatment outcome in youth with (partial) PTSD. It is not, however, without limitations. First, the trauma script driven imagery procedure did not elicit a cortisol stress response in all but two participants. Therefore cortisol reactivity could not be addressed in the current sample, precluding conclusions on differences in cortisol reactivity between treatment responders and treatment non-responders. The potential reasons for the lack of cortisol response are discussed above. Furthermore, the lack of a circadian cortisol secretion measure mitigates interpretation of our results. Inclusion of measures of cortisol levels throughout the day (awakening, morning, noon, afternoon, evening) would have provided the opportunity to distinguish between differences in basal circadian cortisol levels and anticipatory cortisol reactivity to the SDI. Future treatment studies in youth with (partial) PTSD should therefore ideally also include stress paradigms with a social treat component and measures of circadian cortisol levels. Second, salivary cortisol levels are related to many state and trait factors, we have tried to account for most of these confounding factors in the current study to prevent unwanted influences on our results. However, we omitted inquiry on menstrual status, pubertal stage and (oral) contraceptive use, which are known factors to influence cortisol levels and may influence cognitive and emotional processing (Stalder et al., 2016; Sundström Poromaa and Gingnell, 2014). In theory, this could thus have created a spurious relationship between cortisol and treatment outcome. Obviously, future studies should try to include these variables as well. Third, the current analyses on differences between treatment responders and non-responders are based on cross-sectional data, highlighting the need for future longitudinal treatment studies in which cortisol is measured before, during and after treatment. This would enable examination of common and differential longitudinal trajectories of cortisol in treatment responders and non-responders. This could render insight in the working mechanisms of treatments and might provide novel ways to improve treatment efficacy. Fourth, youth were randomized to receive either TF-CBT or EMDR, for the current analysis both treatment conditions were collapsed. Due to limited power it was not feasible to examine differences between treatment responders and non-responders separately for both treatment conditions or examine specific predictors for each treatment separately. Larger RCT's with more statistical power using cortisol measures are therefore warranted. Finally, our study had considerable drop-out rate, as 24% of randomized patients were lost to follow-up. Although, dropout rates in our study reflect routine clinical practice and cortisol measures did not differ between treatment completers and non-completers, there is a possibility that drop-out could have influenced our main findings through attrition bias.

5. Conclusions

To our knowledge, this is the first report of differences in cortisol levels prior to treatment between treatment responders and non-responders in youth with (partial) PTSD. Because the trauma script driven

imagery procedure failed to provoke a cortisol stress response in our sample, the question if cortisol reactivity differs between treatment responders and non-responders remains inconclusive. Our results do however show that higher pretreatment basal cortisol secretion is associated with higher treatment response. This may suggest that cortisol forms a potential indicator of prospective trauma-focused psychotherapy efficacy in youth with (partial) PTSD. However, the current study does not provide clinically applicable biomarkers yet, as our findings do not provide markers which are predictive for individual patients. Future studies should therefore use stress paradigms with a social treat paradigm and data-analysis methods specifically aimed at maximizing classification accuracy, combining cortisol data with other clinical and neurobiological data. Furthermore, longitudinal cortisol measures during the course of treatment contribute to delineate the association between cortisol over time and treatment response. This could help to determine if cortisol may be a potential target as add-on therapy to improve trauma-focused psychotherapy efficacy in youth with (partial) PTSD.

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