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Functional reorganization of neural networks involved in emotion regulation following trauma therapy for complex trauma disorders

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ABSTRACT

Objectives: We investigated whether patients with complex interpersonal trauma engage neural networks that are commonly activated during cognitive reappraisal and responding naturally to affect-laden images. In this naturalistic study, we examined whether trauma treatment not only reduces symptoms but also changes neural networks involved in emotional control.

Methods: Before and after eight weeks of phase-oriented inpatient trauma treatment, patients (n = 28) with complex posttraumatic stress disorder (cPTSD) and complex dissociative disorders (CDD) performed a cognitive reappraisal task while electroencephalography (EEG) was registered. Patients were measured as a prototypical dissociative part that aims to fulfill daily life goals while avoiding traumatic memories and associated dissociative parts. Matched healthy controls (n = 38) were measured twice as well. We examined task-related functional connectivity and assessed self-reports of clinical symptoms and emotion regulation skills.

Results: Prior to treatment and compared to controls, patients showed hypoconnectivity within neural networks involved in emotional downregulation while reappraising affect-eliciting pictures as well as viewing neutral and affect-eliciting pictures. Following treatment, connectivity became normalized in these networks comprising regions associated with cognitive control and memory. Additionally, patients showed a treatment-related reduction of negative but not of positive dissociative symptoms.

Conclusions: This is the first study demonstrating that trauma-focused treatment was associated with favorable changes in neural networks involved in emotional control. Emotional overregulation manifesting as negative dissociative symptoms was reduced but not emotional underregulation, manifesting as positive dissociative symptoms.

1. Introduction

Patients with posttraumatic stress disorder (PTSD) tend to have overly strong and/or overly weak emotional reactions to reminders of traumatizing events (Frewen and Lanius, 2006; Lanius et al., 2006, 2010, 2012). Many recurrently re-enact their traumatic experiences. Experimental evidence suggests that one prototypical kind of re-enactment is associated with increased autonomic arousal (e.g., elevated heart rate and blood pressure) and low medial prefrontal cortex (mPFC) and rostral/dorsal anterior cingulate cortex (rACC/dACC) activation that reflects insufficient prefrontal inhibition of limbic emotional networks including the amygdala and insula. Lanius and colleagues refer to this psychobiological reaction pattern as “emotional underregulation” (Frewen and Lanius, 2006; Lanius et al., 2010). In contrast, 12%–30% of the PTSD population respond to trauma-related cues in experimental settings with psychobiological “emotional overregulation”: subjective feelings of derealization and depersonalization (Lanius et al., 2010; Stein et al., 2013; Wolf et al., 2012), along with hyperactivity in frontal areas involved in top-down regulation of emotional neural networks and autonomic hypoarousal.

Patients with a dissociative identity disorder (DID) had dissociative part-dependent neurophysiological activation patterns that paralleled the over- and underregulated patterns in PTSD patients (Nijenhuis, 2015; Reinders et al., 2014). Participants were measured as an Apparently Normal Part of the personality (ANP) and an Emotional Part of the personality (EP, subtype active defense). As ANP, patients aim to fulfill

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activity of daily living and to avoid traumatic memories and EPs. EPs recurrently reenact traumatic memories and in this context engage in defense behavior. As ANP, DID patients showed a profile consistent with the emotional overregulation response. As this type of dissociative part, they generated negative dissociative symptoms (e.g., derealization, depersonalization, emotional numbing) in reaction to trauma-related cues. As EP, the patients had an activation pattern that paralleled underregulated emotional reactivity (Reinders et al., 2006; Schlumpf et al., 2013, 2014). That is, as EP the patients generated positive dissociative symptoms (e.g., intrusions, flashbacks) in reaction to trauma-related stimuli. Hence, there is a striking neurophysiological and clinical overlap between DID and PTSD patients (Nijenhuis, 2015; Reinders et al., 2014).

Since emotional dysregulation is a core feature of all trauma-related disorders, trauma therapies generally aim to enhance emotion regulation skills. Although exposure therapy is effective in reducing (simple) PTSD symptoms (Schnyder, 2000), clinical observations of complex trauma patients such as complex PTSD (cPTSD) and dissociative disorder patients indicate that exposure can have strong side effects in terms of exacerbation, compliance problems, and high drop-out rates (Flatten et al., 2004). Individuals with chronic and early-life trauma-related disorders benefit more from exposure therapy and show fewer adverse effects when they are initially provided with skills helping them to manage distress and strong aversive feelings (Cloitre et al., 2002, 2010). Therefore, the current standard of care for cPTSD and dissociative disorders is a phase-oriented treatment approach (Courtois, 1999; Ford et al., 2005; International Society for the Study of Trauma and Dissociation, 2011; Steele et al., 2001, 2004, 2005). Usually it comprises three recurrent phases, which are 1) stabilization, 2) confrontation, and 3) integration.

Prospective studies demonstrate an improvement in emotion regulation ability across Cognitive Behavioral Treatment (CBT) in PTSD patients (Cloitre et al., 2002; Hinton et al., 2009; Price et al., 2006). PTSD symptom reduction was related to improvement in emotion regulation skills. The studies used self-report questionnaires to assess emotion regulation capacity. Two types of emotion regulation styles, “cognitive reappraisal” and “expressive suppression”, have attracted particular interest in the trauma literature (Gross, 1998; Gross and Thompson, 2007). Cognitive reappraisal involves an attempt to generate a positive interpretation of a traumatizing event to reduce excessive emotionality. Expressive suppression names the attempt to modulate negative emotions by hiding, inhibiting, or reducing the behavioral response to a stressful event. Cognitive reappraisal, but not expressive suppression, is effective in reducing physiological arousal and negative emotions (Gross, 2002; Gross and Levenson, 1997; Hagemann et al., 2006) and is associated with beneficial physiological and psychological outcomes (Aldao et al., 2010; John and Gross, 2004). Within the context of PTSD, expressive suppression was associated with higher levels of PTSD symptoms (Eftekhari et al., 2009; Ehring and Quack, 2010; Moore et al., 2008; Shepherd and Wild, 2014; Sippel et al., 2016).

Neuroimaging studies indexed emotion regulation capacity via the inhibitory control of cortical over subcortical regions that mediate posttraumatic emotional reactivity. In these studies (Felmingham et al., 2007; Peres et al., 2007), participants were instructed to attend to emotionally arousing cues. Following therapy involving exposure-based and cognitive restructuring, PTSD patients demonstrated increased activity in the PFC (i.e., rACC, frontopolar cortex) and hippocampus, and decreased activity in the amygdala. Treatment-induced changes in PTSD symptoms correlated positively with PFC activity. These results are consistent with enhanced top-down control of emotional reactivity and modification of traumatic memories.

In all aforementioned studies, participants' reactions to aversive cues were tested without giving them an explicit instruction to regulate their emotional responses. However, emotionally challenging tasks evoke explicit (i.e., effortful) or implicit (i.e., nonconscious) emotion regulation. Only one fMRI study investigated treatment-specific connectivity changes during explicit emotion regulation using cognitive reappraisal in PTSD patients (Fonzo et al., 2017). Compared to a waiting-list control group, patients, who received prolonged exposure therapy, demonstrated increased functional connectivity between prefrontal regions during reappraisal.

Emotional dysregulation characterizes all trauma-related disorders. However, treatment-related changes in emotion regulation have been examined for PTSD and cPTSD patients, but not for complex dissociative disorder patients. In the present study, explicit and implicit emotion regulation tasks were conducted pre- and post-treatment. Patients with cPTSD, dissociative disorder not otherwise specified type 1 (DDNOS-1), and DID were instructed to either cognitively reappraise or attend to emotional arousing stimuli while electroencephalography (EEG) was registered. Patients were exclusively measured as ANP. EEG-based functional connectivity on the source level was examined. EEG has the clear advantage of a high time resolution. Thus, compared to functional magnetic resonance imaging (fMRI), it offers the possibility to measure functional brain networks at a faster time-scale. It is known from the literature that fMRI can result in dizziness (Heinrich et al., 2014), increase in anxiety (Mutschler et al., 2014) or anticipatory stress and cortisol release (Keulers et al., 2015) in healthy individuals. These side effects can confound data acquisition, particularly during emotion eliciting tasks. EEG is easier to apply and less intrusive compared to fMRI and is therefore more suited for the particular study group we were measuring here.

Clinical symptoms and emotion regulation ability were measured before and after treatment using self-report measures. We hypothesized that patients as ANP show treatment-related changes in functional networks associated with emotion regulation and that these changes are related to improved self-reported emotion regulation skills and clinical symptom reduction. As it is difficult to extract subcortical generators of scalp-recorded EEG (Michel et al., 2009), our hypotheses with respect to functional network changes were restricted to cortical regions involved in posttraumatic emotional reactivity and emotion regulation (i.e., PFC, ACC, insula, hippocampus).

2. Materials and methods

2.1. Subjects

Patients were recruited from the two specialized wards for inpatient trauma treatment at the Psychiatric Hospital Clienia Littenheid AG, Littenheid, Switzerland. These two wards offer the same treatment program. Treatment includes psychotherapy in individual and group settings, cognitive stabilization groups, body-oriented and movement therapy as well as other non-verbal therapies (e.g., music, art, and occupational therapy), and pharmacotherapy. The inpatient trauma therapy setting consists of three phases, as mentioned above: stabilization, confrontation, and integration. This inpatient period may be repeated several times according to the patient's needs with adequate intervals of about 6 months in community settings. The majority of patients included in this study were in the first or second treatment period. Supplementary Table 1 provides more details on the individual treatments.

Only patients with chronic and severe interpersonal trauma and cPTSD (Herman, 1992; Pelcovitz et al., 1997; Van der Kolk, 2001), DDNOS-1, or DID (American Psychiatric Association, 2013) were included. Patients had experienced chronic abuse (i.e., emotional, physical, or sexual) and/or emotional neglect beginning in childhood. In all patients but one, the main perpetrators were the primary caregivers. Three patients additionally lived traumatizing war experiences. None underwent recent traumatizing events. The clinical diagnoses of DID, DDNOS-1, and PTSD were checked using the German versions of the Structural Diagnostic Interview for DSM-IV for Dissociative Disorders (SCID-D; Steinberg, 1993) and the Posttraumatic Diagnostic Scale (PDS;

Ehlers et al., 2009). cPTSD is not yet recognized as an official diagnosis. The consensus diagnostic criteria of cPTSD were verified using the German Version of the Structured Interview for Disorders of Extreme Stress, that is, the *Interview zur Komplexen Posttraumatischen Belastungsstörung* (IK-PTBS Sack and Hofmann, 2001). DDNOS-1 and DID overlap, but DDNOS-1 patients do not meet all criteria of DID (American Psychiatric Association, 2013). As these diagnoses were not clearly distinguishable in all patients, we treated them as one subgroup of "Complex Dissociative Disorder" (CDD) patients. Thus, the patient group consisted of 23 CDD and 21 cPTSD patients. Prior to measurement, patients were instructed to select an ANP for participation in the experiment. They were also asked post facto which dissociative part or parts had actually been present during the experiment to check for unintentional switches to or co-activations of unwanted dissociative parts. All patients reported to have participated with the intended dissociative part and that no inadvertent switches or co-activations had occurred.

Exclusion criteria for patients were underweight (Body Mass Index < 17), comorbid attention deficit disorder, psychosis, alcohol and substance abuse (for example cannabis, LSD or cocaine), acute suicidality, known structural brain damage or neurological disorders. Psychotropic medication and comorbid diagnoses are described in more detail in Supplementary Table 2. In addition to the patient group, we also recruited a healthy control group ($n = 40$). For controls, exclusion criteria were regular alcohol and substance abuse, known structural brain damage or neurological disorder or a lifetime history of any mental disorder. Using the PDS (Ehlers et al., 2009), we examined whether candidate controls had lived potentially traumatizing events. Those who did and who had posttraumatic symptoms were excluded from the study. Trauma exposed individuals without subsequent symptoms were included. Healthy controls were paid CHF 200.- for participation.

There were several drop-outs due to premature discharge from hospital (2 cPTSD), disability to perform the experimental task (4 CDD, 4 cPTSD), low data quality (1 cPTSD patient, 1 CDD, 1 healthy control), storage failure (1 healthy control) or a technical issue during EEG data acquisition (4 cPTSD). The final analysis included 18 CDD patients, 10 cPTSD patients, and 38 healthy controls. For more details on characteristics of participants, see Table 1.

After possible risks and side-effects of the experiment were explained in detail, all subjects provided written informed consent prior to study participation. Patients were informed that non-participation or withdrawal from the study would not influence their ongoing therapy. Two local ethics committees (of the cantons Thurgau and Zurich) approved the study, which was performed in compliance with the Declaration of Helsinki.

2.2. Experimental procedures

Each participant was tested at two time points. The patient group was examined at the beginning of their inpatient stay (pre-treatment) and before discharge from the hospital (post-treatment). Controls were measured twice within a time interval of 5 to 10 weeks. At each measurement point, subjects filled out questionnaires and performed an EEG experiment.

2.3. Emotion regulation ability

Two self-report questionnaires were used to assess emotion regulation capacity pre- and post-treatment: the German version of the Emotion Regulation Questionnaire (ERQ; Abler and Kessler, 2009) and the German version of the Difficulty in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004). The ERQ includes 10 items and two subscales: cognitive reappraisal and expressive suppression. Items are scored on 7-point scales (range per subscale: 5–35). The higher the subscale score, the more an individual engages in the corresponding strategy. The DERS is a 36-item self-assessment tool, which was developed to test emotion regulation strategies. The DERS total scale consists of six subscales: 1) nonacceptance of emotional responses, 2) difficulty in goal-directed behavior, 3) difficulty controlling impulses, 4) lack of emotional awareness, 5) lack of access to emotion regulation strategies, and 6) lack of emotional clarity. Items are rated on 5-point scales (range: 36–180). Higher scores indicate more emotion regulation difficulties.

2.4. Clinical symptoms

The civilian version of the Posttraumatic Stress Disorder Checklist (PCL−C; Weathers et al., 1994), a 17-item self-report measure, was used to assess DSM-IV symptom criteria of PTSD. Items are scored on 5-point scales. A total PTSD symptom severity score comprising of intrusion, hyperarousal, and avoidance/numbing symptom-cluster scores was obtained (range: 17–85). The severity of cognitive-emotional and several other dissociative symptoms was assessed with the *Fragebogen Dissoziativer Symptome* (FDS; Spitzer et al., 2004). Participants have to circle the percentage (0–100%) of time they experience each item on the scale. The mean score of the 44 items was calculated (range: 0–100). The Somatoform Dissociation Questionnaire (SDQ-20; Nijenhuis et al., 1996), a 20 item self-report instrument, was used to determine the severity of somatoform (i.e., sensorimotor) dissociative symptoms. Items are scored on 5-point scales (range: 20–100). Depressive symptoms were collected using the Beck's-Depression Inventory II (BDI-II; Beck et al., 1996), a 21-item self-report questionnaire. Items are rated on 4-point scales (range: 0–63). We also included the trait part of the Stait and Trait Anxiety Inventory (STAI-T; Laux et al., 1981), a self-report inventory consisting of 20 items. Items are scored on 4-point scales (range: 20–80). Details on handling incomplete data in self-report data on emotion regulation ability and clinical symptoms are provided in the Supplementary materials.

2.5. EEG paradigm

In order to investigate explicit and implicit emotion regulation capacity, an emotion regulation task was conducted pre- and post-treatment. The task was adapted from previous cognitive reappraisal EEG studies (Ertl et al., 2013; Hajcak and Nieuwenhuis, 2006; Moser et al., 2006, 2009; Parvaz et al., 2012). The stimulus set consisted of 40 highly arousing and 40 neutral, low arousing color images taken from the International Affective Picture System (IAPS; Lang et al., 1999). An unpleasant picture set was created including 40 images of threat, grief, and humiliation. A neutral picture set consisted of 20 pictures representing household objectives, landscapes, and plants (neutral object). The set also included 20 pictures of neutral faces or neutral interpersonal scenes (neutral human) to control for human features (for more details on the picture selection process, see Supplementary materials).

Each trial of the task consisted of four sequentially presented episodes, a relaxation period (5 s), an emotion-regulation instruction period (2 s) followed by a fixation cross (1 s), and the picture presentation (4 s) from either the unpleasant or neutral picture type set, resulting in a total of 80 trials. In trials in which an unpleasant picture was presented, either a horizontal or a vertical arrow pointing downwards was shown on the screen during the emotion regulation instruction period, indicating whether the subject was asked to have her natural emotional responses to an upcoming picture (UnpleasantNatural) or to reduce (i.e., "downregulate") the emotional reaction (UnpleasantDownregulation; see Fig. 1A). Prior to the experimental task the participants were trained to apply a self- and a situation-focused strategy (according to Ochsner et al., 2004). During the experiment, participants could freely choose which of the two strategies they applied for each UnpleasantDownregulation trial. The self-focused strategy involved (a) viewing the pictures from a detached, third-person

Table 1
Demographic and clinical measures of the participants under investigation.

Demographic measures	Patients (n = 28)	Controls (n = 38)	Group difference (p-value)
Sex	22 female/6 male	31 female/7 male	n.a.
Education	Secondary school: 10%, high school: 50%, college: 40%	Secondary school: 10%, high school: 30%, college: 70%	n.a.
Age (mean ± SD)	42.04 (10.18)	41.37 (12.71)	0.81

Clinical measures (mean ± SD)	Patients (n = 28)				Controls (n = 38)				Main effect group		Interaction effect (group × time point)	
	Post-hoc *t*-test				Post-hoc *t*-test							
	Pre	Post	p-value	Effect size	Pre	Post	p-value	Effect size	p-value	Effect size	p-value	Effect size
DERS Total	108.35 (23.86)	104.57 (23.82)	–	–	55.00 (16.40)	53.63 (14.00)	–	–	< .0001***	0.64	.29	0.002
DERS ACCEPT	18.75 (7.91)	17.82 (6.49)	–	–	9.32 (5.01)	8.45 (3.49)	–	–	< .0001***	0.40	.96	< 0.0001
DERS GOALS	15.96 (4.30)	15.54 (4.23)	–	–	8.05 (2.72)	7.86 (2.70)	–	–	< .0001***	0.56	.72	0.0003
DERS IMPULSE	13.46 (4.17)	12.46 (4.43)	–	–	8.03 (2.25)	7.92 (2.03)	–	–	< .0001***	0.37	.21	0.004
DERS AWARE	21.10 (5.39)	20.43 (4.98)	–	–	12.22 (4.65)	12.46 (5.68)	–	–	< .0001***	0.41	.58	0.0009
DERS STRATEGIES	22.96 (5.92)	22.43 (6.97)	–	–	10.45 (4.16)	10.29 (3.56)	–	–	< .0001***	0.59	.38	0.001
DERS CLARITY	16.67 (4.21)	15.89 (4.29)	–	–	6.79 (1.88)	6.63 (2.06)	–	–	< .0001***	0.70	.21	0.004
ERQ Reappraisal	20.85 (7.61)	24.85 (6.36)	.001***	−0.57	30.82 (6.37)	31.18 (5.41)	.69	−0.06	< .0001***	0.29	.01**	0.02
ERQ Suppression	17.44 (5.58)	17.89 (4.51)	–	–	11.57 (4.78)	11.00 (4.44)	–	–	< .0001***	0.32	.23	0.004
PCL–C Total	56.40 (10.45)	50.83 (10.94)	< .0001***	0.52	19.44 (4.02)	19.24 (4.16)	.89	0.05	< .0001***	0.84	.0002***	0.03
PCL–C Intrusions	16.93 (4.53)	15.63 (4.83)	–	–	5.82 (1.56)	5.55 (1.18)	–	–	< .0001***	0.73	.14	0.006
PCL-C Hyperarousal	16.33 (3.52)	14.63 (3.90)	.0009***	0.46	5.81 (1.20)	5.70 (1.05)	.84	0.10	< .0001***	0.78	.009**	0.03
PCL-C Avoidance/Numbing	23.11 (5.76)	20.56 (5.03)	.0002***	0.47	7.78 (1.93)	7.97 (2.86)	.71	−0.08	< .0001***	0.76	.001***	0.04
FDS	24.17 (14.51)	20.66 (12.85)	.002**	0.26	2.30 (2.15)	1.65 (1.77)	.54	0.33	< .0001***	0.57	.03*	0.01
SDQ-20	35.26 (9.79)	33.43 (10.18)	–	–	20.66 (1.32)	20.66 (1.55)	–	–	< .0001***	0.52	.22	0.005
PosDiss	15.00 (10.34)	13.55 (9.14)	–	–	1.64 (1.67)	1.35 (1.43)	–	–	< .0001***	0.50	.13	0.004
NegDiss	20.76 (10.89)	17.08 (9.91)	.0005***	0.35	2.67 (2.13)	1.93 (1.62)	.42	0.39	< .0001***	0.59	.02*	0.02
BDI-II	28.30 (11.16)	22.90 (10.15)	.001***	0.51	2.27 (4.71)	1.78 (3.24)	.61	0.12	< .0001***	0.72	.004**	0.02
STAI-T	55.02 (8.40)	54.07 (7.10)	–	–	27.82 (6.63)	27.16 (7.71)	–	–	< .0001***	0.77	.55	0.0006

N.a., not applicable; pre, pre-treatment; post, post-treatment; DERS, Difficulty in emotion regulation scale; ERQ, Emotion regulation questionnaire; PCL—C, Posttraumatic Stress disorder Checklist, civilian version; FDS, Fragebogen Dissoziativer Symptome; SDQ-20, Somatoform Dissociation Questionnaire; PosDiss, Total score positive dissociative symptoms; NegDiss, Total score negative dissociative symptoms; BDI-II, Beck's Depression Inventory; STAI-T, Stait trait anxiety inventory. P-values are two-sided and FDR corrected for post-hoc *t*-tests; post-hoc *t*-tests were only applied if the group × time point interaction effect was significant. Effect sizes were estimated as Cohen's d for *t*-tests and as generalized eta^2 for main and interaction effects.

*** $p \leq .001$.

** $p \leq .01$.

* $p \leq .05$.

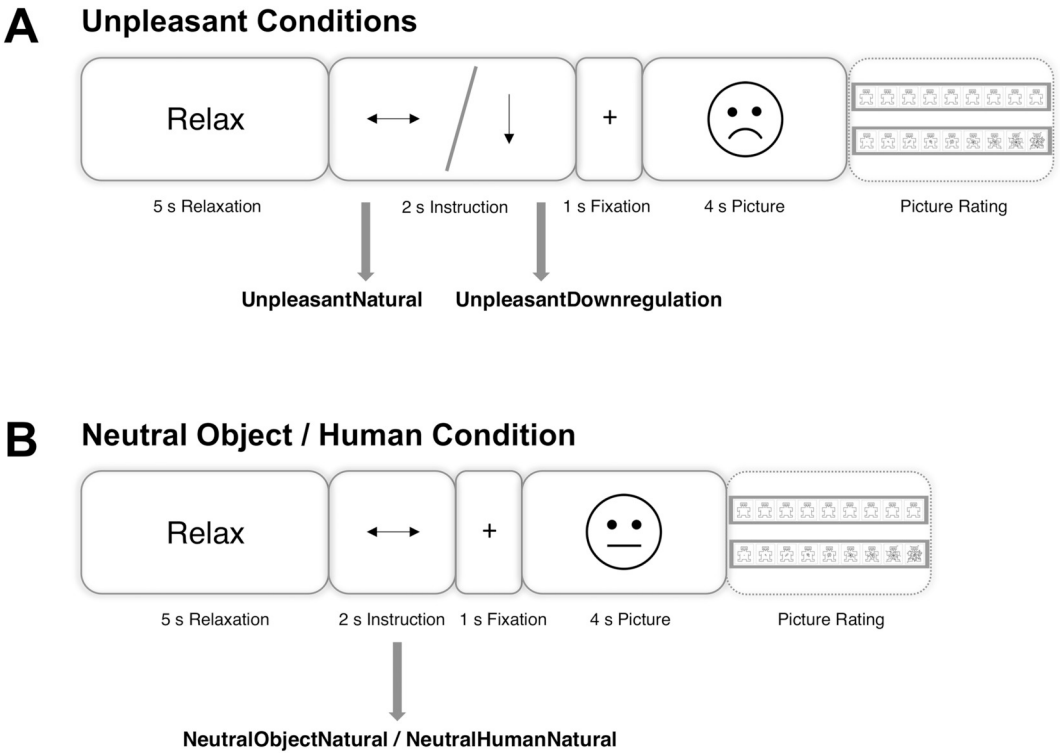

Fig. 1. Schematic representation of trials in the A) unpleasant and B) neutral picture conditions.

perspective, that is, from a personally and emotionally uninvolved point of view, or (b) imagining that the pictures belonged to a movie rather than to a real event. The situation-focused strategy involved imagining that the pictured scene would improve, for example, imagining that the ill person in the picture would get better soon. To become acquainted to the setting, participants performed a practice block of 10 trials prior to the main task and were asked to report which reappraisal strategies they had applied. Once they were able to successfully reappraise unpleasant pictures in either way, the main experiment was started. In trials presenting either neutral objects or neutral human scenes only contained the instruction to naturally respond to the images, resulting in the NeutralObjectNatural and NeutralHumanNatural condition (see Fig. 1B).

In 50% of the trials of each experimental condition, participants had to rate the presented pictures for valence (1 = negative, 9 = very positive) and arousal (1 = not arousing at all, 9 = highly arousing) on 9-point Likert scales using the Self-Assessment Manikin (SAM; Bradley and Lang, 1994). Due to storage failure, there was a missing value in the valence and arousal rating in the controls. Thus, the final rating data comprised 28 patients and 37 healthy controls.

To ensure that the participants had followed task instructions, they were asked immediately after the EEG task what strategies they had used to naturally respond or to reduce their emotional reactions. Stimulus presentation was controlled by the Presentation software (Neurobehavioral Systems, Inc., https://www.neurobs.com). Conditions were presented pseudorandomized by using two different playlists. The two playlists were appointed randomly to the first and second measurement across the participants.

2.6. EEG recording and raw data processing

EEG signals were acquired with cap attached electrodes (actiCAP, Brain Products Inc., http://www.brainproducts.com) involving 64-channels in standard 10–20 electrode placement system. The average of activity at all electrodes was chosen as online reference. During EEG recording, data were amplified by a BrainVision QuickAmp (Brain Products Inc.) 72-channel amplifier sampling at 500 Hz with a band-pass filter between 0.1 and 100 Hz and a notch filter at 50 Hz. Impedance was kept at least below 25 kΩ.

Raw EEG data were preprocessed using the BrainVision Analyzer 2.0 software (Brain Products Inc.). To remove eye activity artefacts (i.e., saccades and eye blinks), we applied an independent component analysis (Jung et al., 2000). We then band-pass filtered the data between 0.1 and 40 Hz. Bad channels were replaced with interpolated values from the surrounding electrodes. To reject remaining artefacts (i.e., movement or muscle artefacts), we ran the automated raw data inspection implemented in BrainVision Analyzer. Data were segmented for each condition separately into epochs of 4 s comprising the data recorded during picture presentation. Participants with < 10 artefact-free segments per condition were excluded from the analysis (3 participants). Using this acceptance criterion, the number of artefact-free data epochs in all participants ranged from 11 to 20 due to individual differences in EEG data quality. More details on data epochs can be found in the Supplementary materials.

2.7. Connectivity analysis on the source level

The artefact-free and segmented data were subjected to the sLORETA toolbox (Version 20,160,611; https://www.uzh.ch/keyinst/loreta.htm) for functional brain connectivity analysis (Pascual-Marqui, 2002). sLORETA allows estimating intracortical current density values on the source level in 6239 voxels based on a MNI152 standard head model. For connectivity analysis, these voxels were reduced to a limited number of regions of interest (ROIs). Here, we used the in sLORETA implemented 84 Brodmann areas (BA, 42 for each hemisphere) and their corresponding centroid voxels. A similar approach has been applied in several previous studies of our lab (Binder et al., 2017; Brauchli et al., 2018; Klein et al., 2016). We used the Juelich Histological and the Harvard-Oxford cortical atlases provided by the fMRIB software (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) and visual inspection for a more detailed description of brain regions. Further details on quality check of the source estimation process in the present study can be found

in the Supplementary materials.

Functional connectivity is a measure of correlation in activation among spatially-distinct brain regions (Friston, 2011). In this study, lagged coherence was used for connectivity measure. Lagged coherence is an acknowledged index for true physiological connectivity, that is, it only includes values with non-zero phase lags between data time series and is therefore not confounded by volume conduction as compared to instantaneous measures (Pascual-Marqui, 2007). After dividing the preprocessed 4 s epochs into 2 s segments to increase the number of segments entering group statistics, lagged coherence values were computed between the centroid voxels of all pairs of ROIs. This analysis was applied separately to the three EEG frequency bands theta (4–8 Hz), alpha (8.5–12 Hz), and beta (12.5–30 Hz) since these frequency bands mostly reflect neurophysiological activity associated with cognitive and emotional processes. In the end, the analysis provided a matrix for each subject including the mean functional connectivity values of the 4 s picture presentation phase (average of 2 × 2 s segments) per condition between all 84 ROIs for each frequency band.

2.8. Network-based statistical analyses

These 84 × 84 connectivity matrices were subjected to Network-based Statistic (NBS, https://www.nitrc.org/projects/nbs/) using MATLAB (version R2015b, http://www.mathworks.com/). The methods of analysis implemented in NBS are validated (Zalesky et al., 2010, 2012) and can be used to identify brain regions with different degrees of connectivity for patients compared to controls within and between the two measurements. CDD and cPTSD patients were pooled together to increase statistical power. In NBS, a two-sample *t*-test was first calculated for each connection (i.e., edges) between all pairs of ROIs (i.e., nodes). The edges exceeding a predefined threshold (i.e., sensitivity threshold) constituted a set of supra-threshold connections. Among these connections, NBS searches for any connected network components, and the size of each network was defined as the number of edges it comprises. Non-parametric permutation testing was then applied to calculate a family-wise error (FWE) corrected *p*-value for each network. Patients and controls were randomly exchanged and the largest network per permutation was registered to yield the empirical null distribution. Finally, a corrected p-value for a network in the original data was estimated by the proportion of permutations for which a network of equal or greater size than the original data network was identified.

First, between-group differences at first measurement were established to figure out pre-treatment network differences. In order to keep the design matrix as simple and interpretable as possible, we ran the analysis within the NBS software for each condition (i.e., UnpleasantNatural, UnpleasantDownregulation, NeutralObjectNatural, and NeutralHumanNatural) and each frequency band (i.e., theta, alpha, and beta) separately. Thus, 12 (four [conditions] × three [frequency bands]) two-sample *t*-tests were computed for both contrasts (i.e., patients > controls; controls > patients). In order to evaluate group × time point interactions, we subtracted the lagged coherence post-treatment values from the lagged coherence pre-treatment values and submitted this difference maps to two-sample *t*-tests. The difference maps were restricted to the networks identified pre-treatment. This approach allowed us to examine if there was any treatment-related change in these networks. We additionally ran two-sample *t*-tests to check for any post-treatment group difference in the aforementioned networks. Finally, we also assessed post-treatment whole-brain group differences in all frequency bands to track for potential network alterations independent from the pre-treatment level.

For all statistical tests, we used 5000 permutations and set p-value to 0.05. There was a significant difference with respect to the pre- to post-treatment time interval between the groups [patients M = 40.90 (1.29), controls M = 49.00 (1.25); $t = -4.51$, $p < .000$, d = −1.10]. Therefore, the number of days between measurements was used as a covariate of no interest in the NBS analyses to control for this potential confounder. Exploratory analyses yielded stable pre-treatment findings in sensitivity thresholds ranging from 2 to 4 (in 0.1 steps) in the NeutralHumanNatural and UnpleasantNatural conditions. A threshold of 3 was chosen on the basis that it detects networks with a manageable amount of edges (i.e., not exceeding 30 edges). The network obtained in the UnpleasantDownregulation condition was the largest of all three conditions. Therefore, in this condition we chose the highest t-threshold reaching a significant result (i.e., $t = 2.6$). For the post-treatment group × time point interactions and group analyses, no t-threshold was applied. This procedure enabled us to sensitively detect the connections of the networks extracted at the initial measurement that had significantly changed over time. Functional brain networks were visualized using the BrainNet Viewer (www.nitrc.org/projects/bnv/; Xia et al., 2013).

2.9. Relationship between functional connectivity and emotion regulation capacity

We explored how treatment-related alterations of the patients' functional connectivity were related to changes in emotion regulation capacity. To this end, the networks' connectivity values per edge (i.e., coherence values) obtained from the group × time point NBS analyses were averaged. Changes in emotion regulation capacity over time were examined by subtracting the pre-treatment score of each patient in the DERS, ERQ Reappraisal, and ERQ Suppression from the corresponding post-treatment score. These difference values (i.e., Diff_DERS, Diff_ERQ Reappraisal, Diff_ERQ Suppression) were correlated with the mean functional connectivity values per network using Spearman's rank correlations.

2.10. Relationship between functional connectivity and clinical symptoms

In addition, we examined how treatment-related alterations in patients' functional connectivity were related to changes in clinical symptoms assessed by the PCL−C, FDS, SDQ-20, BDI-II, and STAI-T. Furthermore, we were interested in relating functional network alterations to changes in positive and negative dissociative symptoms. There is no measure that explicitly examines the severity of positive and negative dissociative symptoms. Therefore, we applied a procedure that has already been used in a previous study (Van Dijke et al., 2010). The items of the SDQ-20 and FDS were subdivided by an expert on dissociation (Ellert Nijenhuis). Only those items were included which were clearly classifiable as positive or negative. The items 9, 12, 15, 16, 19, 21, 24, 26, 29, 30, 31, 33, 37, 38, 40, 42, 43, 44 of the FDS and the items 2, 4, 6, 9, 10, 16, 17, 18, 20 of the SDQ-20 yielded the positive dissociative symptom score (i.e., PosDiss). The negative dissociative symptom score (i.e., NegDiss) comprised the FDS items 1, 2, 5, 7, 8, 10,13, 14, 17, 18, 22, 25, 28, 32, 34, 35, 36, 39, 41 and SDQ-20 items 3, 5, 8, 11, 12, 15, 19. Internal consistency was high in both scales at both measurement points (pre-treatment PosDiss: Cronbach's alpha of 0.91; post-treatment PosDiss: Cronbach's alpha of 0.90; pre-treatment NegDiss: Cronbach's alpha of 0.94; post-treatment NegDiss: Cronbach's alpha of 0.93). The same approach as described above was applied to link functional connectivity measures with clinical symptoms. Thus, mean functional connectivity values per network obtained from the group × time point NBS analyses were correlated with the difference values (i.e., pre-treatment value – corresponding post-treatment value) of the aforementioned questionnaires using Spearman's rank correlations.

2.11. Additional statistical analyses

Two (groups) × two (time points) mixed-design ANOVAs were performed for each self-report instrument on clinical symptoms and emotion regulation capacity. For valence and arousal ratings, we ran

two (groups) × two (time points) × four (conditions) mixed-design ANOVAs.

Apart from NBS analyses, all statistical tests were performed using R (version 3.4.0, https://www.r-project.org). For factorial designs we used the afex package (Singmann et al., 2017). Greenhouse-Geisser correction was applied to within-subject factors if the assumption of sphericity was violated. *P*-values are reported two-tailed, and in post-hoc *t*-tests they were adjusted for multiple comparisons using False discovery rate (FDR) correction (Benjamini and Hochberg, 1995). Effect sizes were estimated as Cohen's d (Cohen, 1988) for *t*-tests and as generalized eta^2 (Bakeman, 2005) for main and interaction effects. If effect sizes for network measures were calculated, the mean functional connectivity per subject was included in the analysis. According to Cohen, effect sizes are defined as small (d = 0.2), medium (d = 0.5), and large (d = 0.8; Cohen, 1988). Bakeman suggests defining effect sizes based on generalized eta^2 as small (generalized eta^2 = 0.02), medium (generalized eta^2 = 0.13), and large (generalized eta^2 = 0.26; Bakeman, 2005).

3. Results

3.1. Arousal and valence ratings

The mixed-design ANOVA of the arousal ratings yielded a main effect of group [$F(1/63) = 34.32$, $p < .0001$, generalized eta^2 = 0.25], a main effect of condition [$F(1.55/97.46) = 62.58$, $p < .0001$, generalized eta^2 = 0.10], as well as a group × condition interaction effect [$F(1.55/97.46) = 4.20$, $p = .03$, generalized eta^2 = 0.007]. The mixed-design ANOVA conducted on the valence ratings revealed a main effect of group [$F(1/63) = 5.13$, $p = .03$, generalized eta^2 = 0.04], a main effect of condition [$F(1.53/96.12) = 127.27$, $p < .0001$, generalized eta^2 = 0.22], and an interaction effect time point × condition [$F(1.30/81.85) = 6.74$, $p = .006$, generalized eta^2 = 0.02]. Fig. 2 indicates that patients rated pictures in all conditions and at both measurement points more arousing and more negative compared to controls. Post-hoc *t*-tests of the arousal and valence data can be found in the Supplementary materials.

3.2. NBS functional connectivity analysis

Pre-treatment, controls showed significantly increased functional connectivity in the beta band compared to the patients in the conditions NeutralHumanNatural [$p = .02$, FWE corrected, Cohen's d = 1.04, NBS-specific threshold at $t = 3.0$], UnpleasantNatural [$p = .02$, FWE corrected, Cohen's d = 1.00, NBS-specific threshold at $t = 3.0$], and UnpleasantDownregulation [$p = .04$, FWE corrected, Cohen's d = 0.90, NBS-specific threshold at $t = 2.6$]. Thus, in response to NeutralHumanNatural pictures the patients showed a pre-treatment hypoconnectivity across intra- and interhemispheric connections comprising 21 nodes and 28 edges involving cingulate/prefrontal areas (i.e., dACC/rACC, dorsolateral prefrontal cortex [dlPFC], ventrolateral prefrontal cortex [vlPFC], ventromedial prefrontal cortex [vmPFC]), mesio-/lateral temporal regions (i.e., parahippocampal gyrus/hippocampus, lateral temporal cortex), a posterior parietal region (i.e., supramarginal gyrus), and insular cortex. Regarding the UnpleasantNatural condition, the pre-treatment hypoconnected network encompassed 17 nodes and 21 edges across mainly left to right connections comprising cingulate/prefrontal regions (i.e., dACC/rACC, dlPFC, vlPFC), mesio-/lateral temporal areas (i.e., parahippocampal gyrus/hippocampus, lateral temporal cortex), and insular cortex. In the UnpleasantDownregulation condition, the analysis revealed reduced predominantly right-sided connections between cingulate/prefrontal (i.e., dACC/rACC, dlPFC, vlPFC, vmPFC), parietal (i.e., primary somatosensory cortex, angular gyrus), and mesio- and lateral temporal regions (i.e., parahippocampal gyrus/hippocampus, lateral temporal cortex) and insular cortex in a network distributed over 36 nodes and 58 edges.

In a next step, changes in functional connectivity from the first to the second measurement in these two networks were analyzed. Group × time point interactions showed significant results in the NeutralHumanNatural, the UnpleasantNatural, and the UnpleasantDownregulation condition. A significant functional change was identified in the entire 28-edge network in the NeutralHumanNatural condition, the entire 21-edge network in the UnpleasantNatural condition, and the entire 58-edge network in the UnpleasantDownregulation condition [NeutralHumanNatural: $p = .038$, FWE corrected, Cohen's d = 0.54, no NBS-specific threshold was applied; UnpleasantNatural: $p = .038$, FWE corrected, Cohen's d = 0.51, no NBS-specific threshold was applied; UnpleasantDownregulation: $p = .009$, FWE corrected, Cohen's d = 0.50, no NBS-specific threshold was applied]. These networks are outlined in Fig. 3 and the edges and nodes included in these networks are listed in Supplementary Tables 3–5. The significant interaction effect was driven by a large increase in the mean functional connectivity (i.e., mean of lagged coherence values) from pre- to post-treatment within the patient group in all conditions and a small decrease within the controls in the NeutralHumanNatural condition (see Supplementary Fig. 1). Individual trajectories from pre- to post-treatment are plotted in Supplementary Fig. 2.

Group differences for neural networks as present at the initial measurement had disappeared post-treatment ($p > .05$, no NBS-specific threshold was applied). That is, the patient's pre-treatment neural hypoconnectivity for the conditions Neutral Human Natural, Unpleasant Natural, and UnpleasantDownregulation had normalized post-treatment. Comparing the groups post-treatment on the whole-brain level regarding all experimental conditions and frequency bands did not yield significant neural network differences either.

3.3. Relationship between network and self-report instruments across treatment

None of the correlations with networks and clinical or emotion regulation reports were significant ($p > .05$).

3.4. Treatment-related changes in emotion regulation ability and clinical symptoms

We performed two (groups) × two (time points) mixed-design ANOVAs for each self-report instrument on emotion regulation capacity and clinical symptoms. For patients compared to controls, we observed higher emotion regulation deficits and more clinical symptoms across all measures at either measurement point. Patients exhibited a significant increase in reappraisal values from pre- to post-treatment. Finally, we found a significant treatment-related symptom reduction in the patient group in overall PTSD symptoms (PCL−C), general dissociative symptoms (FDS), negative dissociative symptoms (NegDiss), and depressive symptoms (BDI-II). Details are provided in Table 1.

4. Discussion

We investigated whether patients with cPTSD or a complex dissociative disorder and healthy controls show network differences when they engage in emotion regulation. Furthermore, we explored functional connectivity changes in the patient group following inpatient trauma therapy. Using EEG, we assessed pre- and post-treatment functional connectivity in neural networks associated with explicit (cognitive reappraisal) and implicit (natural) emotion regulation in response to provoking pictorial material. We also investigated whether occurrent treatment-related connectivity changes were related to changes in clinical symptoms.

Compared to controls and prior to trauma treatment, patients exhibited less functional connectivity in the beta frequency band when (1)

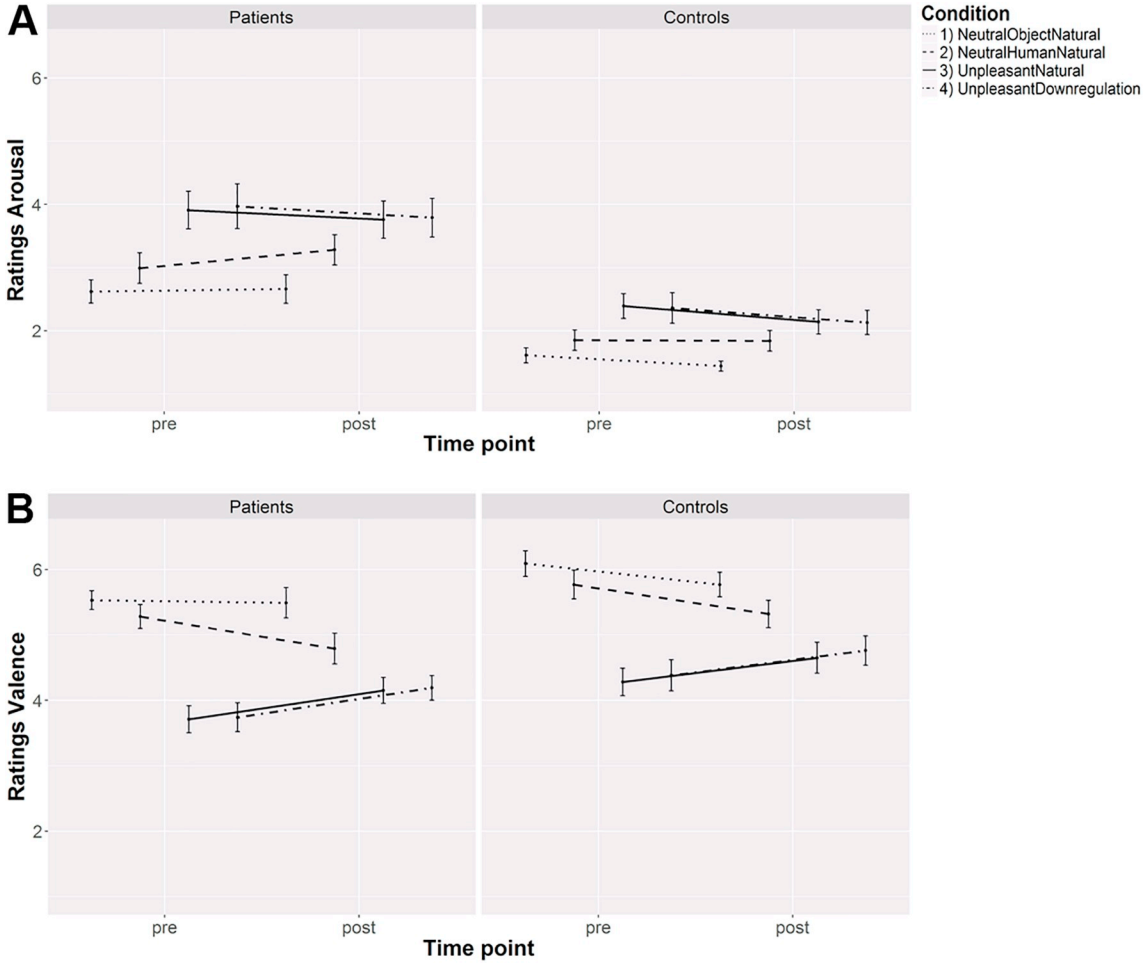

Fig. 2. Ratings within the patients and the controls pre-treatment (pre) and post-treatment (post) in the four conditions. A) arousal ratings, B) valence ratings. Error bars depict ± 1 standard error of the mean.

we instructed them to naturally respond to neutral human and unpleasant pictures or (2) asked them to constrain (i.e., downregulate) their emotional responses to unpleasant pictures using cognitive reappraisal. This difference in connectivity had disappeared after treatment (see Supplementary Tables 3–5 and Fig. 3). Group functional connectivity differences following treatment were not detected regarding any other frequency band. Whereas trauma treatment reduced the subjective trauma symptoms, symptom reduction was not related to network changes.

The functional network change in the condition where patients responded naturally to neutral human pictures comprised cingulate (i.e., dACC, rACC), prefrontal (i.e., dlPFC, vlPFC, vmPFC), mesiotemporal (i.e., parahippocampal gyrus/hippocampus), lateral temporal, and posterior parietal regions. In accordance with the literature, the dACC, dlPFC, vlPFC, posterior parietal cortex, and temporal lobe are consistently engaged during cognitive reappraisal (Buhle et al., 2014; Kalisch, 2009; Kohn et al., 2014). Since brain regions involved in cognitive control such as the dlPFC lack direct connections with the amygdala (Barbas, 2000; McDonald et al., 1996; Stefanacci and Amaral, 2002), it is presently unknown how the involved prefrontal activity can affect amygdala activity. One idea is that prefrontal activity can interfere with the lateral temporal lobes that are associated with memories of fearful events. In turn, the lateral temporal lobes modulate amygdala activity (Buhle et al., 2014). An alternative hypothesis is that the vmPFC engages in reappraisal via connections between cognitive control regions and the amygdala (Delgado et al., 2008; Quirk et al., 2006; Schiller and Delgado, 2010). The vmPFC is involved in implicit forms of emotion regulation, such as reversal learning and fear extinction (Finger et al., 2008; Milad et al., 2007; Schiller and Delgado, 2010).

Our most prominent connectivity finding is a strengthened connection between bilateral dACC and right parahippocampal gyrus/hippocampus, suggesting an interaction between the dACC and regions implicated in memory. Apart from cognitive reappraisal, the dACC has been linked to various processes such as emotional conflict (Egner et al., 2008; Etkin et al., 2006), interoceptive awareness (Critchley et al., 2004a), and generating fear conditioned responses (Etkin and Wager, 2007; LaBar and Cabeza, 2006; Mechias et al., 2010). Parahippocampal gyrus/hippocampal activation is implied in recall, with a right hemispheric predominance for autobiographical (Tulving et al., 1994), affect-laden (Fink et al., 1996), and traumatic memories (Brewin, 2007; Lanius et al., 2004). Taken together, patients in this study showed a pre- to post-treatment increase in functional connectivity for brain regions critically implied in cognitive and emotional re-evaluation, memory, and learning of new associations when naturally responding to neutral human pictures.

The patients' emotional ratings of neutral human faces or interactions (see Fig. 2 and Supplementary materials) and the associated neural network characteristics indicate that the presumed “neutral” cues did not appear neutral but emotional to them. This interpretation is in line with previous research that also revealed this negativity bias in DID patients, particularly when measured as EP (Schlumpf et al., 2013; Seidmann et al., 2014).

In accordance with the notion that patients emotionally engaged in the presumably neutral human pictures, the network in the condition

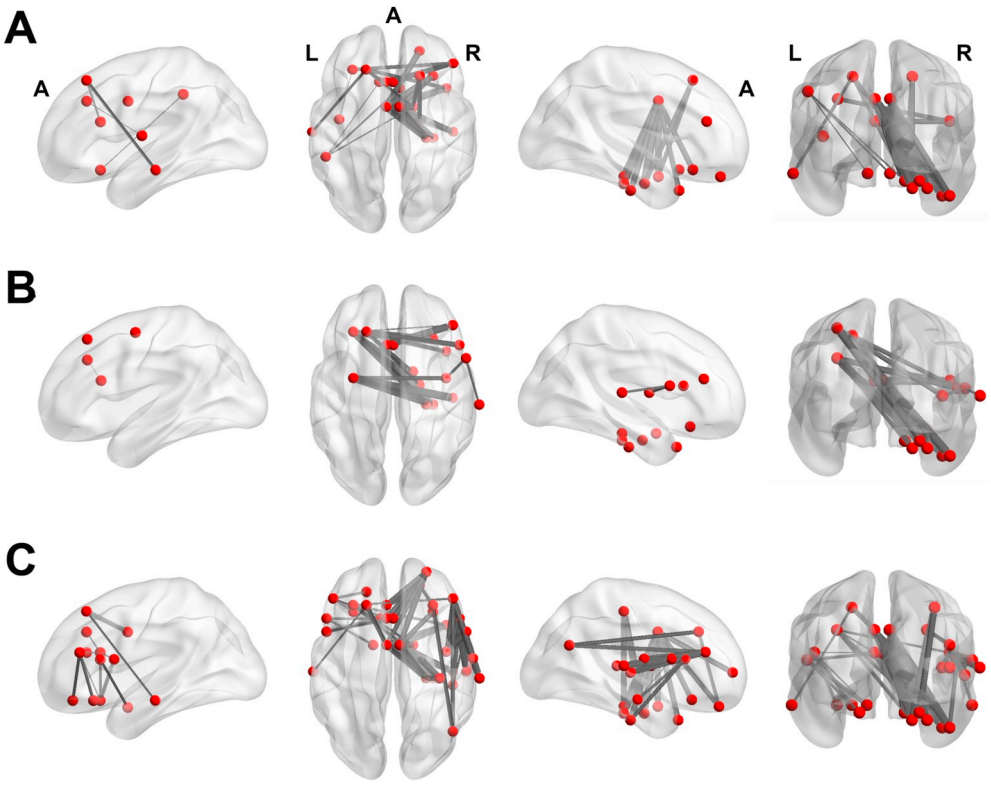

Fig. 3. Functional connectivity increase in the beta frequency band over the course of therapy within the initially reduced network in the patient group (group × time point interaction) in A) the NeutralHumanNatural condition, B) the UnpleasantNatural condition, and C) and the UnpleasantDownregulation condition. The red dots correspond to the nodes, the gray lines depict the connections (edges). The thickness of the lines corresponds to the significance (i.e., t-values) of the single connections [$p < .05$, FWE corrected; no NBS-specific set thresholds were applied]. Left, right, horizontal, and coronal views of the inter- and intrahemispheric connections are outlined. A, anterior, L, left, R, right.

where the patients had to naturally respond to neutral human pictures showed a large overlap with the networks observed in the conditions where patients had to naturally respond to unpleasant pictures and to downregulate their emotional response to unpleasant stimuli. This overlap was particularly present in prefrontal, cingulate, mesiotemporal (i.e., parahippocampal gyrus/hippocampus), and lateral temporal regions and insular cortex. In line with Dunkley and colleagues (Dunkley et al., 2015), our study adds to the evidence that trauma-related disorders are associated with large-scale network disruptions. The areas involved here have been identified as functionally (Badura-Brack et al., 2017; Boccia et al., 2016; Dunkley et al., 2014; Pitman et al., 2012; Rabinak et al., 2011) or structurally (Morey et al., 2012) altered when comparing PTSD patients with healthy controls. Furthermore, treatment studies in PTSD reveal a normalization within these regions following exposure-based therapy (Felmingham et al., 2007; Fonzo et al., 2017; Peres et al., 2007) or training in attentional control (Badura-Brack et al., 2018). Thus, our results may assist to develop a potential biomarker for the diagnosis of trauma-related and dissociative disorders and the monitoring of treatment efficacy.

Although naturally responding to neutral human pictures may share neural features with naturally responding to and reappraising unpleasant stimulus material, condition specific network characteristics could be identified. In the condition where participants had to naturally respond to unpleasant pictures, patients showed more interhemispheric connectivity between left dlPFC and right parahippocampal gyrus/hippocampus following treatment. The left dlPFC is a core region in downregulating negative emotional conditions (Ochsner et al., 2012). Given right hemispheric predominance being associated with the recall of traumatic memories in the right parahippocampal formation, our results may reflect a pre- to post-treatment enhancement of cognitive control over intrusive memories. In addition, the fact that patients rated the unpleasant pictures as significantly less negative following treatment (see Fig. 2B and Supplementary materials) suggests that treatment had helped them to appraise the pictures in a different way and that this effect is in part associated with increased left frontal activity. Left frontal activity has been shown in the literature to be linked with positive mood states (Baxter et al., 1989; Boggio et al., 2009; Canli et al., 1998; George, 2010) and with a positive change in emotional valence ratings of negative pictures (Peña-Gómez et al., 2011). The right vlPFC, particularly the pars opercularis of the right inferior frontal gyrus, has been linked to response inhibition and goal-appropriate response selection (Aron et al., 2004). The prominent involvement of the pars opercularis, when naturally responding to unpleasant pictures, may be associated with the patients' increased ability to engage in the emotionally challenging task. This idea is in line with the investigators' observation and the patients' reports that they put a lot of effort in performing the experiment and suggests a treatment-related improvement in tolerating trauma-related cues.

The network subserving the downregulation of emotional responses in reaction to unpleasant pictures was more comprehensive compared to the other two networks. It may be attributable to the fact that constraining emotional responses is harder than the implicit regulation of emotional responses and consequently recruits additional cognitive control resources. The functional connectivity change in the UnpleasantDownregulation condition, in particular within the connections with the highest lagged coherence values, was predominantly localized on the right hemisphere. A meta-analysis revealed that cognitive reappraisal engages the lateral ventral and dorsal PFC to a greater extent on the right than on the left hemisphere (Ochsner et al., 2012). Thus, our data suggest that the patients' ability to cognitively reappraise unpleasant cues increased from pre- to post-treatment. Remarkably, the strongest functional connectivity was observed between the vlPFC and the insular cortex. The insular cortex is a region with reciprocal connections to cortical areas such as the frontal lobe and subcortical areas such as the amygdala (Gogolla, 2017). Also, the insula comprises a broad range of functions (Gogolla, 2017) and plays a key role in mediating conscious access to emotional states (Craig, 2002, 2003, 2009), awareness of emotionally salient stimuli (Critchley et al., 2004b), and recall of emotional memories (Phan et al., 2002). These findings suggest that the insula, particularly the right-lateralized anterior insula (Craig, 2002, 2009; Critchley et al., 2004b), constitutes a neural hub that is linked to the ability to consciously experience emotional and bodily

states. Other regions involved in the perception of bodily states (i.e., interoception) and the subjective awareness of feelings are the right somatosensory cortices, the ACC, and the orbitofrontal cortex (Adolphs et al., 2000; Critchley, 2005, 2009; Critchley et al., 2004b; Damasio, 1999; Damasio et al., 2000). In our study, these regions were part of the large-scale network mediating the cognitive reappraisal of unpleasant pictures and they showed a significant pre- to post-treatment strengthening in functional connectivity with lateral and medial prefrontal regions in the patient group. Therefore, the results may reflect increased integration of neural regions associated with awareness of emotional and bodily states and the regulation of emotional reactivity following therapy.

In line with our hypotheses, we observed a normalization of networks associated with implicit and explicit forms of emotion regulation. Functional connectivity, the method applied here, only refers to the statistical dependency of signals from distinct areas (Friston, 2011). Since we cannot directly infer from our connectivity results the directions of influences of brain regions, other interpretations are possible. We speculate though that the increased connectivity between fear processing/memory retrieval regions to prefrontal areas reflects enhanced cognitive-emotional integration. This idea is in line with a recent real-time fMRI neurofeedback study in PTSD patients that tested the directions of influences (i.e., effective connectivity) between the PFC and the amygdala (Nicholson et al., 2017b). Downregulation of the amygdala activity using cognitive reappraisal in response to personalized citations from a traumatic event was associated with increased bidirectional influences between the PFC and the amygdala. Consistent with our present findings, effective emotion regulation may thus be associated with the integration of regions involved in cognition and emotional reactivity. This idea is further supported by a resting-state effective connectivity study in PTSD subtypes showing that emotional dysregulation is reflected by a unilateral influence of a brain area on another region. Underregulation of affect was characterized by predominantly bottom-up influences from subcortical areas to prefrontal areas, whereas pathological overregulation was associated with mainly top-down influences from prefrontal to subcortical areas (Nicholson et al., 2017a). Furthermore, Sripada and colleagues summarize that most studies investigating functional connectivity in PTSD patients observed lowered connectivity strength in emotion generation and regulation circuits compared with healthy controls (Sripada et al., 2012). We posit that, in our study, treatment related strengthening of networks and their functional coupling is clinically relevant and reflects recovery of aberrant neural activity in complex trauma and dissociative patients.

The patient group experienced a significant therapy-related reduction in general dissociative symptoms (FDS), negative dissociative symptoms (NegDiss), PTSD symptoms (PCL−C), and depressive symptoms (BDI-II). However, they did not experience less somatoform dissociative symptoms (SDQ-20), positive dissociative symptoms (PosDiss), and trait anxiety (STAI-T; see Table 1). Although we report the results of a clinical observation study, our findings add to the evidence from cross-sectional (Brand et al., 2009a) and longitudinal treatment outcome studies (Brand et al., 2013; Jepsen et al., 2014) that complex trauma and dissociative patients can profit from therapy by well-trained trauma therapists and other clinical personnel in a phasic, trauma- and dissociation-focused treatment setting across various clinical symptoms. The reduction in the severity of negative dissociative symptoms indicates that patients were less depersonalized, derealized, and emotionally numbed (i.e., overregulated) following therapy. The fact that positive dissociative symptoms did not diminish indicates that the involved intrusive and re-experiencing symptoms need further treatment. This is in line with the observation that post-treatment patients continued to have higher scores for all clinical measures than controls. They improved clinically, but did not achieve mental health (see Table 1).

From treatment intake to discharge, there was a significant increase in the patients' use of cognitive reappraisal (ERQ Reappraisal), whereas their use of expressive suppression (ERQ Suppression) and emotion regulation difficulties (DERS) did not change significantly (see Table 1). Meta-analyses suggest that the overuse of maladaptive emotion regulation strategies (i.e., expressive suppression) has more impact on overall psychopathology (Aldao et al., 2010) and PTSD (Seligowski et al., 2015) than the nonuse of efficient strategies (i.e., cognitive reappraisal). Thus, our patients' outcome data may reflect an intermediate step in therapy in which patients as ANP have increased their ability to re-evaluate trauma-related cues, but in which they continue to deal with intense emotions and associated EPs in ineffective ways. Continuation of the treatment is thus indicated.

We exclusively observed functional connectivity changes in the beta frequency band (i.e., 12.5–30 Hz). The functional role of beta oscillatory processes has been less intensely analyzed compared to other frequency bands (Engel and Fries, 2010; Huster et al., 2013). However, an increasing number of EEG studies document that beta oscillatory responses are involved in reacting to cues that elicit emotions (Güntekin and Başar, 2007a, 2007b, 2010; Miskovic et al., 2010; Woodruff et al., 2011), attentional arousal (Kamiński et al., 2012), and stimulus-driven salience (Kisley and Cornwell, 2006). A complementary interpretation is that our results reflect an improvement in inhibitory control, as beta waves have been found to be associated with response inhibition (Huster et al., 2013). Thus, the strengthening of functional coupling in large-scale networks in the beta frequency range may express the patients' increased emotional/attentional (i.e., bottom-up) and cognitive (i.e., top-down) involvement in the stimulus set following therapy.

4.1. Limitations

There are several limitations to this study. First of all, as a naturalistic clinical observation study it comes with the cost of potential confounding factors such as psychotropic medication or comorbid disorders. However, for these very reasons patients with high comorbidity such as complex trauma and dissociative disorders are typically excluded from randomized control trial (RCT) studies (Bradley et al., 2005; Brand et al., 2009b). Further, exclusion of medicated participants is not feasible in patients with complex disorders. Nonrandomized outcome studies are therefore needed to examine the treatment effectiveness in these disorders with high ecological validity and generalizability (American Psychological Association's Presidential Task Force on Evidence-Based Practice, 2006; Brand et al., 2009a). Due to organizational constraints we were not in the position to include a waiting list patient control group. Subsequent treatment studies should enroll this additional subgroup to clearly disentangle intervention effects from time effects. In addition, research is clearly needed to examine effects of pharmacological treatment on EEG functional connectivity. Yet, we did not control for potential treatment effects of pharmacotherapy in this study since all patients received a heterogeneous medical therapy and thus, no directional effects can be expected. Furthermore, it was beyond the aims of the present project to disentangle the impact of any treatment modality (i.e., pharmacotherapy, psychotherapy, non-verbal therapy, body-related therapy). Rather, we evaluated effects of a trauma-focused inpatient treatment as a whole. Future studies will need to run a directed (i.e., effective) connectivity analysis that allows to investigate causal effects of one area on another in a functional brain network (Friston, 2011). In addition, complex trauma and dissociative disorder patients should be tested as ANP and as (different types of) EP in order to address the ways in which these various prototypical parts deal with intense emotions in more depth. As patients showed substantial residual symptoms, a long-term follow-up study is needed to assess sustained alterations. Finally, the development of a questionnaire that measures positive and negative dissociative symptoms is required to further investigate the relationship between emotion regulation difficulties and dissociative symptoms.

4.2. Conclusions

To conclude, the present study suggests that inpatient phase-oriented and multimodal treatment for complex trauma and dissociation is associated with functional connectivity changes in networks mediating explicit and implicit forms of emotion regulation, as well as with a reduction in negative dissociative symptoms and other kinds of trauma-related psychopathology. The reduction of negative dissociative symptoms indicates that this kind of treatment helps individuals with cPTSD and dissociative disorders and as ANP to tolerate arousal and distress (i.e., to reduce emotional overregulation). Although eight weeks of treatment were beneficial, much of the patients' pathology remained. Consistent with recurrent clinical evidence (for example see Nijenhuis, 2017) overcoming complex trauma and dissociation is possible but commonly takes a long breath.

Declaration of interest

None.

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Data sharing statement

Due to the sensitive nature of the patients enrolled in the study, participants were assured that data would remain confidential and would not be shared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101807.

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