Unraveling PTSD and comorbid personality disorders:

insights from neuroimaging and clinical effect studies

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Unraveling PTSD and comorbid personality disorders: insights from neuroimaging and clinical effect studies

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In gedachten sta ik op het dak een dak

Met het gewicht van de wereld in mijn rechterzak

En ik hoop dat 'k 't ergste heb gehad

Froukje, Leeg Restaurant

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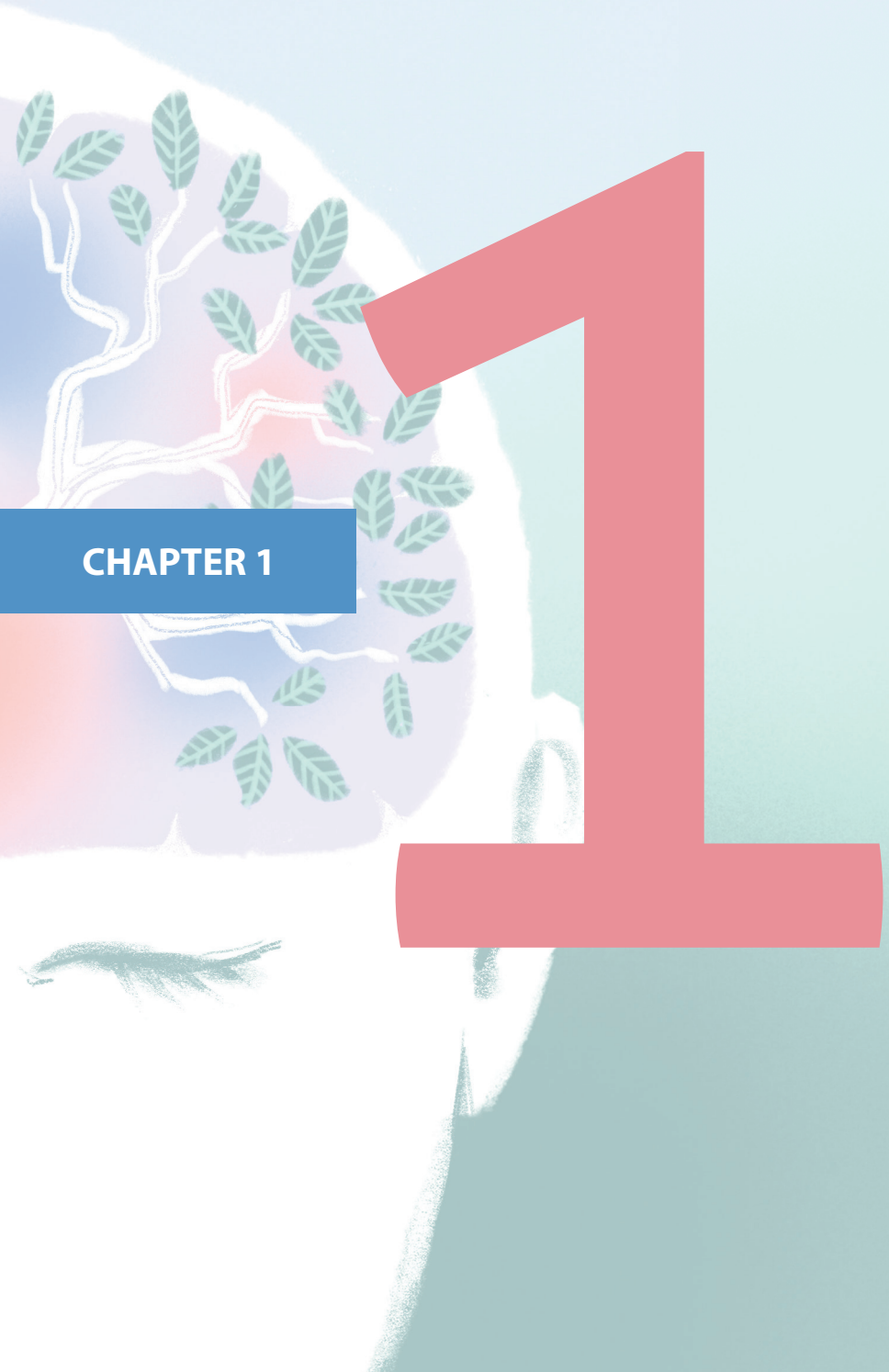

CHAPTER 1

1

General introduction

In this thesis, I report on studies we performed in individuals with posttraumatic stress disorder (PTSD) and comorbid personality disorders. Specifically, the focus is on neurobiological correlates of the disorders and the effect of psychotherapy on these correlates.

General introduction to PTSD and trauma-focused treatment

About 70% of people experiences one or more traumatic events during their lifetime and around 4% of all adults develops PTSD (1). The PTSD diagnosis consists of four symptom clusters: re-experiencing/intrusion, avoidance, negative alterations in mood and cognition and alterations in arousal and reactivity (2). Dissociative symptoms (depersonalization and/or derealization, feeling detached from your body or experiencing unreality of the world around you) can be specified (APA, 2013). See Table 1 for the full list of Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5) PTSD criteria. There is a high comorbidity between PTSD and other disorders. The most common comorbidities include mood disorder, substance use disorder and anxiety disorders (3); around half of all PTSD patients fulfill diagnostic criteria for a Major Depressive Disorder (3, 4). Comorbidity with personality disorders is around 35% (5), with paranoid, borderline and cluster C personality disorders being the most prevalent.

Current guidelines for PTSD include prolonged exposure therapy, trauma-focused cognitive behavioral therapy (CBT) and eye-movement desensitization and reprocessing (EMDR) as first line treatments (6, 7). Previous studies show that psychotherapy has better long-term effects than pharmacotherapy in PTSD (8) and in psychotherapy, there is robust evidence for the efficacy of both EMDR and CBT-based treatments (9, 10). All psychotherapy treatments for PTSD include exposure to the traumatic memory and cognitive restructuring and some form of emotion regulation skills (11).

For borderline personality disorder (BPD), psychotherapy is also the first-line treatment (12, 13). Following the clinical guidelines for BPD, strong evidence exists for efficacy in dialectical behaviour therapy (DBT), mentalization-based therapy, schema therapy (ST) and transference-focused psychotherapy (12, 14). For cluster C personality disorders (CPD), there is no guideline for treatment, but studies show that schema therapy can be effective (15, 16). Although precise mechanisms differ, both DBT and ST aim to improve emotion regulation (17).

There is some evidence that the presence of a comorbid personality disorder can attenuate the effect of trauma-focused treatment (18) and BPD is associated with higher dropout than PTSD: in PTSD, an overall dropout rate of 18% was found (19), while studies in BPD show a dropout of 43% (20, 21). It is a clinical challenge how to diminish dropout. One of the considerations is whether PTSD symptoms should be addressed first or to address PTSD symptoms concurrent with personality disorder symptoms. The PROSPER (PRediction and Outcome Study in PTSD and PERsonality disorders) trial was designed to study the efficacy of two treatment strategies (trauma-focused therapy only, or combined trauma-focused therapy and personality treatment) for individuals with PTSD and comorbid borderline and/or cluster C personality disorders (BPD/CPD; see Table 1 for a full list of DSM-5 criteria). See Box 1 for an explanation of the study design.

Table 1. Diagnostic criteria for posttraumatic stress disorder, cluster C and borderline personality disorders

Disorder	Criteria from the DSM-5 (APA, 2013)
Posttraumatic stress disorder (PTSD)	A. Exposure to actual or threatened death, serious injury or sexual violence (required) B. Re-experiencing (one required of recurrent intrusive memories, nightmares, flashbacks, psychological distress or marked physiological reactions to internal or external cues) C. Persistent avoidance (one required of avoidance of internal or external triggers) D. Negative alterations in cognitions and mood (two required of dissociative amnesia, exaggerated negative beliefs about oneself, others or the world, distorted cognitions about guild, persistent negative emotional state, diminished interest, feelings of detachment or inability to experience positive emotions) E. Alterations in arousal and reactivity (two required of irritable behavior, self-destructive behavior, hypervigilance, exaggerated startle response, concentration or sleep problems) F. Duration more than 1 month G. Clinically significant distress or impairment H. Not attributable to effects of a substance or medical condition Specify whether 1) with dissociative symptoms (depersonalization/derealization), 2) with delayed expression
Personality disorders – general criteria	An enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture, in two or more of the following areas: · Cognition · Affectivity · Interpersonal functioning. · Impulse control. This pattern is durable and pervasive across situation, stable and of long duration (onset in adolescence or early adulthood).
Cluster C personality disorders (CPD)	
Avoidant PD	Four or more of: · Avoidance of occupation-related activities due to fear of criticism or rejection · Unwillingness to get involved with others unless certain of being liked · Showing restraint within intimate relationships because of fear of being shamed · Inhibited in new interpersonal situations because of feelings of inadequacy · Views self as socially inept, unappealing or inferior · Unusually reluctant to take personal risk because of possible embarrassment

Table 1. Continued

Disorder	Criteria from the DSM-5 (APA, 2013)
Dependent PD	Five or more of: · Difficulty making everyday decisions without excessive amount of advice and reassurance · Needs others to assume responsibility for most major areas of their life · Difficulty expressing disagreement for fear of loss of support · Difficulty initiating projects or doing things on their own (because of lack of self-confidence) · Goes to excessive lengths to obtain support · Feels uncomfortable of helpless alone because of fear of being unable to care for themselves · Immediately seeks another relationship when a close relationship ends · Unrealistically preoccupied with fears of being left to take care of themselves
Obsessive-compulsive PD	Four or more of: · Preoccupied with details, order, organization · Perfectionism that interferes with task completion · Excessively devoted to work and productivity · Overconscientious and inflexible about matters of morality, ethics or values · Unable to discard worn-out or worthless objects even without sentimental value · Reluctant to delegate tasks or work with others · Adopts a miserly spending style · Shows rigidity and stubbornness
Borderline PD (BPD)	Five or more of: · Frantic efforts to avoid abandonment · A pattern of unstable and intense interpersonal relationships · Identity disturbance · Impulsivity (at least two areas) · Recurrent suicidal behavior · Affective instability · Chronic feelings of emptiness · Inappropriate, intense anger · Stress-related paranoid or dissociative symptoms

BOX 1: the PROSPER study

The PROSPER (PRediction and Outcome Study in PTSD and PERsonality disorders) study consists of two parallel randomized clinical trials (RCTs); one for participants with PTSD and comorbid BPD, one for participants with PTSD and comorbid CPD. In both trials, participants are randomized to either trauma-focused treatment (12-18x) or trauma-focused treatment (12-18x) plus a year of group-based personality disorder treatment., see Figure 1 for a brief overview of the study design. For an exact description of the study, see Snoek, Beekman (22) for the PTSD+BPD trial and van den End, Dekker (23) for the PTSD+CPD trial. In total, 254 participants were included. For a subset (n=89) of these participants, (functional) magnetic resonance imaging ((f)MRI) brain scans were obtained, as well as for an additional 30 control subjects. This subset is the basis for the studies in this thesis. In **Chapter 2**, the design of this imaging substudy is described in more detail.

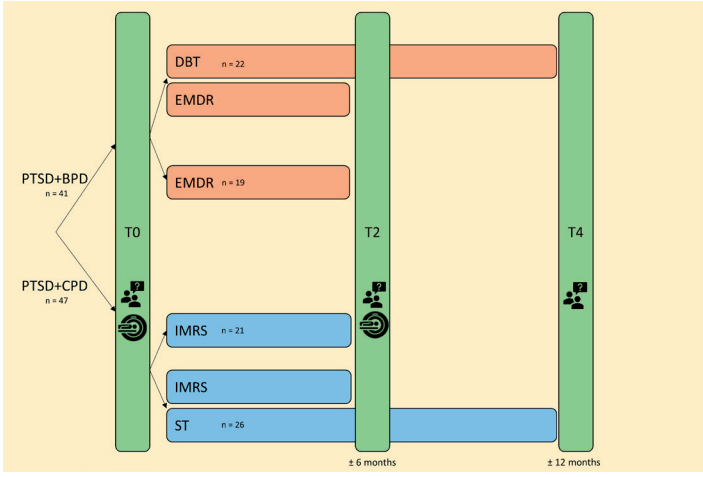

Figure 1. Basic design of PROSPER study

Neurobiological model of PTSD and comorbid PD

There has been a wealth of research on the neurobiological correlates of PTSD. The models for emotional dysregulation in PTSD have been updated over time. In the introduction to **Chapter 4**, we give a short overview of the development of these models. Very briefly, limbic areas (e.g. amygdala, insula) are associated with bottom-up identification of emotional stimulus aspects and automatic regulation, while prefrontal areas (e.g. prefrontal cortex, dorsal anterior cingulate cortex (dACC)) are involved with effortful, top-down regulation of emotions (24). These areas do not work in isolation but are connected in networks. Two neurobiological subtypes of PTSD have been described: a re-experiencing/hyperarousal subtype and a dissociative subtype (25). In the hyperarousal subtype, individuals experience mainly re-experiencing and hyperarousal symptoms and there is high activity in limbic areas and impaired top-down control on

the limbic areas by prefrontal areas. In the dissociative subtype, individuals experience mainly numbing and dissociation symptoms and there is too much control over limbic areas by prefrontal areas resulting in low limbic activity. Later models have expanded on these ideas and have incorporated a network approach. These models include alterations of the salience, central executive and fronto-limbic circuits in PTSD compared to control subjects (26). A few important brain areas in these circuits that have shown aberrant activation in PTSD are the amygdala, insula, dACC, dorsolateral prefrontal cortex (dlPFC) and posterior cingulate cortex (26, 27).

Although there is a lot of neuroimaging research in PTSD, literature on neuroimaging in PTSD and comorbid personality disorders is scarce. However, there are some imaging studies in personality disorders. A recent review about functional magnetic resonance imaging (MRI) findings in PD shows that the limited functional neuroimaging research in PD focuses on BPD (28). Meta-analyses on task-based imaging show altered activation in BPD in the amygdala, ACC, inferior frontal gyrus, superior temporal sulcus and insula, among other areas (27, 29). With regard to the amygdala, there are contradicting findings in the direction of the activation from meta-analyses; Ruocco, Amirthavasagam (30) found lower amygdala activation in BPD compared to controls, while Schulze, Schulze (28) found higher activation. Symptoms of dissociation, medication use and the imaging contrasts used in the tasks may contribute to these conflicting findings (31). Neuroimaging studies in CPD are scarce. In avoidant PD, Zarnowski et al., (28) identified only two task-based MRI studies with avoidant PD as primary group of interest and a few studies with CPD as a control group for BPD. These studies have shown lower dorsal ACC, inferior frontal gyrus, parahippocampal gyrus, and thalamus activation compared to a control group (32). In contrast to control subjects, Koenigsberg et al., (33) found no increase in dorsal ACC activation in individuals with avoidant personality disorder while viewing repeated versus novel pictures. Denny et al., (34) found heightened amygdala reactivity during reappraisal anticipation in avoidant personality disorder compared to control subjects. To the best of our knowledge, there are no task-based MRI studies in individuals with a dependent personality disorder. Lochner and colleagues (35) wrote a review about the neurobiology of obsessive-compulsive personality disorder and found no task-based functional imaging studies.

For PTSD and comorbid PDs, neuroimaging literature is also scarce. Kraus et al., (36) found more amygdala deactivation during pain stimulation in participants with BPD and PTSD, compared to BPD only. In Ludäscher et al., (37), participants with PTSD and BPD showed higher activation in a dissociation-inducing script versus a neutral script in the superior frontal gyrus, inferior frontal gyrus, pre- and postcentral gyrus and dorsal cingulate cortex. These two studies provide some first insight into the neurobiological

underpinnings of PTSD and comorbid BPD, but more research is needed for a comprehensive model and to understand treatment effects in this group.

Research aims and thesis outline

In summary, there are some studies on the effect of treatment on brain function in individuals with PTSD and individuals with BPD (see also **Chapters 4** and **5**), but not in people with both PTSD and comorbid BPD or CPD. This thesis aims to bridge part of this knowledge gap by improving our understanding of 1) the neurobiological correlates of PTSD with comorbid borderline and/or cluster C personality disorders, 2) the effect of psychotherapy on these neurobiological correlates, and 3) factors that predict treatment dropout. In **Chapter 2** we describe the design of the PROSPER neuroimaging sub-study.

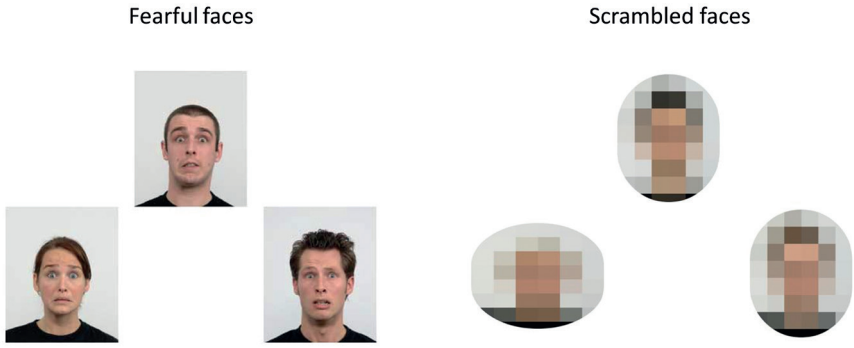

Figure 2. Example trials from the Emotional Faces Task

We used data from this study, and specifically the emotional faces task (see Figure 2) to answer the following research questions:

Does a comorbid personality disorder (BPD, CPD or both BPD and CPD) influence brain activation during emotional processing in PTSD participants?

In **Chapter 3**, we answer this question of the influence of comorbid PD on brain activation by analyzing baseline data from a sample of PTSD participants with comorbid borderline and/or cluster C personality disorders from the PROSPER study. We studied differences in task activation between brain areas from the emotion processing network and at the association between brain activation and clinical measures with both frequentist and Bayesian analysis methods (see Box 2 for a short introduction to Bayesian analyses). We expected higher activation in limbic areas and lower activation in emotion regulation areas in the PTSD+PD groups compared to controls. Furthermore, we expected more

dysfunction in the group with PTSD+BPD+CPD compared to the other groups. Finally, we expected an association between these limbic and emotion regulation areas and several symptom severity measures.

Box 2: Bayesian Multilevel Modeling

Bayesian analyses are a relatively novel technique for neuroimaging analyses. Contrary to traditional frequentist statistical analysis, Bayesian multilevel modeling (BML) is used to estimate the probability of the hypothesis given the data. We used the Region-Based Analysis program from Chen, Xiao (38) for our BML analyses. A posterior distribution is calculated with both the empirical data and prior expectations and summarized with a positive posterior probability or P+ value. In neuroimaging, BML allows for incorporating shared information across regions instead of analyzing them all separately. There is no (arbitrary) cutoff point for a significant effect, but the further the median of the posterior distribution is shifted from zero, the stronger the effect. As a guideline, P+ values of >.90 or <.10 can be interpreted as moderate support for an effect, values of >.95 or <.05 as strong and >.975 or <.025 as very strong.

How does psychotherapy affect activation in brain areas involved in negative emotion processing in PTSD?

In **Chapter 4**, we study the effect of psychotherapy on brain activation by conducting a seed-based *d* mapping meta-analysis of existing studies. We meta-analyzed 12 studies that performed pre- and post-psychotherapy imaging with a negative emotional processing task in participants with PTSD. Additionally, we performed a meta-regression to assess the relationship between change in brain activation and improvement of PTSD symptoms.

In **Chapter 5**, we investigated changes in brain activation after either trauma-focused treatment or trauma-focused treatment + personality treatment in the PROSPER sample. We also studied the relation with change in clinical measures. We hypothesized that activation in emotion regulation areas would decrease after trauma-focused treatment, with an additional decrease in activation in participants who also received personality treatment. We also expected that change in brain activation was related to improvement of symptom severity. As secondary analyses, we studied differential change in brain activation after treatment for responders and non-responders, and the effect of medication status.

What factors predict treatment dropout in participants with PTSD and comorbid personality disorders?

In **Chapter 6**, we use a broad range of potential clinical and demographic predictors to predict treatment dropout based on the two PROSPER RCT samples combined. Demographic, symptom severity, patient-therapist and therapist variables for 255 participants with PTSD/personality disorders are used in a model to predict the number of sessions participants attended.

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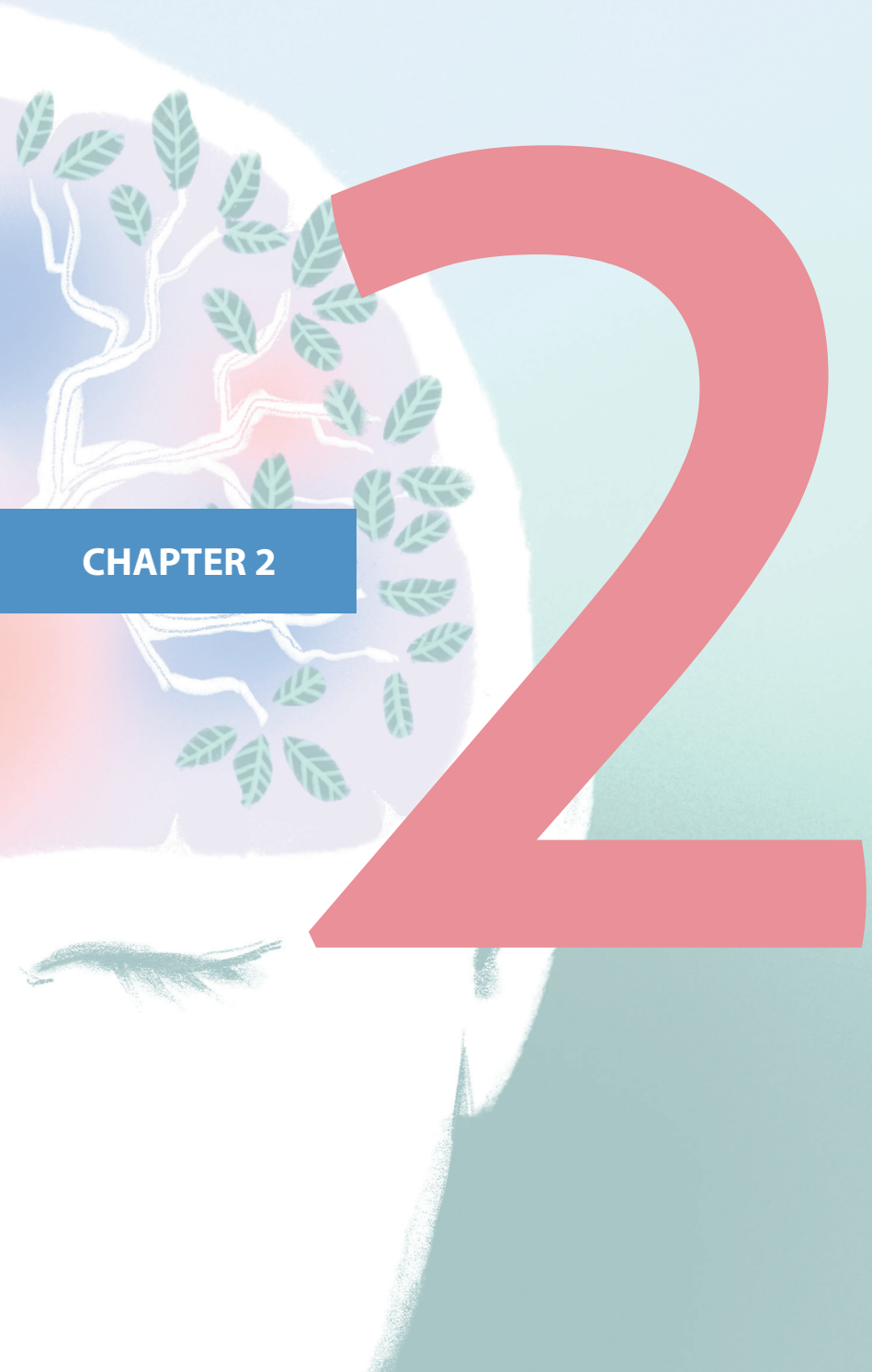

CHAPTER 2

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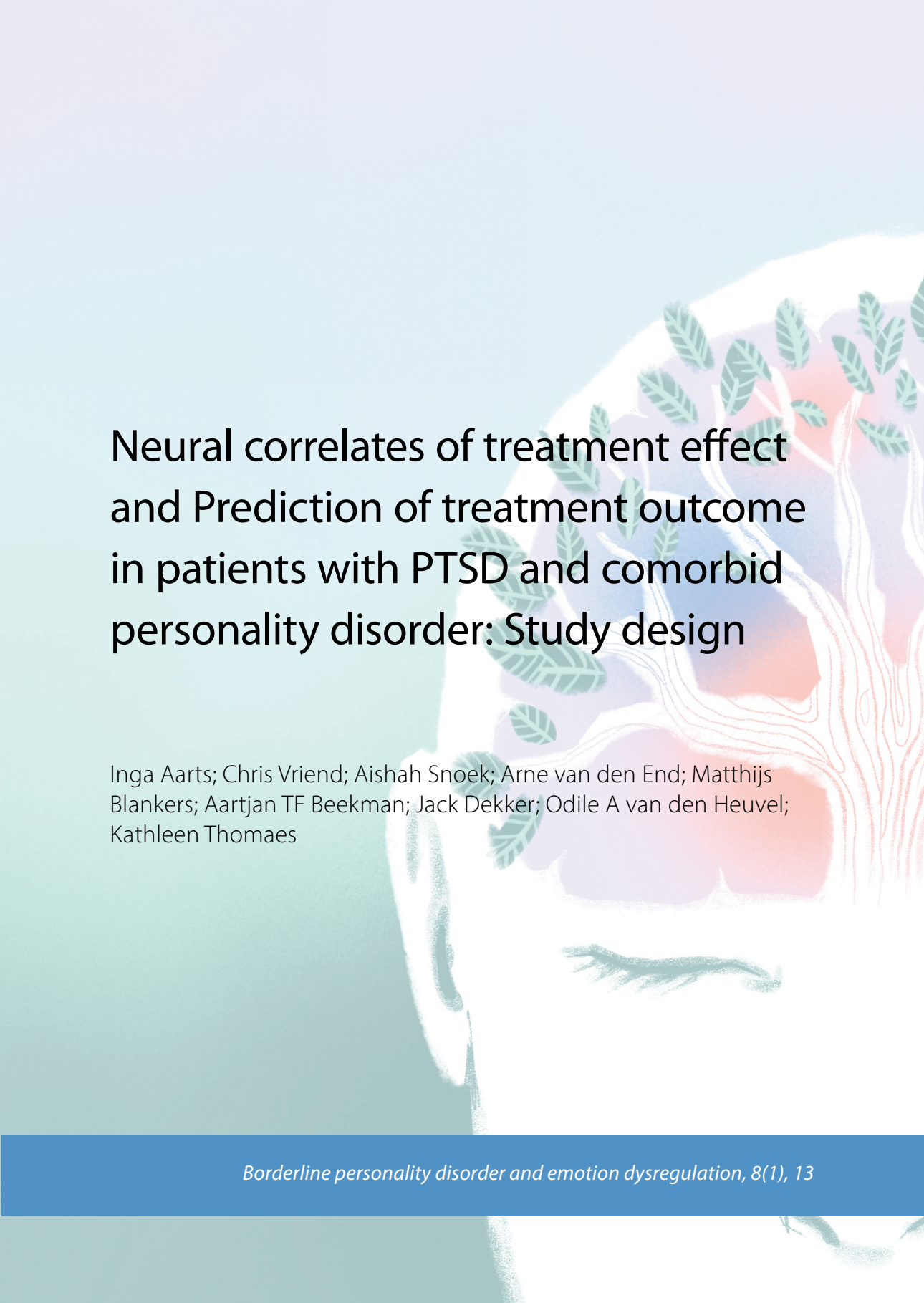

Neural correlates of treatment effect and Prediction of treatment outcome in patients with PTSD and comorbid personality disorder: Study design

Inga Aarts; Chris Vriend; Aishah Snoek; Arne van den End; Matthijs Blankers; Aartjan TF Beekman; Jack Dekker; Odile A van den Heuvel; Kathleen Thomaes

Borderline personality disorder and emotion dysregulation, 8(1), 13

Abstract

Background Neural alterations related to treatment outcome in patients with both post-traumatic stress disorder (PTSD) and comorbid personality disorder are unknown. Here we describe the protocol for a neuroimaging study of treatment of patients with PTSD and comorbid borderline (BPD) or cluster C (CPD) personality disorder traits. Our specific aims are to 1) investigate treatment-induced neural alterations, 2) predict treatment outcome using structural and functional magnetic resonance imaging (MRI) and 3) study neural alterations associated with BPD and CPD in PTSD patients. We hypothesize that 1) all treatment conditions are associated with normalization of limbic and prefrontal brain activity and hyperconnectivity in resting-state brain networks, with additional normalization of task-related activation in emotion regulation brain areas in the patients who receive trauma-focused therapy and personality disorder treatment; 2) Baseline task-related activation, together with structural brain measures and clinical variables predict treatment outcome; 3) dysfunction in task-related activation and resting-state connectivity of emotion regulation areas is comparable in PTSD patients with BPD or CPD, with a hypoconnected central executive network in patients with PTSD+BPD.

Methods We aim to include pre- and post-treatment 3T-MRI scans in 40 patients with PTSD and (sub)clinical comorbid BPD or CPD. With an expected attrition rate of 50%, at least 80 patients will be scanned before treatment. MRI scans for 30 matched healthy controls will additionally be acquired. Patients with PTSD and BPD were randomized to either EMDR-only or EMDR combined with Dialectical Behaviour Therapy. Patients with PTSD and CPD were randomized to Imaginary Rescripting (ImRs) or to ImRs combined with Schema Focused Therapy. The scan protocol consists of a T1-weighted structural scan, resting state fMRI, task-based fMRI during an emotional face task and multi-shell diffusion weighted images. For data analysis, multivariate mixed-models, regression analyses and machine learning models will be used.

Discussion This study is one of the first to use neuroimaging measures to predict and better understand treatment response in patients with PTSD and comorbid personality disorders. A heterogeneous, naturalistic sample will be included, ensuring generalizability to a broad group of treatment seeking PTSD patients.

Trial registration Clinical Trials, NCT03833453 & NCT03833531. Retrospectively registered, February 2019. Available through https://clinicaltrials.gov/ct2/show/NCT03833453 & https://clinicaltrials.gov/ct2/show/NCT03833531

Key words borderline personality disorder; cluster C personality disorder; treatment; neuroimaging; prediction

Introduction

Posttraumatic stress disorder (PTSD) is a common mental disorder with a lifetime prevalence of approximately 4-8% (1-3). PTSD can develop after experiencing a traumatic event and involves symptoms of re-experiencing, avoidance, hyperarousal and alterations in mood and cognition (4). Abnormal fear conditioning and extinction learning are important processes in the pathophysiology of PTSD (5). Psychotherapy for PTSD (trauma-focused therapy, TFT) focuses on normalizing these processes through exposure to the patients' traumatic memories and trauma-related cues. TFT has moderate to large effect sizes (6, 7). Previous trials have often excluded comorbidity such as suicidality, so despite the high incidence of comorbidity in PTSD, the efficacy of TFT in this heterogeneous group is not well known. As many as 35% of PTSD patients have a comorbid personality disorder, such as borderline personality disorder (BPD) or avoidant, dependent or obsessive-compulsive (cluster C, CPD) personality disorders (8). One study has shown that TFT in patients with PTSD and personality disorders (BPD was excluded) is effective (9). There is also evidence that TFT is effective in patients with PTSD+BPD (10), although a recent meta-analysis shows lower effect sizes for TFT in patients with PTSD and comorbid personality disorders, compared to patients with PTSD-only (11). Well-established therapies for BPD and CPD are group-based dialectical behavioral therapy (DBT; 12) and schema focused therapy (SFT; 13), respectively.

The amygdala has long been thought to play a crucial role in the pathophysiology of PTSD, because of its involvement in the processing and appraisal of emotional stimuli (14, 15) and its role in the salience network (SN) and limbic network (16). Although there is some evidence that suggests a smaller volume of the amygdala in PTSD patients (17), other studies found no differences in its morphology compared to healthy controls (18, 19). In contrast, amygdala volume is consistently lower in BPD patients relative to healthy controls (14), while to the best of our knowledge only one study has been conducted in CPD (20), showing no difference in amygdala volume between patients with avoidant personality disorder and healthy control subjects.

In functional MRI studies, PTSD is associated with hyperreactivity of the amygdala in patients who watch trauma-related stimuli and more generic salient stimuli such as emotional pictures or faces (21, 22). In BPD, one meta-analysis showed *decreased* activity in the amygdala and associated networks (23), while another meta-analysis (24) showed *increased* left amygdala activity during tasks with a negative emotion versus neutral condition. A possible explanation for these contrasting findings is the heterogeneity of the samples. In line with earlier findings (25), the hyperactivity of the amygdala was not observed in medicated patients (24). Psychotherapy for PTSD or BPD has been shown to decrease the hyperactivation of the amygdala (26, 27). This decreased hyperactivation

was associated with a decrease in clinical symptoms in PTSD (26) and improved emotion regulation in BPD (28, 29).

Beyond the amygdala, PTSD and personality disorders are also associated with dysfunction of brain areas such as the anterior cingulate cortex (ACC), dorsolateral and dorsomedial prefrontal cortex (dlPFC/dmPFC), insula and the hippocampus (e.g. 30, 31, 32). These regions are all involved in emotion processing and regulation (14, 33), processes that treatments for personality disorders aim to improve (34). There is some evidence that shows that activity in the above-mentioned brain areas normalizes after treatment. For example, hyperactivation of the ventromedial PFC and ACC normalized after psychotherapy for PTSD (26), and in BPD activation of the ACC decreased after dialectical behavior therapy (27).

Structural and functional connectivity between brain areas is also disrupted in PTSD and personality disorder. In PTSD, as compared to healthy controls, a hyperconnected SN and less well interconnected default mode network (DMN) are found (35-37). Compared to healthy controls, BPD patients consistently showed hyperactivity of the posterior cingulate cortex (PCC) – a major hub of the DMN – and hypo-activity of the dorsolateral prefrontal cortex (dlPFC) during resting-state functional magnetic resonance imaging (fMRI; 23, 24). BPD patients also showed increased resting state connectivity of the frontopolar cortex and insula (38). To our knowledge, no neuroimaging connectivity studies have yet been performed in PTSD patients with comorbid personality disorder.

Possible predictors for treatment success in PTSD include clinical features such as the severity of dissociative symptoms (39), baseline PTSD severity and presence of comorbid depressive disorder (see 40, 41 for recent systematic reviews). Previous studies have also shown that neuroimaging measures can be used to predict TFT efficacy, using resting-state functional connectivity measures (42-44), task-related activation patterns (45-49), and regional brain volume (50, 51). In these studies, the brain areas or networks that are involved in the pathophysiology of PTSD, such as the amygdala, insula and ACC, are also generally the ones that predict TFT outcome. To date, only one study in BPD has reported on treatment outcome prediction, showing that both left amygdala volume and lower amygdala activity during a cognitive reappraisal task associated with better treatment response (52). No study has yet been performed in patients with CPD.

In the present protocol, we describe a treatment outcome study into the predictive value and pre-post changes of brain function and structure in a comorbid PTSD and personality population see also 53, 54). We additionally include a healthy control group for comparison. The first aim is to study the neural alterations induced by PTSD treatment (trauma-focused therapy, TFT) versus integrated PTSD-personality disorder

treatment (TFT+PT) in patients with PTSD and comorbid (sub)clinical BPD and/or CPD. Based on previous studies, we expect that 1a) pre-treatment task-related hyperactivity, relative to healthy controls, of the amygdala, ACC and ventromedial PFC will normalize after trauma-focused therapy in both treatment conditions. We further expect that 1b) hyperconnectivity within the SN and hypoconnectivity within the DMN during resting-state normalize towards healthy controls in all patients, regardless of the treatment condition. We additionally expect 1c) more increase in task-related activation in emotion regulation-related areas (e.g. rostral PFC and dlPFC) in patients in the TFT+PT compared to the TFT condition. Finally, we expect 1d) that normalization of brain function is related to improvements in emotion regulation. The second aim is to predict treatment outcome on group and the individual level. Based on previous research, we hypothesize that 2a) a successful treatment outcome can be predicted by lower pretreatment task-related activation of the amygdala, dorsal ACC and insula, 2b) larger volumes of the ACC and hippocampus and 2c) higher severity of PTSD at baseline, higher severity of dissociative symptoms and presence severity of comorbid depressive disorder are related to worse treatment outcomes. Our third and final aim is to compare differences and similarities in the neural alterations in patients with PTSD+BPD and PTSD+CPD, compared to healthy control subjects. We expect 3a) all patients to show pre-treatment dysfunction in task-related activation and resting state connectivity of emotion regulation areas, such as the ACC, insula, dlPFC and hippocampus. In addition, we expect that 3b) in PTSD+BPD patients brain regions of the central executive network (CEN) are hypoconnected. For CPD, these analyses will be more explorative.

Methods

Design

This MRI study collects neuroimaging data for patients that participate in the two randomized controlled trials (RCTs) of the PROSPER (Prediction and outcome study in PTSD and personality disorders) study, which is registered under NCT03833453 & NCT03833531 at clinicaltrials.gov (55, 56). For the MRI study we additionally recruit matched healthy control participants. The study has been approved by the medical ethical committee of the VU University medical center and all participants provide written informed consent in accordance with the Declaration of Helsinki. The PROSPER study consists of two RCTs, with four treatment arms (see Figure 1). First, patients are divided based on their comorbid personality problems, in either BPD or CPD. Second, they are randomized into the TFT or TFT+PT condition. We use a block-randomization with blocks of six and one random block of four. A researcher not involved in data collection generated the randomization list and an independent person prepared sealed envelopes with assigned treatment condition according to this list. In PTSD+BPD, TFT is

eye-movement desensitization and reprocessing (EMDR), TFT+PT consists of EMDR+DBT. In PTSD+CPD, TFT is imaginary rescripting (ImRs), TFT+PT consists of ImRs+SFT. A subset of patients will be asked to additionally participate in the here described add-on MRI study, which involves magnetic resonance imaging (MRI) scan sessions before (T0) and after (T2) TFT in all four conditions. Only the parts of the design relevant to the MRI study will be reported in this paper.

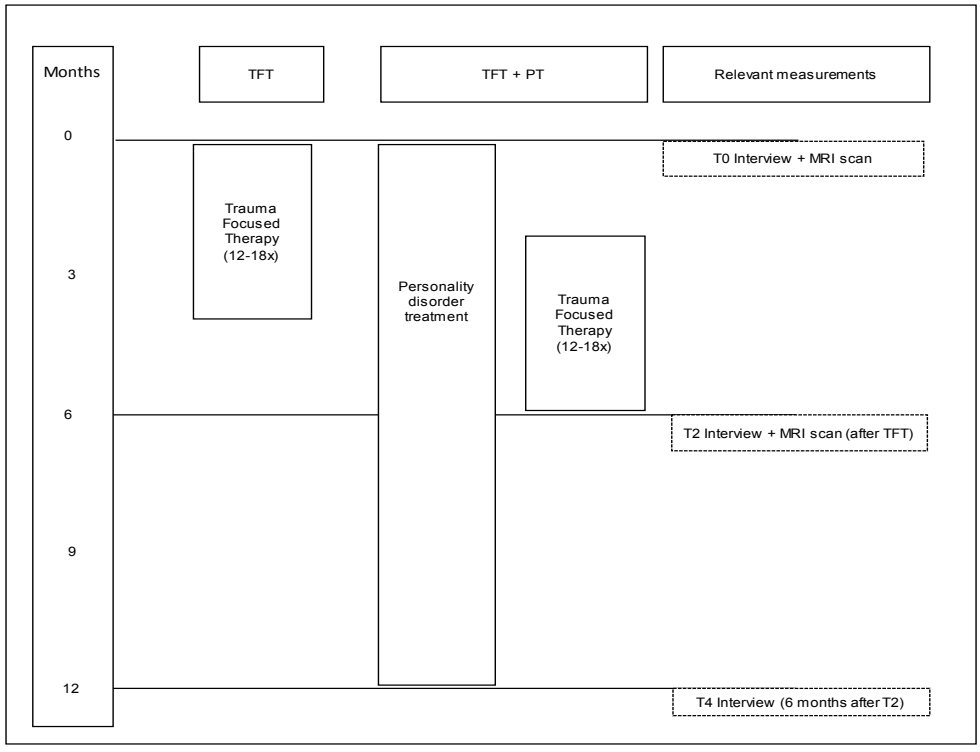

Figure 1. Overview of the timeline for treatment and measurements

Sample

We aim to include approximately 80 patients who are enrolled in the PROSPER study, 40 with PTSD+BPD and 40 with PTSD+CPD. We expect to have MRI scans at T2 of at least 40 of these patients (20 BPD and 20 CPD). The inclusion criteria are a primary diagnosis of PTSD and a diagnosis of (sub)clinical BPD or CPD, measured by the SCID-5-PD (57). We include patients fulfilling at least the required number of SCID-5-PD criteria as defined by the DSM-5 (4) minus one, as to guarantee sufficient generalizability of the population under study. Included patients have an age between 18 and 65 years, have sufficient understanding of the Dutch language and provide written informed consent. Patients are excluded if they have a comorbid disorder that interferes with treatment

or randomization; severe outward aggression, addiction or eating disorders interfering with treatment, current psychosis, mental retardation (IQ < 70) or a primary personality disorder diagnosis other than BPD or CPD. Benzodiazepine use exceeding 3 times 10 mg per day oxazepam or equivalent is also an exclusion criterion. Other psychotropic medications need to be stable for at least 3 weeks prior to study participation. For T2 scans, we include patients that have completed their TFT, defined by having received at least 75% of their TFT sessions. Further exclusion criteria related specifically to the MRI study are pregnancy, metal implants, somatic disorders interfering with brain functioning such as head trauma, epilepsy and claustrophobia. Immediately prior to the MRI scan, patients and healthy controls are asked about medication and substance use in the previous 24 hours. Use of any benzodiazepines is not allowed in the 24 hours before the scan.

We additionally recruit 30 healthy controls through advertisements and Hersenonderzoek.nl (www.hersenonderzoek.nl). The same inclusion and exclusion criteria are used. In addition, healthy controls are excluded if they have a current diagnosis for a mental disorder. This control group will be matched to the patient group average on age, sex and education level.

Sample size

For reliable fMRI results, a minimum of 20 participants but preferably more than 27 participants has been proposed (58), with more participants a plateau is reached. Furthermore, a minimal sample size of 12 has been proposed with 80% power at $\alpha=0.05$ at the single voxel level (59) and we use the same task as a previous study (60) where a robust amygdala activation was found with a sample size of 41 patients. In our study, we include 40 patients with PTSD+BPD and 40 patients with PTSD+CPD. With a predicted dropout of 25-50%, at least 20-30 participants per condition should be available for a second scan. If from the first 80 patients less than 40 return for a second scan, we will continue inclusion until at least 40 post-treatment scans are acquired. Healthy controls will only participate in one scanning session; therefore we include 30 participants.

Interventions

The treatment protocol is described more detailed in (61, 62), but described here briefly. Patients in the TFT condition will receive EMDR (PTSD+BPD) or ImRs (PTSD+CPD) for a minimum of 12 and a maximum of 18 sessions, delivered within 6 months. TFT sessions are delivered individually, for 75 minutes weekly. In the TFT+PT condition, patients with PTSD+BPD additionally receive DBT. This consists of six individual pretreatment sessions of 45 minutes. Patients then start group sessions for 48 weeks, with weekly group sessions of 150 minutes and biweekly individual 45-minute DBT sessions. EMDR starts after six weeks of group training.

For patients with PTSD+CPD, the TFT+PT condition consists of ImRs+SFT. For SFT, there are four individual pretreatment sessions of 45 minutes, after which patients enroll in a group with 90-minute weekly sessions for 40 weeks. Additionally, patients receive 18 sessions of group schema focused psychomotor therapy during the course of the SFT-group.

All treatment sessions are recorded on audio (ImRs) or video (EMDR, DBT, SFT) to check treatment adherence. Therapists also fill out a short form about the session, where they note which trauma target was treated and whether there were any protocol violations. Therapists have received accredited training and participate in biweekly supervision meetings. Furthermore, all therapists receive supervision from a trained supervisor. All treatment sessions are recorded on audio (ImRs) or video (EMDR, DBT, SFT) to check treatment adherence. Therapists also fill out a short form about irregularities in the session. Therapists have received accredited training and participate in biweekly intervision meetings. Furthermore, all therapists receive supervision from a trained supervisor.

MRI acquisition

MRI scans are acquired using a GE Discovery MR750 3-Tesla MRI scanner (General Electric, Milwauki, WI, USA) with a 32-channel head coil at the Amsterdam UMC, location VUmc. We acquire 1) a 3D T1-weighted structural magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo (MP RAGE) according to the ADNI-3 protocol (63), 2) 10 minutes resting state functional MRI (rsfMRI), 3) fMRI during an emotional faces task, and 4) multi-shell single-spin echo acquisition diffusion weighted images (DWI). Table 1 shows the scan parameters. During the rsfMRI the lights are dimmed and participants are instructed to keep their eyes closed but to not fall asleep. For fMRI and DWI scans, blip-up, blip-down scans with opposite phase encoding directions with the same field-of-view are acquired to correct for susceptibility induced distortions. We use high order shimming to homogenize the B0 magnetic field during the functional scans and the DWI.

Table 1. Scan parameters

	3D T1 – MPRAGE	Resting-state fMRI	Task-based fMRI	Multi-shell DWI
TR (ms)	6.9	2200	2200	N/A
TI (ms)	900	N/A	N/A	N/A
TE (ms)	3	28	26	81
Flip angle	9°	80°	80°	90°
# slices	168	42	42	56
# volumes	-	272	205*	80
in plane resolution (mm)	1 x 1	3.3 x 3.3	3.3 x 3.3	2.5 x 2.5
Slice thickness	1	3	3	2.5
Slice gap (mm)	N/A	0.3	0.3	N/A
Matrix size	256 x 256	64 x 64	64 x 64	96 x 96
Scan direction	N/A	Axial ascending according to HYFA	Axial ascending according to HYFA	Axial ascending According to HYFA
Shells	N/A	N/A	N/A	73 directions: interleaved 25 b1000, 24 b2000, 24 b3000 + 7 b0

TR = repetition time; TE = echo time; TI = inversion time; MPRAGE = magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo; fMRI = functional magnetic resonance imaging; HYFA = imaginary straight line from the ventral hypophysis to the fastigium in the roof of the fourth ventricle.

* Number of volumes for task-based fMRI varies because the scan is manually stopped around 3s after the end of the task.

Emotional faces task

In the scanner, patients and healthy controls complete an emotional faces task (EFT) adapted from Frijling (60). Here we use the conditions: fear, anger and neutral. These face images are contrasted with scrambled faces. Pictures are taken from the Radboud University Database (64). Three pictures at a time are presented, one at the top and two underneath. For the (emotional) faces, participants have to match the sex of the picture on top to either one on the bottom by clicking a button with their left or right hand. For the scrambled faces, patients have to match the shape of the frame surrounding the scrambled face to the upper picture. Subjects are presented six pseudo randomized blocks of neutral or scrambled faces and five blocks of fearful and angry faces. The same face condition is never presented twice in a row. Each block lasts 20 seconds (4900 ms stimulus, 100 ms stimulus interval) and contains four different trials of scrambled, neutral or emotional faces. Total task duration is approximately 7 min. We use two counterbalanced versions of the task, one at T0 and one at T2. Pictures are matched on intensity, clarity, attractiveness and valence between the versions. See Supplementary Table 1 for an overview of the models in the task. The images are presented to participants through a projector connected to a computer running

E-prime version 2.0.10.353 (Psychology Software Tools, Pittsburgh, PA). Participants see the screen through a mirror mounted on the head coil. For responses, participants press left or right on a button using a Designs Fiber Optic Response Box (FORB) model 932.

Image processing and quality check

MRI acquisition quality will be checked in several steps. All data will be visually inspected, for example for movement artefacts and ghosting. For fMRI and DWI, the reversed phase-encoded blips to correct for susceptibility-induced distortions are processed using a tool from the FMRIB Software Library (FSL); FSL top-up (65, 66). To further check quality of T1 and fMRI sequences, the MRI Quality Control Tool (MRI QC; 67) will be used. Quality parameters such as framewise displacement and signal to noise ratio will be calculated for fMRI and DWI sequences and used to assess whether the quality of a scan is acceptable. As an example, scans with a framewise displacement of more than 0.5mm will be removed before analyses (68).

Structural T1 scans will be processed using FreeSurfer to derive morphometric measures such as volume, surface area and cortical thickness. We will employ the 'fmriprep' pipeline to preprocess the fMRI scans (69); see also below. DWI scans will be preprocessed using the FSL EDDY tool (70) to correct for susceptibility-induced distortions, eddy currents and motion. MRtrix3 (www.mrtrix.org (71)) will be used for tractography and DTI-TK (72) for registering the individual DWI scans to a common space to subsequently perform tract-based spatial statistics (TBSS).

Outcome measures

MRI outcome measures

For each MRI modality, we mention the main outcome measures here briefly, they will later be described more fully in pre-registered data analysis plans through the Open Science Framework Project (73).

Structural T1 weighted scans

In the structural T1-weighted scans, we will focus mainly on morphometric (cortical thickness, surface area, volume) features of brain areas such as the ACC, insula, hippocampus and amygdala. For the amygdala and hippocampus, we will make sub-segmentations. We will define these brain regions according to standard atlases (e.g. Desikan-Killiany (74) or Brainnetome (75) atlas) and segment these areas on the individual level using FreeSurfer software. Where necessary, we will use voxel-based morphometry for more detailed, parallel analyses.

rsfMRI

The main focus of rsfMRI will be on the connectivity of resting-state networks implicated in the pathophysiology of PTSD and personality disorder: the SN, CEN and DMN. Functional connectivity matrices will be made using an atlas-based approach, using standard atlases such as the Brainnetome (75) or Schaefer (76) atlas. This connectivity matrix will then be used to calculate connectivity within and between the three resting-state networks of interest and the connectivity of the amygdala. We will also use graph measures calculated from this matrix to study changes in the topology of the brain network, including global efficiency, clustering coefficient and modularity (see for example 77, 78).

fMRI during emotional face task

In the fMRI during the emotional face task, the main contrast of interest is the fearful faces versus scrambled faces. In addition, we will study the angry versus scrambled faces and neutral versus scrambled faces contrasts as secondary analyses. Our regions of interest include the amygdala, dorsal ACC, anterior insula, vmPFC, dlPFC, dmPFC, hippocampus and visual areas. We will specify the exact coordinates for the regions of interest in the preregistered data analysis plans. For additional connectivity analyses, we will use a generalized form of context-dependent psychophysiological interactions (gPPI; 79)

DWI

Integrity of white matter fiber bundles will be measured using standard diffusivity measures: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) using DTITK (72) and FSL TBSS. In addition, we will perform whole brain tractography using MRTRIX3 to study between-group differences and treatment-induced changes in structural connectivity and characteristics of the structural connectome using graph measures.

Clinical outcome

The main clinical outcome measure is the clinician-administered PTSD scale for DSM-5 (CAPS-5, 80). The CAPS-5 is administered before treatment (T0), directly after TFT (T2) and six months after the TFT ends (T4; see Figure 1 for overview) by trained independent assessors, blind to treatment condition. For this study, the PTSD symptom change between T0 and T4 as measured by the CAPS-5 will be calculated to see whether our imaging outcome measures correlate with and predict clinical improvement. For responder/non-responder analyses, responders will be classified as patients who show an improvement of ≥ 0.5 standard deviation in pre- to post-treatment CAPS-5 scores (81).

Statistical analysis

Treatment effect

To test hypotheses 1a-1c and analyze treatment effect, we will use linear mixed-models with the above-described MRI outcome measures as dependent variables. For hypothesis 1a, this means amygdala, ACC and vmPFC activation. For 1b, connectivity in resting-state networks and for 1c, activation in emotion regulation areas (such as the rostral PFC and dlPFC). For hypothesis 1d, we will correlate changes in brain activation (from hypotheses 1a-1c) with change in emotion regulation, as measured with change in the Difficulties in Emotion Regulation Scale (DERS; 82) from T0 to T2. We are interested in the main effect of time (T0, T2) and the interaction effect of time x type of treatment (TFT or TFT+PT). The value of the outcome measure at T0 will be added as covariate and a random factor for participants will be added to the model. Additionally, we will make a model with PTSD and personality disorder severity (measured with the CAPS-5 and SCID-5-PD respectively) at baseline, age and sex as covariates. For exploratory analyses, we will compare differences in neural response in treatment responders versus non-responders.

Prediction of treatment effect

To predict treatment outcome at T4 (hypotheses 2a-2c), we use CAPS-5 score at T4 as a continuous dependent variable in a multiple linear regression model with MRI outcomes at T0 as independent variables. For hypothesis 2a, task-related amygdala, dACC and insula activation will be added to the model. For hypothesis 2b, volumes of the ACC and hippocampus will be added to the model. For hypothesis 2c, PTSD severity, presence and severity of depressive disorder and dissociative symptoms will be added to the model. Medication use will be used as a covariate.

To predict response versus non-response, we will use logistic regression. Dichotomous treatment response status is the dependent variable, with the predictors mentioned above as independent variables.

We will also conduct more exploratory prediction analyses, using features derived from the different MRI modalities, e.g. resting-state network measures, whole brain activation during the task and DTI-derived measures such as FA and structural connectivity. We will preregister our analysis plan for these analyses prior to data analysis (73).

Furthermore, we will perform sensitivity analyses for patients who use psychotropic medication versus patients who do not use medication, for patients with and without comorbid depression and patients with and without the dissociative subtype of PTSD (measured with the CAPS-5) by running the analyses with and without these groups.

Comparison BPD, CPD and healthy controls

To assess differences in brain activation (hypotheses 3a-3b), connectivity and brain morphology between patients with PTSD+BPD, patients with PTSD+CPD and healthy controls, we will use a regression model with diagnosis as independent variable and imaging outcome measures as dependent variables. For hypothesis 3a, task-related activation and resting state activation of emotion regulation areas will be added to the model, for hypothesis 3b, connectivity in resting-state networks will be added to the model. If possible, we will do the analyses separately for medicated and non-medicated patients. We will also analyze the difference in clinical comorbidity and its relation to neuroimaging measures between the groups.

Discussion

The here described neuroimaging study aims to investigate the neural effects of TFT versus TFT+PT in PTSD patients with a personality disorder, as well as the utility of neuroimaging measures to predict treatment outcome and to study similarities and differences between patients with PTSD and BPD or CPD. This study can provide important insight into a patient group that has not received extensive study until now. We include a heterogeneous group of PTSD patients with (sub)clinical personality disorders, which makes our study generalizable to a broad patient population that is characteristic of the clinical population, since as many as 35% of PTSD patients have a comorbid personality disorder (8).

A downside of this naturalistic approach within a heterogeneous sample, is that there may be confounding factors in interpreting the results. One of these is medication use. While other studies often exclude patients that use medication, patients in our sample use medication that has been stable for at least three weeks. This medication may influence structural and functional characteristics of the patients' brains. Schulze (24) found in their meta-analysis that unmedicated patients show hyperactivation of the amygdala compared to healthy controls, while medicated patients do not. Since lower amygdala activity is expected to predict successful treatment outcome, it is possible that medicated patients react better to treatment. It is also possible that the effects of our TFT or TFT+PT on the brain differs between medicated and unmedicated patients, which we plan to study by running our analyses with and without medicated patients.

Another source of heterogeneity is the presence of other comorbid disorders that may influence our results, such as major depressive disorder (MDD). A meta-analysis showed that 52% of PTSD patients also meet criteria for MDD (83). PTSD patients with MDD and other comorbid disorders may differ in their underlying neural characteristics. PTSD

and BPD are for example associated with a hyperactive amygdala during an emotional task compared with healthy subjects, while MDD is associated with hypoactivation of the amygdala (84). Secondly, some PTSD patients suffer from dissociative symptoms (4). Dissociation is related to increased inhibition of the limbic response by areas such as the dorsal ACC and mPFC (39). Finally, most research in personality disorders has been done in BPD, and data are sparse in the three personality disorders that make up CPD (85). Different neural mechanisms could underlie these different disorders, but this is hitherto unknown. Where possible, we intend to study patients with and without these comorbid conditions separately to disentangle the confounding comorbidity.

Conclusion

In conclusion, this neuroimaging study is the first to study neural correlates of treatment effects in patients with PTSD and comorbid personality disorder and imaging-derived biomarkers predicting response. We also aim to study the different underlying neural mechanisms in PTSD patients with BPD and CPD. With this study, we hope to shed light on a population that has so far received little attention in neuroimaging research.

Acknowledgements

Healthy control participant recruitment will be accomplished through Hersenonderzoek.nl, a Dutch online registry that facilitates participant recruitment for neuroscience studies www.hersenonderzoek.nl. Hersenonderzoek.nl is funded by ZonMw-Memorabel (project no 73305095003), a project in the context of the Dutch Deltaplan Dementie, Gieskes-Strijbis Foundation, the Alzheimer's Society in the Netherlands and Brain Foundation Netherlands.

Supplementary materials

The supplementary materials for this chapter can be accessed through https://surfdrive.surf.nl/files/index.php/s/Pufgdt0eTPz2VWs.

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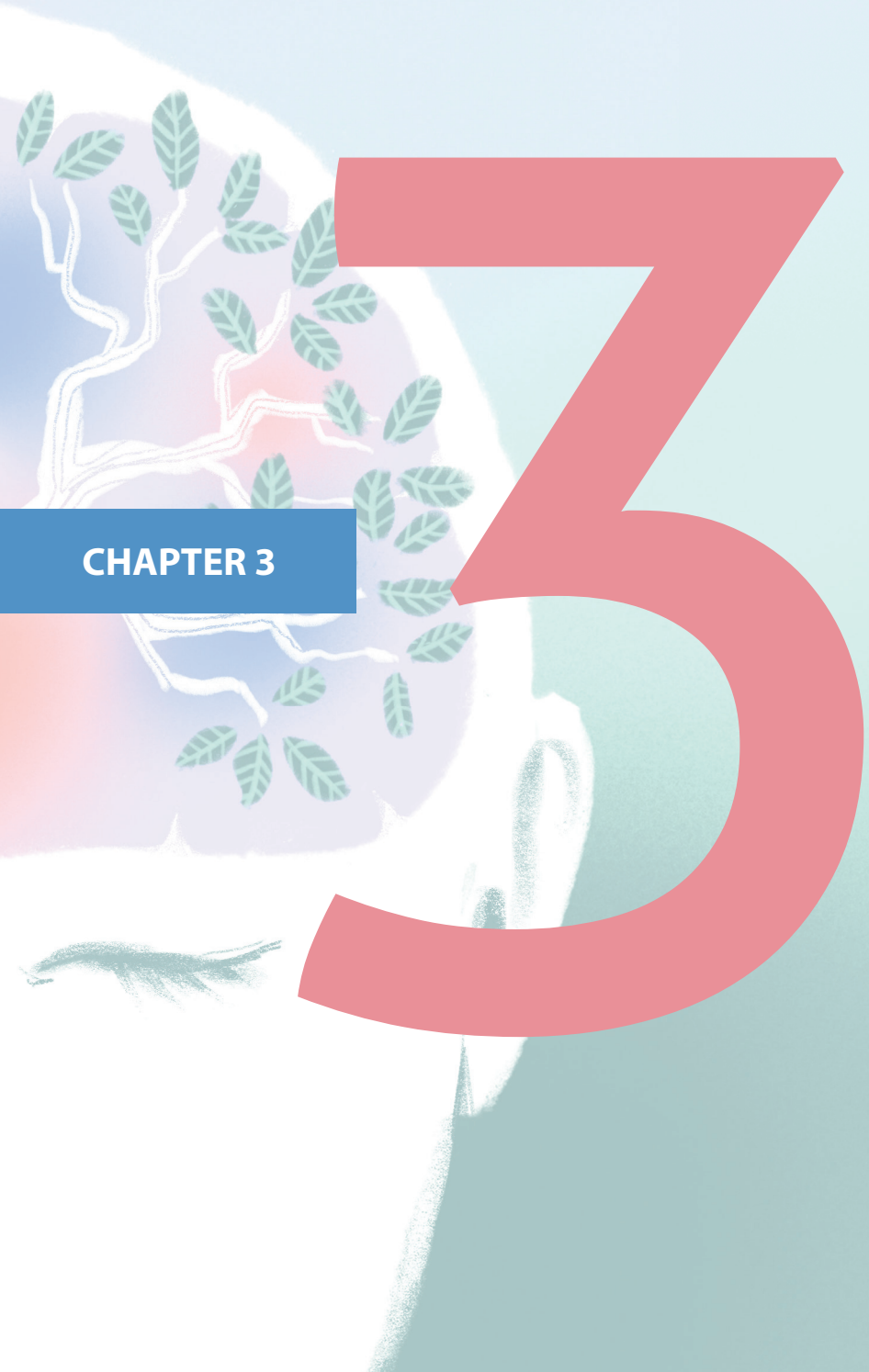

CHAPTER 3

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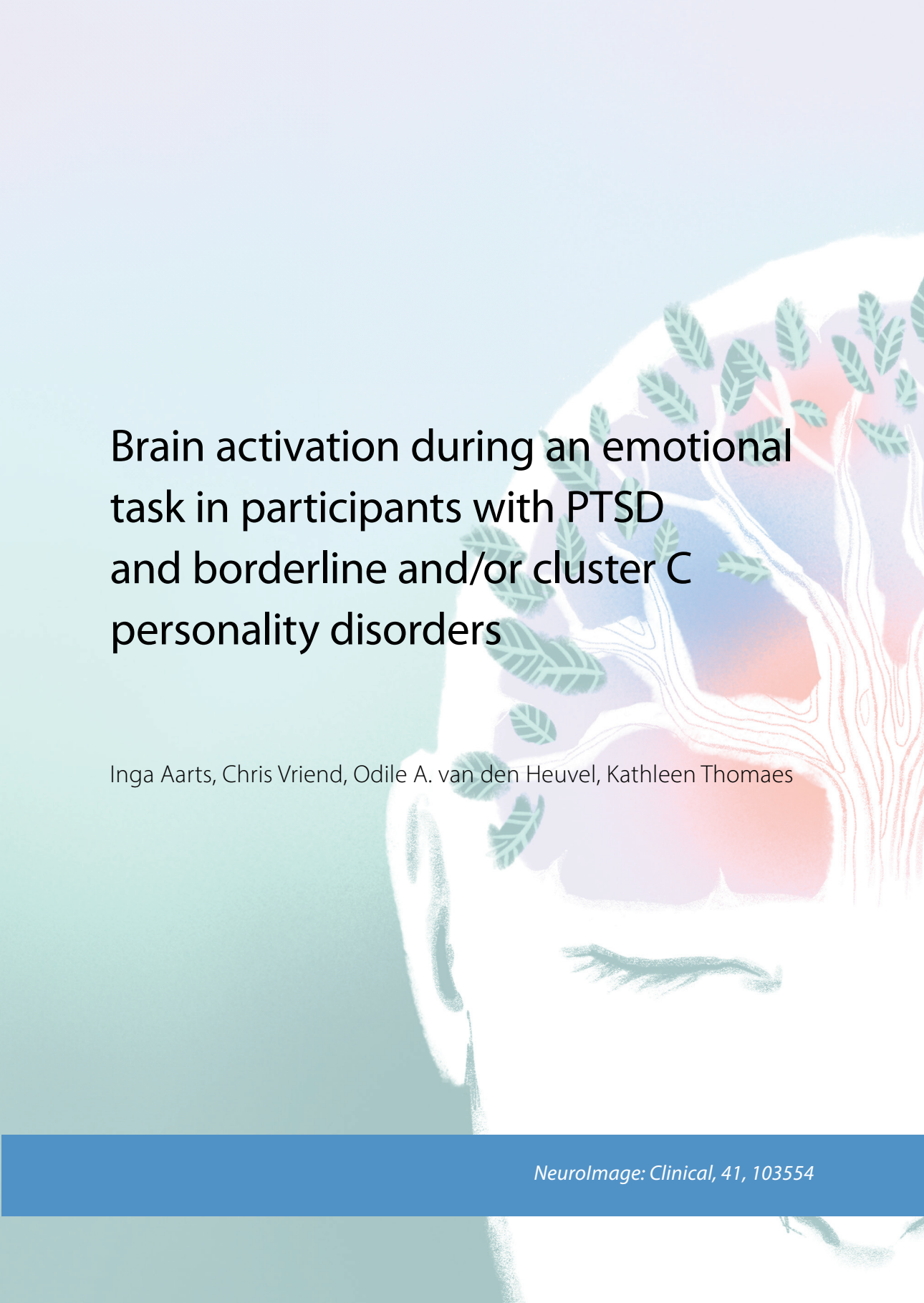

Brain activation during an emotional task in participants with PTSD and borderline and/or cluster C personality disorders

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Abstract

Introduction: Although comorbidity of post-traumatic stress disorder (PTSD) with borderline personality disorder (BPD) and/or cluster C personality disorders (CPD) is common, neural correlates of this comorbidity are unknown.

Methods We acquired functional MRI scans during an emotional face task in participants with PTSD+CPD (n=34), PTSD+BPD (n=24), PTSD+BPD+CPD (n=18) and controls (n=30). We used ANCOVAs and Bayesian analyses on specific ROIs in a fearful vs. scrambled faces contrast. We also investigated associations with clinical measures.

Results There were no robust differences in brain activation between the groups with ANCOVAs. Transdiagnostically, we found a negative association between severity of dissociation and right insula and right dmPFC activation, and emotion regulation problems with right dmPFC activation. Bayesian analyses showed credible evidence for higher activation in all ROIs in the PTSD+BPD+CPD group compared to PTSD+BPD and PTSD+CPD.

Discussion Our Bayesian and correlation analyses support new dimensional conceptualizations of personality disorders.

Introduction

Post-traumatic stress disorder (PTSD) is a debilitating disorder that may occur after experiencing a traumatic event and is characterized by re-experiencing, avoidance, negative changes in mood and cognitions and hyperreactivity (2). PTSD has a lifetime prevalence of around 4% (3). There is a high comorbidity between PTSD and personality disorders, with more than a third of PTSD patients also fulfilling the diagnosis for a personality disorder (4), such as borderline personality disorder (BPD, comorbidity 22%) or cluster C, i.e. avoidant, dependent and obsessive-compulsive personality disorders (CPD; comorbidity 8-23%). Conversely, more than 45% of individuals with a personality disorder suffer from a comorbid PTSD (5) and specifically, more than 50% of people with BPD has a lifetime PTSD diagnosis (6).

Imaging studies have shown dysfunction in brain areas associated with emotion processing and regulation both in PTSD and borderline personality disorder. The amygdala is typically associated with emotion processing and hyperactive in people with PTSD upon being exposed to trauma-related and emotionally charged stimuli (7, 8). In BPD findings are more heterogeneous, with one meta-analysis showing lower activity in the amygdala and associated networks during tasks with a negative emotion versus neutral condition (9), while another more recent meta-analysis (10) showing higher left amygdala activity. Possible explanations are the heterogeneity of the samples and the suppressing effect of psychotropic medication on amygdala activity in medicated participants (10). Also, severity of state dissociation during scanning – that is associated with blunting amygdala activation - might have contributed to variation in amygdala activation (11). For CPD, functional neuroimaging studies are scarce, although one study showed higher amygdala activation in CPD participants compared to controls in the anticipation phase during a reappraisal task (12).

Next to the amygdala, both BPD and PTSD participants showed hypoactivation of the posterior right insula and left postcentral gyrus compared to control participants and hyperactivation of the right middle frontal gyrus and left inferior frontal gyrus showed hyperactivation (13). In one study, both BPD and CPD participants showed lower activation in the dorsal ACC during habituation to negative images compared to controls (14). The dlPFC is involved in effortful regulation and executive functions (15) and seems to be hyperactive in PTSD participants and hypoactive in participants with BPD, compared to controls (13). The activation pattern in these brain areas in participants with both PTSD and a comorbid personality disorder is yet unknown

Emotion dysregulation and dissociation are symptoms of both PTSD and BPD (2, 17). Dissociation involved disruptions in neurological, psychological and cognitive functions

(11, 18). A recent meta-analysis identified brain areas from the emotion regulation network that were related to dissociation across the dissociative symptom spectrum; lower limbic activation in the amygdala, parahippocampus and insula, and higher activation in the hippocampus, cingulate cortex and medial frontal gyrus were found to be related to dissociative symptoms (16).

We studied brain activation during emotional processing in participants with PTSD and a comorbid BPD and/or CPD. The main research question was whether the brain response in areas involved in emotional processing during an emotional face task is influenced by type of comorbid personality disorder (BPD, CPD or both BPD and CPD) in PTSD participants. First, we focused our analyses on regions of interest (ROI) related to emotion processing in PTSD: i.e. bilateral amygdala, right insula, right dlPFC and right dmPFC. We expected higher activation of the amygdala in all PTSD + personality disorder groups compared to control participants and lower activation in the insula, dlPFC and dmPFC. Little is known about the neurobiological underpinnings of CPD. However, since both BPD and CPD are associated with impairment and poor functioning (19) and the combination of BPD+CPD is associated with a higher prevalence of a comorbid anxiety disorder (5), we hypothesized that PTSD participants with both comorbid BPD and CPD show more dysfunction than participants with PTSD+BPD or PTSD+CPD compared to controls, i.e. higher activation in the amygdala and lower activation in insula, dlPFC and dmPFC. The second research question is how brain activation relates to clinical measures in all PTSD participants together (transdiagnostically). We studied PTSD severity, emotion regulation problems, anger, dissociation, borderline symptom severity and depressive symptom severity. We hypothesized higher task-related activation in the amygdala, dlPFC and dmPFC, and lower activation in the insula to be related to higher PTSD severity, anger, emotion regulation problems and borderline symptoms. We expected lower amygdala activation to be related to more severe dissociation. This study was preregistered on the open science framework, osf.io/9842Q.

Methods

Participants

Participants in this study were part of two larger randomized controlled trials in the PROSPER-study, see also Snoek, Beekman (20), van den End, Dekker (21). Inclusion criteria were at least three traits of avoidant or obsessive-compulsive personality disorder, and/or four traits of dependent or BPD (i.e. one trait under the cutoff score for the classification); age between 18 and 65 years, sufficient understanding of the Dutch language and ability to provide written informed consent. Exclusion criteria were severe outward aggression, addiction or eating disorders interfering with treatment,

current psychosis, mental retardation, a primary personality disorder other than BPD or CPD, benzodiazepine use exceeding three times 10mg oxazepam equivalent per day. Other psychotropic medication needed to be stable for at least three weeks prior to study participation. In this study, we used a subset of data of participants from the PROSPER-trials that agreed to the scanning sessions, see (22). We recruited 88 participants with PTSD for the current study. Control participants were recruited through hersenonderzoek.nl (www.hersenonderzoek.nl), an online registry where you can match characteristics of your sample to control subjects. An additional exclusion criterion for control participants was any current diagnosis for a mental disorder. The 30 included control participants were matched to the patient groups' distribution of age, sex and education level. The study was approved by the ethics committee of VU Medical Center.

Procedure

We screened participants for the PROSPER trial with the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD), a semi-structured interview to assess personality disorders (23, 24). Based on the SCID-5-PD, we included participants in the PTSD+BPD trial or the PTSD+CPD trial, see Aarts, Vriend (22). For the current study, we classified participants who fulfilled full criteria for both BPD and CPD in the PTSD+BPD+CPD group. All participants were asked to participate in the magnetic resonance imaging (MRI) part of the study. We then screened them with an MRI safety checklist and planned an appointment for the scanning session before participants' treatment started. Prior to the scanning session, participants filled out a medication list to assess medication use in the previous 24 hours. In a separate appointment, there was a clinical interview to assess PTSD symptoms and participants filled out questionnaires online. The full scanning protocol can be found in Aarts, Vriend (22). Control participants came to the location once for the MRI scan and two neuropsychological tests.

Clinical measures

PTSD severity was measured with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), a semi-structured interview that can be used to diagnose PTSD and gives a severity score with a total range between 0 and 80 (25, 26). We assessed a range of clinical symptoms with questionnaires. Problems in emotion regulation were measured with the Difficulties in Emotion Regulation Scale (DERS, range 41-205; Gratz and Roemer (27)). Anger was measured by the State Trait Anger Scale (STAS; Van der Ploeg, Defares and Spielberger (28), Kroner and Reddon (29)). For this study, we used only the 10 items assessing trait anger (range 10 – 40). Dissociative symptoms were measured with the Dissociative Experiences Scale (DES, range 0-100; Van IJzendoorn and Schuengel (30), Bernstein (31). Borderline symptoms were measured with the Personality Assessment Inventory-Borderline Features Scale (PAI-BOR, range 0-72; Morey (32), Distel, de Moor

and Boomsma (33)). A PAI-BOR score of 38 or higher is indicative of BPD. Depressive symptoms were measured with the Beck Depression Inventory (BDI, range 0-60; 34, 35). Finally, we asked participants to rate their tension level before and after the task, on a scale from 0 to 100.

Emotional faces task

Brain activation was measured with functional MRI (fMRI) during an emotional face paradigm (adapted from Frijling et al. (2016)) and consisted of four conditions: fearful, angry, neutral and scrambled faces. Participants saw three faces at the same time and had to match the sex of the top picture to one of the bottom two. In the scrambled condition, participants had to match the orientation of the frame of the top picture to either one on the bottom. See Figure 1 for picture examples. The task consisted of six pseudo-randomized blocks of neutral or scrambled faces, and five blocks of angry or fearful faces. Each block consisted of four trials. Our main contrast of interest was the fearful faces vs scrambled faces, secondary contrasts are angry vs scrambled and neutral vs scrambled. See Aarts, Vriend (22) for more details. Task performance was calculated as proportion of correct responses.

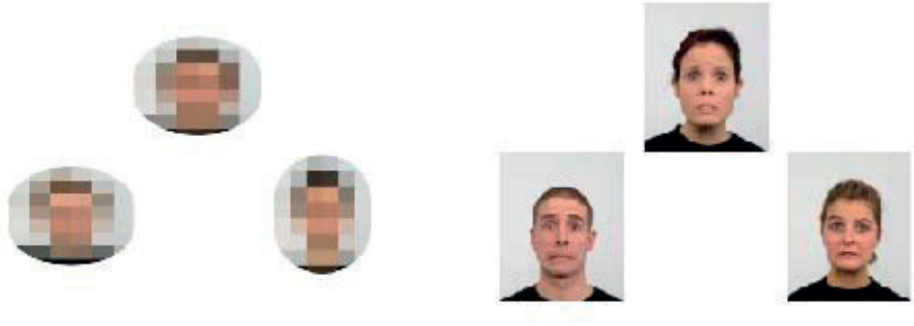

Figure 1. Example trials from the emotional faces task
Scrambled faces trial (left) and fearful faces trial (right)

MRI acquisition and preprocessing

Full imaging parameters of the task and scans are described in Aarts et al. (2021). Briefly, the scans were acquired on a GE Discovery MR750 3-Tesla scanner (General Electric, Milwauki, WI, USA) with a 32-channel head coil. First, an anatomical T1 scan was acquired (TR = 6.9ms, TI = 900ms, TE = 3ms, flip angle = 9°, 168 slices, slice thickness 1 mm, matrix size 256x256). For the functional MRI scans, we acquired blip-up, blip-down scans with opposite phase encoding directions with the same field-of-view to correct for susceptibility induced distortions and high order shimming to homogenize the B_0

magnetic field during the functional scans. We manually stopped the task scan after the task ended, around 205 volumes were acquired (TR = 2200ms, TE=26ms, flip angle = 80°, 42 slices, slice thickness = 3mm, matrix size = 64x64, 3.3 x 3.3 in plane resolution).

We processed functional images through the 'fmriprep' pipeline (version 21.0.1; 36; see supplements for full boilerplate) and smoothed by applying an 8mm full-width half-maximum smoothing kernel and first-level analyses in Statistical Parametric Mapping 12 (SPM 12; Wellcome Trust Centre for Neuroimaging, London, UK).

MRI acquisition quality was checked in several steps. First, we removed participants who did not have a complete task scan because of technical problems. Then, we (visually) inspected all functional imaging data, for example for movement artefacts and ghosting. To further check the quality of T1 and fMRI sequences, the MRI Quality Control Tool (MRI QC; 37) and reports from fmriprep were used. We calculated quality parameters such as framewise displacement for fMRI sequences and used them to assess whether the quality of a scan was acceptable. We excluded scans with a mean framewise displacement of more than 0.5mm from the analyses (38).

Statistical analyses

We preregistered our analysis on the Open Science Framework, see osf.io/9842Q. The main contrast of interest in the emotional face task was the fearful faces versus scrambled faces. Task activation for all participants are shown in Supplementary Figure 1. We based the coordinates for our regions of interest (ROIs) for the main analysis on the meta-analysis by Schulze, Schulze (13). These ROIs included the bilateral amygdala, right dlPFC (36, 40, 24), right dmPFC (2, 64, 20) and the right insula (36, -4, 8). For the subcortical areas (i.e. the amygdala) we used the Automated Anatomical Labeling (AAL) atlas. For the cortical areas (insula, dlPFC, dmPFC), we constructed 5mm spherical ROIs around the specified coordinates. The activation levels for our main contrast of interest, fearful versus scrambled faces, were extracted from the ROIs and compared between participants with PTSD+CPD, PTSD+BPD, PTSD+BPD+CPD and control participants.

For the main research question, we used an Analysis of CoVariance (ANCOVA) with diagnosis as independent variable, task contrast parameter as dependent variables and age and sex as covariates. We used a planned simple contrast with the control participants as the reference group. We checked bootstrapped results with 1000 permutations in case of violated assumptions for the ANCOVAs. We used a D/AP-SIDAK correction for multiple analyses across the ROIs. This correction uses the mutual correlation *r* between outcomes (39). These were computed using the online tool on https://www.quantitativeskills.com/sisa/calculations/bonhlp.htm. For our second research question, we ran a non-parametric Spearman's correlation analysis on the brain activation in the

specified ROIs with the seven above-mentioned clinical measures. We checked clinical data for outliers, but did not remove clinical data unless there was an invalid value or measurement error.

In addition, we ran the following secondary analyses. First, we did two types of sensitivity analyses with regard to medication status (as measured by use in last 24 hours): a) the ANCOVAs with medication status as a covariate and b) subgroup comparisons of brain activation in all medicated PTSD participants vs. controls and in all non-medicated PTSD participants vs. controls. Second, we repeated the ANCOVAs on the contrasts angry vs. scrambled faces and neutral vs. scrambled faces. Third, we used Bayesian multilevel modeling to compare all groups to each other on the fearful vs. scrambled contrast. Bayesian modeling incorporates all outcomes into one integrative model, instead of fitting separate models for each ROI as in standard null-hypothesis significance testing (40). Bayesian analysis calculates a posterior distribution and the positive posterior probability (represented in a P+ value). The further away the median of the distribution is from zero, the larger the effect and the larger the area under the curve (i.e. P+ value), the more evidence for that effect. P+ values that are either high (e.g. >.975) or low (e.g. <.025) provide very strong support for the effect, values >.95 or <.05 provide strong support and values >.90 or <.10 moderate support. In this Bayesian analysis, we included all ROIs from the main analyses, now bilaterally (amygdala, dlPFC, dmPFC, insula), plus the hippocampus (defined by the AAL atlas), superior occipital gyrus (±24, -96, 14; coordinates from Schulze et al., 2019), vmPFC (±4,41,-8; coordinates from Hayes, Hayes and Mikedis (41)) and dorsal ACC (±18,40,17; Hayes, Hayes and Mikedis (41)). Finally, to check for differences in regions not included in earlier analyses, we ran an exploratory whole-brain analyses with $p < .001$, uncorrected and a minimum extent cluster threshold of 5 voxels using SPM12.

Results

Sample

After applying exclusion criteria, the final sample consisted of 76 participants with PTSD and comorbid personality disorder (34 PTSD+CPD, 24 PTSD+BPD, 18 PTSD+BPD+CPD), and 30 control participants (see flowchart in Figure 2). Table 1 shows the demographic information and scores on the clinical measures per group. There were no significant differences between groups in age, sex, PTSD severity and task performance, but there were statistically significant between-group differences in emotion regulation, depression, anger, dissociation, borderline symptoms, tension before the task and tension after the task. Games-Howell corrected post-hoc tests showed significantly higher emotion regulation problems, anger scores, depression severity, dissociation

severity and borderline symptom severity in participants with PTSD+BPD+CPD compared to PTSD+CPD, and higher anger scores and borderline symptom severity in PTSD+BPD than PTSD+CPD. An overview of the medication/psychoactive substances used in the 24 hours before the scan is shown in Supplementary Table 1. Medication use did not differ significantly between groups ($\chi^2(2)=.997$, $p=.607$).

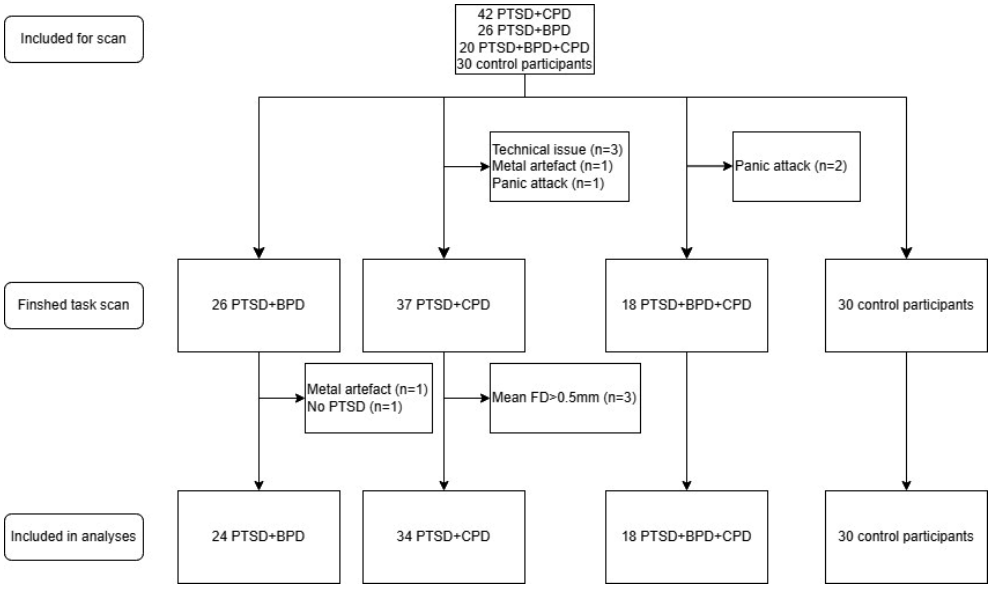

Figure 2. Flowchart of Participants

Table 1. Demographic Information and Clinical Measures (total N = 106)

	PTSD+CPD			PTSD+BPD			PTSD+BPD+CPD			Control participants			Test statistic (df)	p
	n	M	SD	n	M	SD	n	M	SD	n	M	SD		
Age	34	38.97	12.76	24	36.42	10.27	18	39.33	7.63	30	40.43	12.97	$F(3,102)=0.552$	.648
Sex (% f)		70.6%			83.3%						76.7%		$\chi^2(3, N=106)=1.297$	.730
CAPS-5	34	40.44	10.98	24	41.63	10.95	18	45.72	9.82	N/A	N/A	N/A	F(2,73)=1.460	.239
DERS	33	113.67	16.97	19	120.89	23.72	14	130.43	21.41	N/A	N/A	N/A	F(2,63)=3.524	.035*
BDI	33	32.03	11.96	21	31.52	12.77	15	40.67	9.98	N/A	N/A	N/A	F(2,66)=3.286	.044*
STAS	33	16.39	6.21	19	22.37	7.63	14	25.86	6.10	N/A	N/A	N/A	F(2,31.25)=12.659	<.001**
DES	23	15.48	10.29	18	22.06	15.19	14	37.47	21.98	N/A	N/A	N/A	F(2;25.975)=6.491	.005**
PAIBOR	33	34.67	8.40	19	40.16	6.73	14	44.36	5.18	N/A	N/A	N/A	F(2,63)=9.110	<.001**
Distress rating before task	16	29.44	25.08	19	40.68	26.94	14	43.21	27.92	29	21.07	23.40	F(3,74)=3.470	.020*
Distress rating after task	11	33.64	28.99	9	40.33	26.23	11	39.36	19.66	29	19.94	19.03	F(3,56)=3.304	.027*
Task performance	34	.78	.25	24	.84	.22	18	.80	.25	30	.89	.08	F(3,102)=1.549	.207

Note. PTSD = posttraumatic stress disorder, BPD = borderline personality disorder, CPD = cluster C personality disorder, BDI = Beck Depression Inventory, CAPS-5 = Clinician-Administered PTSD Scale for DSM-5, DES = Dissociative Experiences Scale, DERS = Difficulties in Emotion Regulation Scale, PAIBOR = Personality Assessment Inventory-Borderline Features Scale, STAS = State Trait Anger Scale.

* $p < .05$, ** $p < .01$

ANCOVAs

Table 2 shows the results of the ROI analysis. For the fearful > scrambled faces contrast, results showed a significant difference between groups in the right dlPFC ($F(3,100) = 4.200$, $p = .008$) that was driven by lower activation in both PTSD+BPD (95% confidence interval [0.062 - 0.267], $p = .002$) and PTSD+CPD groups (95% confidence interval [0.023 - 0.183], $p = .019$) compared to control participants. The other contrasts (anger > scrambled and neutral > scrambled) revealed no significant differences between the groups. When controlling for medication status, the between-group difference in activation in the right dlPFC was no longer significant (right dlPFC $F(3,91) = 1.773$, $p = .178$). Figure 3 shows the task-related activation for all groups in all ROIs.

For the fearful > scrambled contrast among all PTSD participants, severity of dissociation showed a statistically significant negative association with activation in the right insula ($r(53) = -.35$, $p < .01$) and right dmPFC ($r(53) = -.28$, $p < .05$). Emotion regulation problems showed a statistically significant negative association with right dmPFC activation ($r(64) = -.26$, $p < .05$). Other clinical measures did not show statistically significant correlations with brain activation, see Table 3 for all correlations.

Medicated, as compared to unmedicated PTSD participants, showed higher brain activation in the fearful > scrambled contrast in the left amygdala ($t(66) = -2.790$, $p = .007$), right dmPFC ($t(66) = -2.280$, $p = .026$) and right insula ($t(66) = -2.657$, $p = .010$). There was no significant difference between medicated and unmedicated participants in the right amygdala ($t(66) = -1.794$, $p = .077$) and right dlPFC activation ($t(66) = -0.989$, $p = .326$, (see Supplementary Figure 2 for a visualization). Medicated participants showed similar clinical characteristics as unmedicated participants, except for a lower borderline symptom severity (PAIBOR: $t(58) = 2.036$, $p = .046$) (see Supplementary Table 2).

Table 2. ROI Analysis of Covariance for the Effect of Diagnosis on Brain Activation

Region of interest	F (3, 100)	p
Contrast fear > scrambled		
Left amygdala	1.634	.186
Right amygdala	1.133	.339
Right dmPFC	0.981	.405
Right dlPFC	4.200	.008**
Right insula	1.711	.170
Contrast anger > scrambled		
Left amygdala	0.662	.577
Right amygdala	0.461	.710
Right dmPFC	0.921	.434
Right dlPFC	0.804	.372
Right insula	1.007	.393
Contrast neutral > scrambled		
Left amygdala	0.471	.704
Right amygdala	0.155	.926
Right dmPFC	1.799	.152
Right dlPFC	2.069	.109
Right insula	1.601	.194

Note. dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex.

** $p < .017$ (Sidak's correction through D/AP method).

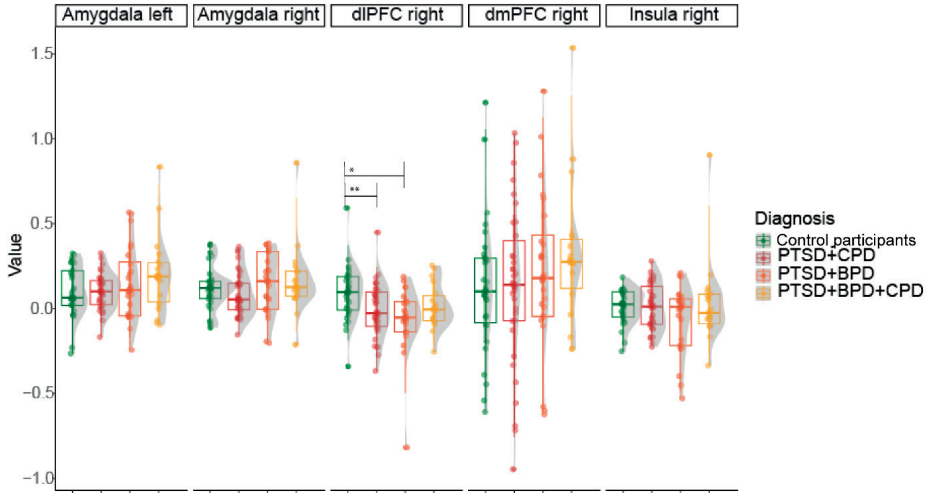

Figure 3. Raincloud Plots for Activation in the ROIs in the Fearful > Scrambled Faces Contrast

Note. BPD = borderline personality disorder, CPD = cluster C personality disorder, PTSD = posttraumatic stress disorder, dmPFC = dorsomedial prefrontal cortex, dlPFC = dorsolateral prefrontal cortex.

** $p < .01$; not significant when corrected for medication status

Table 3. Spearman Correlations for Brain Activation in Fearful > Scrambled Contrast and Clinical Measures

	Left amygdala	Right amygdala	Right dmPFC	Right dlPFC	Right insula	Emotion regulation problems	PTSD severity	Anger	Dissociation severity	Borderline severity	Depression severity	Tension before scan	Tension after scan
Left amygdala	-	-	-	-	-	-	-	-	-	-	-	-	-
Right amygdala	.734** (n=106)	-	-	-	-	-	-	-	-	-	-	-	-
Right dmPFC	.364** (n=106)	.336** (n=106)	-	-	-	-	-	-	-	-	-	-	-
Right dlPFC	.155 (n=106)	.265** (n=106)	.072 (n=106)	-	-	-	-	-	-	-	-	-	-
Right insula	.300** (n=106)	.308** (n=106)	.179 (n=106)	.364** (n=106)	-	-	-	-	-	-	-	-	-
Emotion regulation problems	-.127 (n=66)	.023 (n=66)	-.256* (n=66)	-.049 (n=66)	-.142 (n=66)	-	-	-	-	-	-	-	-
PTSD severity	-.053 (n=76)	-.005 (n=76)	-.018 (n=76)	.025 (n=76)	-.082 (n=76)	.329** (n=66)	-	-	-	-	-	-	-
Anger	.017 (n=66)	.096 (n=66)	-.131 (n=66)	-.187 (n=66)	-.191 (n=66)	.388** (n=66)	.265* (n=66)	-	-	-	-	-	-
Dissociation severity	-.206 (n=55)	-.078 (n=55)	-.276* (n=55)	-.069 (n=55)	-.348** (n=55)	.410** (n=55)	.462** (n=55)	.596** (n=55)	-	-	-	-	-
Borderline severity	.038 (n=66)	.162 (n=66)	-.095 (n=66)	-.103 (n=66)	-.167 (n=66)	.574** (n=66)	.385** (n=66)	.637** (n=66)	.436** (n=55)	-	-	-	-
Depression severity	-.060 (n=69)	.033 (n=69)	-.196 (n=69)	.041 (n=69)	-.040 (n=69)	.601** (n=66)	.479** (n=69)	.369** (n=66)	.435** (n=55)	.524** (n=66)	-	-	-
Distress rating before task	-.005 (n=78)	.072 (n=78)	-.169 (n=78)	-.178 (n=78)	.149 (n=78)	.183 (n=41)	.256 (n=49)	.206 (n=41)	.348* (n=40)	.181 (n=41)	.428** (n=43)	-	-
Distress rating after task	-.019 (n=60)	.110 (n=60)	.048 (n=60)	-.116 (n=60)	.152 (n=60)	-.051 (n=26)	.333 (n=31)	.183 (n=26)	.498* (n=25)	.001 (n=26)	.326 (n=27)	.854** (n=59)	-

Note. dmPFC = dorsomedial prefrontal cortex; dlPFC = dorsolateral prefrontal cortex; PTSD = posttraumatic stress disorder

* p <.05; ** p < .01

Bayesian analysis

There was moderate to strong credible evidence for lower activation in the bilateral superior occipital cortex in participants with PTSD+BPD (P+ = 0.957 left and P+ = 0.947 right), and PTSD+CPD (P+ = 0.990 left and P+ = 0.976 right) compared to control participants, while there was very strong credible evidence for higher activation in these occipital areas in participants with PTSD+BPD+CPD compared with participants with PTSD+BPD (P+ = 1.000 left and right), participants with PTSD+CPD (P+ = 1.000 left and right) and control participants (P+ = 0.002 left and P+ = 0.004 right). There was moderate support for higher activation in the bilateral dmPFC in participants with PTSD+BPD+CPD than control participants (P+ = 0.067 and 0.073). Activation in all ROIs was higher in the participants with PTSD+BPD+CPD than both participants with PTSD+BPD and PTSD+CPD, with moderate to strong support for the difference in almost all ROIs. See Supplementary Table 3 for all mean differences, standard deviations and P+ values, Supplementary Figure 3 for boxplots of the activation in all brain areas from this analysis and Supplementary Figure 4-9 for the posterior distributions of all the contrasts.

Whole-brain analysis

After Family-Wise Error correction ($p < .05$), one area showed significant differences between the groups. In the left supramarginal gyrus, activation was higher in the PTSD+BPD+CPD group than the PTSD+BPD group (Montreal Neurological Institute coordinates (-44,-24,18*; Z* = 4.85, $p_{FWEcorr}$ = .020, cluster size = 6). See Supplementary Table 4 for the full list of uncorrected findings from the whole-brain analyses.

Discussion

In this study, we investigated differences in brain activation during an emotional face task between participants with PTSD and comorbid CPD and/or BPD and with matched control participants. There were no significant differences in activation between the groups using ANCOVAs, when corrected for medication status. Bayesian analyses showed credible evidence for higher activation in almost all ROIs in the PTSD+BPD+CPD participants, which is the group with statistically significant more clinical symptoms, compared to the PTSD+BPD and PTSD+CPD groups. Transdiagnostically, i.e. across all PTSD groups, dissociation severity was negatively related to right insula and right dmPFC activation, and severity of emotion regulation problems was negatively related to right dmPFC activation.

It is remarkable that we did not observe a case-control difference in amygdala, dmPFC, insula and dlPFC (corrected for medication status) activation, despite this being a robust finding in PTSD and BPD literature (e.g. 13). It is possible that comorbid dissociation

and depression symptoms clouded our results. Specifically, dissociation scores in our PTSD+BPD+CPD group appear to be higher than the scores in the samples used in a meta-analysis on amygdala activation in PTSD and BPD (42). In general, dissociation has been related to lower amygdala and insula activation (see 11 for an overview). Furthermore, depression scores in our sample indicate severe depression (35) and activation in the amygdala, insula and middle frontal gyrus have been found to be lower in depressive patients than control participants or than participants with PTSD or BPD (13). Finally, individuals with PTSD and comorbid personality disorders, as included in the present study, might use opposite neurobiological circuits during emotional processing and cancel each other out. In fact, participants with PTSD showed higher dlPFC activation compared with control participants, while this was lower in participants with BPD (Schulze, Schulze (13).

All together, we did not find robust support for categorical differences between PTSD+BPD and PTSD+CPD participants, while symptom severity associates with specific brain activation patterns taking the categories together. The transdiagnostic negative association between emotion regulation problems and dmPFC activation is in line with earlier studies showing that the dmPFC is involved in reappraisal of negative emotions, with activation related to planning of a response to imminent threat and regulation of the amygdalar response (43). The negative association between dissociation severity and activation in the right dmPFC and right insula is also in line with the conceptualization of dissociation as a coping mechanism of overmodulation of emotions, where increased activation of prefrontal areas (dmPFC) associates with decreased activation of emotion processing areas (amygdala, insula) (11, 16). Although the negative association between dissociation and insula activation fits within this model, the negative association between dissociation and dmPFC activation does not. In a systematic review, Roydeva and Reinders (44) describe higher dmPFC activation in dissociation across disorders and paradigms. In fact, the Bayesian analyses show support for higher activation in all ROIs (such as the amygdala, hippocampus, dlPFC, dmPFC) in participants with PTSD+BPD+CPD than participants with PTSD+BPD or PTSD+CPD. This is in line with new ways of conceptualizing personality disorders, such as in the latest revision of the International Classification of Diseases, where personality disorders are no longer classified categorically but are rated along a severity scale (45).

Strengths of this study are the participation of a rarely studied, clinically relevant group with comorbid PTSD, borderline and/or cluster C personality disorders. As far as we know, this is one of the first fMRI studies in this group. Another strength is the application of Bayesian analyses in fMRI research. The present study showed a difference in the findings between the case-control analyses and the Bayesian analyses, where the Bayesian analysis seems to be more sensitive to detect activation differences between

the groups. An important advantage of a Bayesian over a classic ANOVA analysis, is that it integrates information from all ROIs, instead of analyzing them as separate entities and then later correcting for multiple testing (40). This makes the Bayesian analysis more efficient. Importantly, traditional statistical analyses give dichotomous results as the main outcome, giving rise to loss of a lot of information from the data. Bayesian analyses leave room for more dimensional and nuanced interpretations (46).

Some limitations apply. First, we did not include a PTSD-only or a BPD/CPD-only control group. This could have helped interpretation of the findings by isolating the clinical symptoms and diagnoses of participants. Secondly, we did not include a measure for state dissociation during scanning. Evidence suggests that dissociation-related brain alterations in BPD may be best detected during acute dissociation in the scanner (47), while we measured trait dissociation outside of the scanner. Future studies could include an adapted version of the Response to Script Driven Imagery Scale (48) in their scanning protocols to measure state dissociation. Thirdly, we do not have clinical measures for the control subjects. Although we would expect little variation and generally low scores in this group, it could be interesting to compare correlations between clinical and brain activation measures between PTSD and control subjects. Finally, we lack information about the indication for medication prescription. We unexpectedly found higher activation in the amygdala in the medicated participants when compared to unmedicated PTSD participants.

There are no differences on clinical measures or level of distress during the scan between these groups, except for lower borderline symptoms in the medicated group. Medication is not a first-line treatment for PTSD and only two types of medication are approved for use in PTSD (sertraline and paroxetine; see 49 for an up-to-date overview of pharmacological intervention in PTSD). This means that participants in our sample could be prescribed specific medication ór for a comorbid (affective) disorder, ór for specific PTSD symptoms, making it more difficult to interpret our findings.

Conclusion

This is one of the first studies that investigates brain activation in participants with PTSD and a comorbid personality disorder, a group that is very prevalent in clinical practice. All in all, we did not find support for categorical differences between the PTSD+BPD and PTSD+CPD groups, but found significant associations between severity of clinical symptoms (transdiagnostically and in the PTSD+BPD+CPD group) and activation in the right insula and right dmPFC. Our findings fit in a transdiagnostic and dimensional approach to personality disorders.

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Supplementary materials

The supplementary materials for this chapter can be accessed through https://surfdrive.surf.nl/files/index.php/s/Pufgdt0eTPz2VWs.

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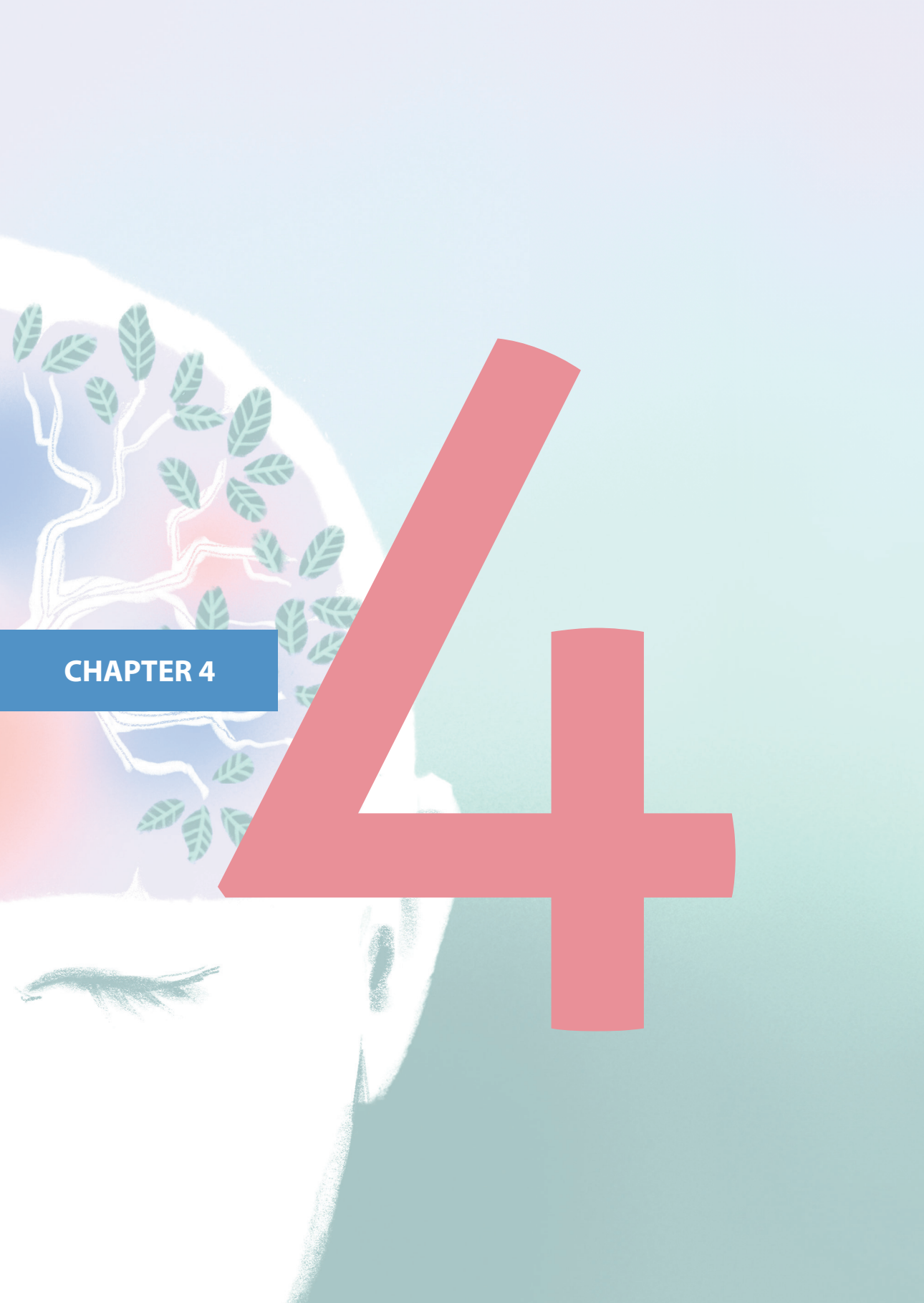
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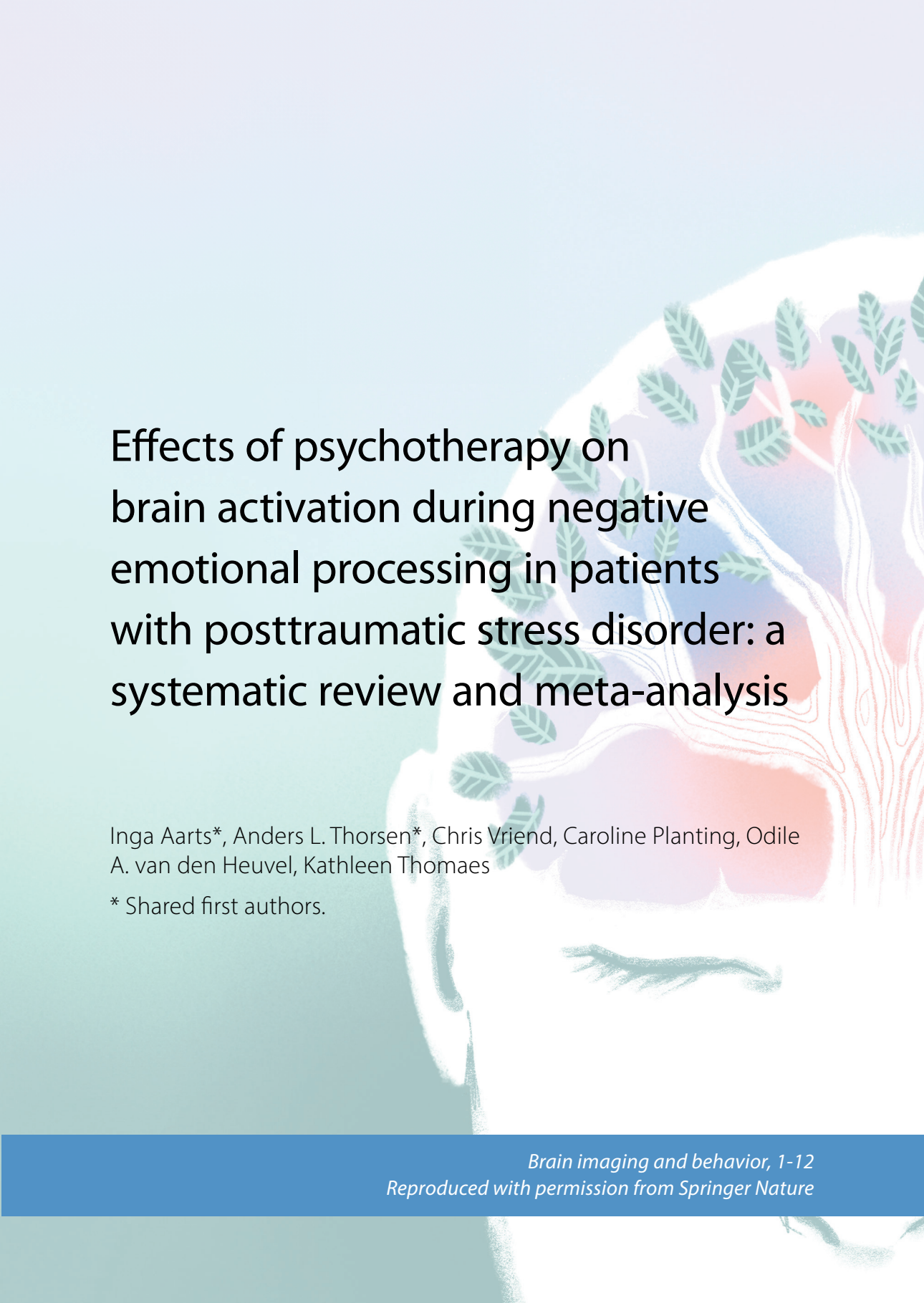

Effects of psychotherapy on brain activation during negative emotional processing in patients with posttraumatic stress disorder: a systematic review and meta-analysis

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Brain imaging and behavior, 1-12

Abstract

Introduction

Post-traumatic stress disorder (PTSD) is a debilitating condition which has been related to problems in emotional regulation, memory and cognitive control. Psychotherapy has a non-response rate of around 50% and understanding the neurobiological working mechanisms might help improve treatment. To integrate findings from multiple smaller studies, we performed the first meta-analysis of changes in brain activation with a specific focus on emotional processing after psychotherapy in PTSD patients.

Methods

We performed a meta-analysis of brain activation changes after treatment during emotional processing for PTSD with seed-based *d* mapping using a pre-registered protocol (PROSPERO CRD42020211039). We analyzed twelve studies with 191 PTSD patients after screening 3700 studies. We performed systematic quality assessment both for the therapeutic interventions and neuroimaging methods. Analyses were done in the full sample and in a subset of studies that reported whole-brain results.

Results

We found decreased activation after psychotherapy in the left amygdala, (para) hippocampus, medial temporal lobe, inferior frontal gyrus, ventrolateral prefrontal cortex, right pallidum, anterior cingulate cortex, bilateral putamen, and insula. Decreased activation in the left amygdala and left ventrolateral PFC was also found in in eight studies that reported whole-brain findings. Results did not survive correction for multiple comparisons.

Discussion

There is tentative support for decreased activation in the fear and cognitive control networks during emotional processing after psychotherapy for PTSD. Future studies would benefit from adopting a larger sample size, using designs that control for confounding variables, and investigating heterogeneity in symptom profiles and treatment response.

Keywords: posttraumatic stress disorder; meta-analysis; seed-based *d* mapping; psychotherapy

Introduction

Many people experience a traumatic event during their lifetime (around 70%), and around 5% subsequently develop post-traumatic stress disorder (PTSD; 1). Patients with PTSD suffer from re-experiencing symptoms, hypervigilance to possible threats, avoidance of trauma-related situations and feelings, negative alterations in cognitions and mood, as well as alterations in arousal and reactivity (2). PTSD is a debilitating condition which has been related to problems in emotion regulation and cognitive control and this is reflected in recent neuroimaging studies. Meta-analyses on fMRI studies using paradigms that elicit fear or other aversive emotions (such as the emotional faces task, conditioned fear paradigm or symptom provocation) have shown altered activation in PTSD patients compared to healthy controls in the amygdala, insula, striatum, and temporal gyrus (3, 4). The level of activation was also partly found to be positively associated with PTSD severity (5).

Neurobiological models of emotion dysregulation in PTSD have evolved over time. Rauch, Shin and Phelps (6) based the first model on fear conditioning models, where amygdala hyperactivation fails to be regulated by (medial) prefrontal regions and the hippocampus, while hippocampus overaction leads to impairments in fear contextualization/generalization. Lanius, Vermetten (7) later described two subtypes of PTSD with their own model of emotion dysregulation. The original re-experiencing/hyperarousal subtype, with failing inhibition of limbic areas such as the amygdala accompanied by the lower activation in medial prefrontal regions (e.g. the ventromedial prefrontal cortex (vmPFC) and rostral anterior cingulate cortex (rACC)) is specified as the "undermodulation" of emotions (7). The dissociative subtype, on the other hand, shows an unusually high activation in emotion regulation areas such as the dorsal ACC and medial PFC, and is specified as the "overmodulation" of limbic areas (7).

Later neurocircuitry models of PTSD and have been extended to include the salience and central executive networks as well as the fronto-limbic circuit (8). The salience network is involved in emotion regulation, conflict management and reward processing and is overactive in PTSD (8). Important regions in the salience network are the amygdala, insula and dorsal ACC. Conceptually the salience network overlaps partly with the fear network (LeDoux and Daw, 2018, LeDoux and Pine, 2016). The central executive network is involved in attentional control and working memory and has been found to be hypoactive in patients with PTSD (8). The central executive network overlap with the cognitive control network (9, 10). Important brain regions involved in this network are the dorsolateral PFC and lateral parietal cortices. Patients with PTSD show less activation in the default mode network, which includes areas such as the medial PFC, posterior

cingulate cortex and parahippocampal gyrus and is involved in internal processes such as self-referential thinking (8)

There is some evidence that the altered activation in areas in the salience, central executive and default mode networks might be normalized by psychological treatment. Current first-line psychological treatments for PTSD includes trauma-focused psychotherapies such as prolonged exposure therapy, eye-movement desensitization and reprocessing (EMDR), and cognitive processing therapy (11). Common elements in al therapies are exposure to the memory of the traumatic event, cognitive processing, targeting of emotions and emotion regulation skills (12). Trauma-focused psychological treatment for PTSD generally has clinically relevant positive effect (13) with large effect sizes (14), but nonresponse rates can go up to 50% (15). Understanding how activation in the brain changes after therapy might help to improve treatment response, e.g. through transcranial magnetic stimulation (16).

So far, three systematic reviews have been published on the effect of psychotherapy on the brain in PTSD, both structural and functional. Thomaes, Dorrepaal (17) conclude that studies show a decrease in amygdala activation and an increase in dlPFC activation after therapy. Malejko, Abler (18) also conclude a decrease in amygdala activation after successful therapy, next to a decrease in the insula, and an increase in dorsal ACC and hippocampus activation. Manthey, Sierk (19), on the other hand, conclude that change in amygdala activation is unclear and that there is some evidence of increased activation in the mPFC, albeit in different areas across studies and not in all studies. These diverging conclusions highlight the importance of meta-analysis for quantitatively assessing how robust the reported findings are (20). A possible reason for the diverse conclusions from these reviews is the heterogeneity of included studies, which included a range of scanning paradigms and both pharmacological and psychotherapeutic interventions.

To overcome some of the limitations of the previous reviews, we performed a pre-registered coordinate-based meta-analysis of functional neuroimaging studies to identify the most consistent findings of change in brain activation patterns after trauma-focused psychotherapy for PTSD (PROSPERO CRD42020211039). As impaired emotion processing is a core symptom of PTSD and to improve homogeneity between the studies, we limited the inclusion of studies to those that probed emotional processing by directly comparing negative emotional and neutral stimuli using a pre- to post-treatment design.

Method

Study Selection

A systematic literature search was conducted in PubMed, APA PsycInfo (EBSCO), Embase (Embase.com), and Web of Science (Clarivate), from inception until December 14th, 2021. Search terms were a combination of various forms of the terms: "PTSD" and "Imaging" (see supplementary materials for the full list of search terms). To be as inclusive as possible, we chose not to include 'psychotherapy' as a search term but manually select the intervention studies during the screening procedure. To increase homogeneity between studies, we only included studies that used a negative versus neutral contrast. Inclusion criteria were that the studies: 1) included a sample of patients with PTSD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD); 2) used an emotional paradigm with a negative emotional and a neutral condition during functional neuroimaging (functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT) or positron emission tomography (PET); 3) used this paradigm before and after trauma-focused psychotherapy; 4) reported activation data for a contrast of a negative emotional condition versus a neutral condition. We did not have any exclusion criteria.

After removing all duplicates, two authors (IA and ALT) independently screened all titles and abstracts through Rayyan (https://rayyan.qcri.org) followed by all remaining full texts. Disagreements were solved by consensus. This study was preregistered in PROSPERO (CRD42020211039).

Data extraction and quality assessment

Data were extracted from the papers by two authors (IA and ALT). We extracted information about patient demographics (age, sex), diagnosis (PTSD severity before and after treatment, type of trauma, comorbidity), treatment (type of treatment, number of sessions), and medication use in patients. We also extracted data on time between scans, type of scanner, scanning sequence parameters, software used to analyze the data, statistical methods and thresholds, coordinates of significant peak voxels where patients showed changes in brain activation during a negative versus neutral emotional condition, as well as the corresponding t-value. Finally, we extracted data about task design, stimuli presentation, and timing, as well as the contrasts being used.

All included papers were independently assessed for methodological quality (by IA and ALT), using a 22-item rating scale developed for psychotherapy studies (range: 0-44, 21) and 15 items from the COBIDAS checklist for neuroimaging studies (See Supplemental Materials; range: 0-15, 22)). We determined the intraclass correlation between the raters

with a two-way random model with absolute agreement while the final quality ratings were settled through consensus.

Statistical analyses

Preprocessing and meta-analysis of significant peak coordinates from the included studies was performed using seed-based *d* mapping (SDM; https://www.sdmproject.com; 23). SDM handles both positive and negative peak coordinates using reported t-values in a single map per study, leading to more nuanced statistical parametric maps. Hedge's g effect size was estimated per voxel, and the map was smoothed by an anisotropic Gaussian kernel using a gray-matter-specific template (24). The statistical parametric maps were then included in a random-effects meta-analysis weighted by sample size and within- and between-study heterogeneity. This resulted in a whole-brain map of changes in brain activation from pre- to post-treatment. First, we investigated changes in brain activation after psychotherapy using all available data, including studies with whole-brain analyses and those using regions of interest (ROIs, see Supplementary materials for full list of ROIs included in the studies). We included as a covariate whether a study included ROI findings (yes/no). To further ensure that findings were not driven by ROI-based studies with less stringent statistical thresholds we re-ran the analyses by including only whole-brain studies. We used a meta-regression to investigate the relationship between changes in activation after psychotherapy and the effect size of the treatment on clinical symptoms (Cohen's *d*), calculated as [PTSD severity pre-treatment - PTSD severity post-treatment)/SD pre-treatment]. We report results at an uncorrected statistical level (two-tailed $p<.05$ for the overall change in activation after therapy and $p<.005$ for the meta-regression) and corrected for multiple comparisons using threshold-free cluster enhancement (TFCE) correction ($p<.05$). Publication bias was assessed using Egger's test and I^2 as a measure of the heterogeneity.

Results

Characteristics of the included studies

Our search identified 3700 unique records. After title/abstract screening, 39 studies remained for full-text screening. We excluded 27 studies for the following reasons: absence of post-treatment scan (n=2), absence of relevant negative emotional vs. neutral contrast (n=11), absence of activation data (n=5), patients not receiving treatment (n=4), no PTSD sample (n=1), or insufficient details e.g., on the statistics (n=4). Attempts were made to contact the corresponding authors in cases where information was missing or ambiguous. Eleven fMRI studies and one PET study were included in the final analyses, where eight included data from whole-brain analyses (see Figure 1 for the full flow chart). Four of the twelve studies did not report a t-value or statistics that could

be converted to a t-value (25-28). We, therefore, coded peaks of increased activation from pre- to post-treatment as "positive" and decreased activation as "negative", as is standard practice in SDM.

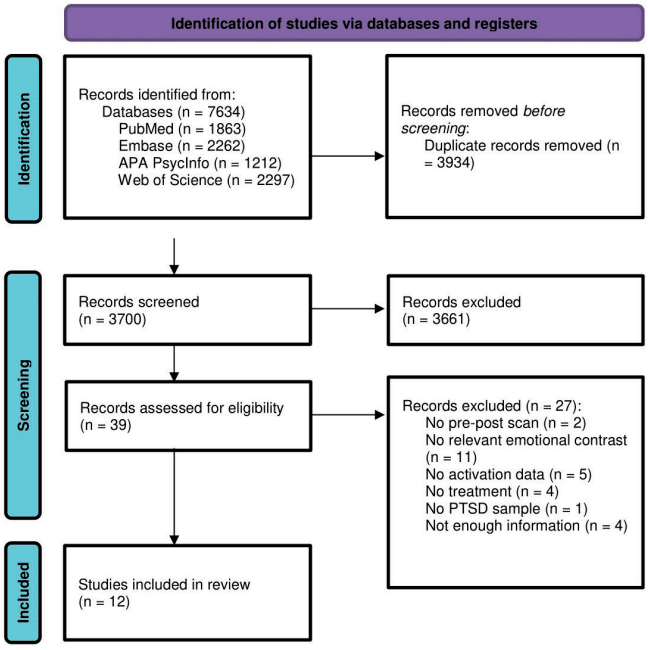

Figure 1. Flow chart of included studies

The 12 included studies included a total sample of 191 patients with PTSD with both pre- and post-treatment scans (See Table 1 for full information about the samples). Of the included studies, 11 included an adult sample (>18 years) while one included an adolescent sample (26). Since activation patterns for adolescents can be similar to adults (29) we have included this study in our meta-analysis. Most studies used the Clinician-Administered PTSD Scale–DSM IV (CAPS-IV) as the main PTSD severity measure, while two studies (26, 30) used the self-reported UCLA PTSD Reaction Index for DSM-IV (PTSD-RI) or PTSD Checklist Scale (PCL-S), respectively. Two studies included patients with partial PTSD who did not all fulfill the full diagnostic criteria (25, 31). In one study, 79% of patients had full PTSD but analyses were not reported separately for full and partial PTSD (25). In another study of working police officers all patients fulfilled the re-experiencing and hyperarousal criteria but not the numbing or avoidance criteria (31). Treatment duration ranged from a mean of 2.5 to 20 sessions. Eight studies used cognitive behavioral therapy/prolonged exposure (25-27, 31-35), two used mindfulness-based therapies (28, 36), and two used either EMDR or a mix of EMDR and cognitive

behavioral therapy (30, 37). (See Table 2 for estimated standardized mean difference changes in symptom severity after psychotherapy). Five studies used an emotional faces task (26, 28, 30, 32, 33), three used symptom provocation (31, 36, 37), one used fear extinction (34), and three used cognitive tasks with emotional stimuli (25, 27, 35).

Table 1. Characteristics of the included studies

Paper	N	Mean age (SD)	% Women	Type of trauma	% Comorbid depression	Other comorbidities	PTSD severity measure	Intervention (Mean number of sessions)	Control group	% Concurrent medication use	Imaging method	Task paradigm	Whole-brain contrast
Randomized controlled trials													
Bremner, Mishra (36)	9	34 (7)	0	War (veterans)	Not reported	Not reported	CAPS-IV	Mindfulness-based stress reduction; MBSR (9)	Present-centered group therapy	0 (last four weeks)	PET	Symptom provocation (trauma related pictures & sounds)	No
Fonzo et al. (2017)	36	34.42 (14.72)	64	Not specified	50	Not reported	CAPS-IV	Prolonged exposure; PE (9-12)	Waitlist	8.3%	3T fMRI	Emotional faces (fearful vs neutral)	Yes
King, Block (28)[#]	14	32.43 (7.54)	0	War (veterans)	93	21% anxiety, 21% substance abuse	CAPS-IV	Mindfulness-based exposure therapy; MBET (13.5)	Present-centered group therapy	86%	3T fMRI	Emotional face task (fearful vs shapes)	Yes
Thomaes et al. (2012)	16	35.20 (9.9)	100	Child abuse	62	76% anxiety, 75% personality disorder	CAPS-IV	Psychoeducation, skills training, CBT techniques and TAU (20)	TAU	66%	1.5T fMRI	Emotional Stroop task (trauma words vs neutral words)	No
Pre-post design													
Aupperle, Allard (25)	14	40.07 (7.44)	100	Intimate partner violence	Not reported	Not reported	CAPS-IV	Cognitive therapy for battered women; CTT-BW (11.57)	No	0 (last four weeks)	3T fMRI	Continuous performance task with trauma unrelated affective stimuli	Yes
Felmingham, Kemp (32)	8	36.80 (8.8)	62.50	Assault or car accident	50	Not reported	CAPS-IV	Cognitive behavior therapy	No	25%	1.5T fMRI	Emotional faces (fearful vs neutral)	Yes
Garrett et al. (2019)	20	15.30 (1.9)	90	Interpersonal trauma	50	35% anxiety	PTSD-RI	Trauma-focused Cognitive behavior therapy; TF-CBT (max. 20)	Healthy controls	0	3T fMRI	Emotional faces (angry vs scrambled)	Yes

Table 1. Continued

Paper	N	Mean age (SD)	% Women	Type of trauma	% Comorbid depression	Other comorbidities	PTSD severity measure	Intervention (Mean number of sessions)	Control group	% Concurrent medication use	Imaging method	Task paradigm	Whole-brain contrast
Helpman, Marin (34)	16	35.31 (9.89)	73.33	Not specified	0	Not reported	CAPS-IV	PE (10)	Trauma-exposed healthy controls	0 (last four weeks)	1.5T fMRI	Fear conditioning – extinction recall	No
Peres et al. (2011)	12	31.20 (5.8)	0	Gunfire attack (police officers)	0	0%	CAPS-IV	Exposure based therapy and cognitive restructuring (15)	Trauma-exposed healthy controls and waitlist	0	1.5T fMRI	Symptom provocation (trauma related sounds)	Yes
Rousseau, El Khoury-Malhame (30)	16	35.40 (8.4)	43.75	Single traumatic event	56.25	12.5% social phobia, 37.5% generalized anxiety disorder, 18.75% panic disorder, 37.5% agoraphobia, 6.25% alcohol abuse	PCL-S	EMDR (2.5)	Healthy controls	25% antidepressants, 6.25% antidepressants and anxiolytics	3T fMRI	Emotional faces (Fearful/ angry vs shapes)	Yes
Simmons et al. (2013)	9*	32.90 (7.2)	0	War (veterans)	88	56% anxiety, 22 % personality disorder	CAPS-IV	PE (12)	Non-responders	0 (last two weeks)	3T fMRI	Continuous performance task with trauma related vs unrelated stimuli	Yes
Van Rooij et al., 2016	21*	35.20 (9.3)	0	War (veterans)	47.62	15% anxiety disorder	CAPS-IV	CBT/EMDR (duration unknown)	Non-responders	50%	3T fMRI	Symptom provocation (trauma unrelated pictures)	No

[#] Partial randomized controlled trial *Remitters only. CAPS-IV = Clinician Administered PTSD Scale (DSM-IV); CBT = cognitive behavior therapy; EMDR = Eye movement desensitization and reprocessing; PCL-S = PTSD Check List Scale; PFC = prefrontal cortex; PTSD = posttraumatic stress disorder; PTSD-RI = PTSD Reaction Index; ROI = region of interest; SD = Standard deviation; TAU = treatment as usual.

Table 2. Changes in PTSD severity from pre- to post-treatment and treatment effect size

Study	Pre-treatment PTSD severity Mean (SD)	Post-treatment PTSD severity Mean (SD)	PTSD severity measure	Cohen's d*
Aupperle, Allard (25)	66.07 (16.78)	16.29 (16.81)	CAPS-IV	2.97
Bremner, Mishra (36)	56 (29)	28 (20)	CAPS-IV	0.97
Felmingham, Kemp (32)	78.1 (20)	28.9 (20.3)	CAPS-IV	2.46
Fonzo et al. (2017)	66.33 (15.17)	29.6 (21.26)	CAPS-IV	2.42
Garrett, Cohen (26)	39.1 (10.6)	22.9 (9.5)	PTSD-RI	1.53
Helpman, Marin (34)	78.53 (16.31)	28.6 (Unknown)	CAPS-IV	3.06
King, Block (28)	72.29 (18.32)	56.29 (Unknown)	CAPS-IV	0.87
Peres et al. (2011)	48 (3.62)	19 (5.03)	CAPS-IV	8.01
Rousseau, El Khoury-Malhame (30)	59.7 (10.9)	26.3 (4.9)	PCL-S	3.06
Simmons et al. (2013)	86.7 (15.4)	25.8 (16.5)	CAPS-IV	3.95
Thomaes et al. (2012)	88.5 (13.9)	66.2 (22)	CAPS-IV	1.60
Van Rooij et al. (2016)	66.3 (12.6)	24.3 (14.1)	CAPS-IV	3.33

*Cohen's D calculated as (PTSD severity pre-treatment – PTSD severity post-treatment)/SD pre-treatment. CAPS-IV = Clinician Administered PTSD Scale (DSM-IV); PCL-S = PTSD Check List Scale; PTSD = Posttraumatic stress disorder; PTSD-RI = PTSD Reaction Index; SD = standard deviation.

Changes in brain activation after therapy

The main meta-analysis of all 12 studies found six significant clusters of decreased activation after psychotherapy at an uncorrected threshold ($p<.05$, two-tailed, see Table 3 and Figure 2). The largest cluster (Figure 2A) encompassed the left amygdala, putamen, hippocampus, parahippocampus, and medial temporal lobe. The second cluster (2B) included the right putamen, pallidum and posterior insula, the third cluster (2C) included the inferior frontal gyrus (pars orbitalis), the fourth cluster (2D) the right anterior cingulate cortex, the fifth cluster (2E) the left ventrolateral PFC, and the sixth cluster (2F) included the left anterior insula. No cluster survived TFCE correction for multiple comparisons. There were no brain areas that showed a significant increase in activation after psychotherapy. A meta-regression showed no significant relationship between change in symptom severity and change in brain activation after treatment. We also found no evidence for publication bias based on Egger's tests or funnel plots, and the I^2 suggested little to moderate heterogeneity in the findings.

Decreased activation in the left amygdala, medial temporal lobe cortex and left ventrolateral PFC after psychotherapy was also found when the meta-analysis was restricted to the eight studies that reported whole-brain results, but these were not significant after TFCE-correction for multiple comparisons.

Table 3. Changes in brain activation after psychotherapy

Peak region	MNI (X/YZ)	SDM-Z	P-value	Number of voxels	I^2	Egger's test
Including all studies						
Left amygdala, putamen, (para) hippocampus, medial temporal lobe	-20,8,-18	-2.619	0.0044	216	19.88	n.s.
Right putamen, pallidum, insula	28,-2,-4	-2.485	0.0065	77	7.62	n.s.
Left inferior frontal gyrus (orbitalis)	-40,18,-16	-2.343	0.0096	20	10.40	n.s.
Right anterior cingulate	12,40,22	-2.216	0.0134	6	34.41	n.s.
Left ventrolateral prefrontal cortex	-56,4,10	-2.007	0.0224	2	4.67	n.s.
Left insula	-36,12,-10	-1.996	0.0230	2	48.01	n.s.
Including only studies assessing the whole brain						
Left amygdala, medial temporal lobe	-24,2,-20	-2.761	0.0029	79	8.25	n.s.
Left ventrolateral prefrontal cortex	-56,2,12	-2.266	0.0117	17	6.76	n.s.

MNI = Montreal Neurological instite; SDM = seed-based d mapping.

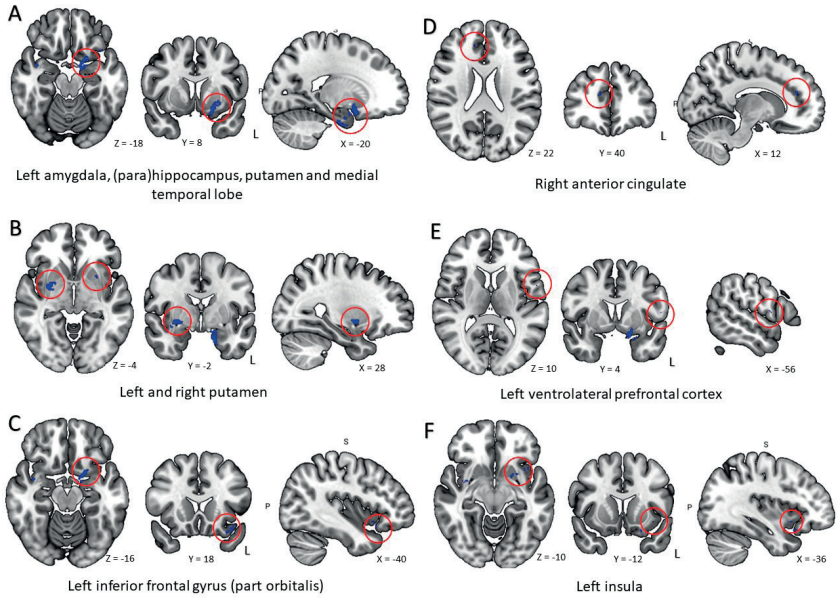

Figure 2. Changes in brain activation after psychotherapy

Results show a decrease of activation after psychotherapy in the A) left amygdala, (para)hippocampus, putamen, and medial temporal lobe; B) left and right right putamen; C) left inferior frontal gyrus (pars orbitalis); D) right anterior cingulate; E) left ventrolateral prefrontal cortex; F) left insula.

Methodological quality

As shown by the psychotherapy methodology rating scales (see Supplementary Table 2), most studies used reliable and specific outcome measures in a well described and representative sample. Four studies (33%) were randomized controlled trials, while 8 studies (66%) did not include a treatment control group. Many studies did not use blinded evaluators, only measuring symptoms and/or brain function at two time points, while also not providing information about the therapist training and competence. Most studies did not perform a power analysis and did not describe how concominant psychological and pharmacological treatments were controlled.

With regard to neuroimaging information as assessed by an adaptation of the COBIDAS checklist, most studies reported the basic parameters about the type of scanner, scanning parameters and preprocessing pipeline. Most studies also provided an adequate description of the task parameters. However, not all studies provided information about the characteristics of the scan session, summary statistics for the task or information about randomization of the stimuli within the task. The intra-class correlation coefficient for the quality ratings between the two raters was high (0.88; 95% CI 0.55-0.97). The final consensus ratings can be found in Supplementary Table 2.

Discussion

We conducted the first coordinate-based meta-analysis on trauma-focused psychotherapy-induced changes in brain activation during emotional processing in PTSD. Our findings tentatively suggest that PTSD patients show decreased activation in several regions of the fear and cognitive control networks after therapy, including the amygdala, (para)hippocampus, putamen, pallidum, insula, inferior frontal gyrus, anterior cingulate cortex, and ventrolateral PFC, although these findings did not survive correction for multiple comparisons. Decreased activation in the left amygdala and ventrolateral PFC was also found when only studies assessing the whole-brain were included, but these findings were not significant after correction for multiple comparisons.

The emotional tasks used in the included studies are designed to induce distress, fear and trauma memories. A core component of trauma-focused psychotherapy is to learn how to manage distress and intrusive memories, address negative trauma-related cognitions, and discriminate traumatic memories from the present (38). In general, patients in the included studies responded well to treatment and showed improvement in PTSD symptoms. These symptoms include hyper responsivity to threats and avoidance. We theorize that this is associated with the reduced activation we found in regions of the

fear network after successful therapy due to the reduced need for detecting threats and engaging in defensive behaviors. This is supported by previous research highlighting the role of the amygdala in the processing of immediate threats and intrusive memories and the putamen in the preparation and execution of defensive behaviors (9, 10, 39). Reduced activation in regions of the cognitive control network after therapy may reflect a decreased demand for processes such as the conscious evaluation of threat using working memory and integration with previous experiences mediated by the regions of the PFC and hippocampus (9, 10, 40, 41), or the integration of body signals involving the insula (9, 10, 42). Despite the common elements of the different types of treatment, precise working mechanisms differ. For example, EMDR works through taxing working memory and prolonged exposure through reevaluation of negative cognitions (12, 43). This might result in different changes in brain activation and might therefore lead to our current non-significant result. Because some studies compared responders to non-responders and we could not include the whole sample in our analysis and other studies reported data for all patients (responders and non-responders together), it is unclear how change in activation pattern is related to clinical improvement. Our metaregression did not give an indication for an association between treatment effect size and change in brain activation.

An important limitation of the current meta-analysis is that only twelve studies could be included, which limits the power and generalizability of the findings. Our results should therefore be seen as preliminary evidence of changes in brain activation after treatment. The patient samples in the included studies differed on many clinical characteristics, including type and duration of traumatic events, comorbidity, medication status, and type and duration of treatment. Although the variation in these clinical characteristics reflects the diversity in the causes, presentations, and consequences of having PTSD, it likely also leads to less consistent patterns of altered brain activation at the group level (44, 45). Dissociation was not assessed in most of the studies, while dissociative symptoms in PTSD have been linked to less amygdala activation and more anterior cingulate and medial PFC activation (46).

There were also some important methodological differences and shortcomings in the included studies, which should be taken into account when interpreting the results from the meta-analysis. The studies used different emotional processing tasks such as symptom provocation, cognitive tasks with emotional stimuli or fear extinction. While all studies were designed to elicit a negative emotional response, the tasks might invoke slightly different circuits in the brain. Unfortunately, we do not know of any studies that compare these different task directly. Most studies were small, which makes it unlikely to detect moderate to small changes in brain activation. A minority of studies also did not report data at the whole-brain level but only for specific ROIs, which may increase the

probability of both false positive and negative findings (47). Less statistical power due to more stringent thresholds in studies using whole-brain contrasts likely resulted in the difference between our results when including all studies versus when only including studies assessing the whole-brain.

We recommend researchers to report not only ROI results but include whole-brain analysis in their studies, to aid future meta-analyses. The majority of studies used a non-randomized pre-post treatment design without a control group or with only a healthy control group to adjust for the passage of time or repetition effects in task-related distress and brain activation. Furthermore, many studies did not report on essential elements of the training of therapists and raters which makes it hard to properly rate the quality of the treatments. The few available studies make it difficult to run meaningful meta-regressions investigating the impact of comorbidity, medication, task paradigms, or specific treatments. Future studies should include information about these clinical characteristics to aid interpretation and comparison of results.

Conclusion

Studying the neural correlates of effective treatment for PTSD is vital to identify the brain regions and mechanisms of recovery. The present meta-analysis suggests that there is tentative support for decreased activation in the fear and cognitive control networks during emotional processing after psychotherapy for PTSD. Our findings are in line with prevailing models highlighting the role of normalized threat detection, monitoring, and action preparation in clinical recovery, but fail to provide evidence for increased prefrontal activation related to cognitive control and emotion regulation (9, 10, 48). There are several limitations in the studies that influence the interpretability of these findings, the most important one the limited number of includable studies. Future studies would be strengthened by adopting a larger sample size, using designs that control for confounding variables, and investigating heterogeneity in symptom profiles and treatment response.

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Supplementary materials

The supplementary materials for this chapter can be accessed through https://surfdrive.surf.nl/files/index.php/s/Pufgdt0eTPz2VWs.

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CHAPTER 5
5

Treatment effect of posttraumatic stress disorder treatment with or without concurrent personality disorder treatment on brain activation during an emotional face task

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Abstract

Introduction The effect of trauma-focused treatment on brain activation in individuals with posttraumatic stress disorder (PTSD) and comorbid personality disorders (PD) is not yet clear. We studied differential effects of trauma-focused or integrated trauma-focused + personality treatment in individuals with PTSD+PD.

Methods Thirty-eight participants with PTSD+PD underwent 3T functional MRI scanning with an emotional faces task before and after either trauma-focused (n=22) or integrated (n=16) treatment. We used Bayesian multilevel analysis to study the main effect of treatment, differences between conditions, and the association with change in clinical measures (PTSD, depression, borderline, dissociation and emotion regulation problem severity) on task-related brain activation. Secondary analyses included a comparison of responders to non-responders.

Results In the total group, analyses showed no credible evidence for change in brain activation after treatment (all P+ values >.10 and <.90), nor difference between treatment conditions or association with clinical measures. However, there was strong credible evidence for a larger decrease in bilateral ventromedial prefrontal cortex activation in responders compared to non-responders.

Conclusion Contrary to our hypotheses, we found no credible support for change in brain activation after treatment. Responders showed decreased activation in the ventromedial prefrontal cortex in responders that might reflect a normalized emotional processing after successful treatment. It is possible that the emotional faces task was not sensitive for detecting subtle treatment effects in the brain. This study is one of the first to study the effect of treatment on brain activation in PTSD+PD.

Trial registration: Clinicaltrials.gov, NCT03833453 & NCT03833531

Clinical impact statement: In individuals with PTSD and comorbid personality disorder, we did not find credible support for change in brain activation After trauma-focused or trauma-focused and concurrent personality treatment. This is surprising considering the large clinical improvement. Possibly, an emotional face task is not sensitive enough to measure change in brain activation after treatment.

Keywords: PTSD; borderline personality disorder; cluster c personality disorder; functional MRI; emotional face task; psychotherapy

Introduction

After experiencing a traumatic event, people may develop a posttraumatic stress disorder (PTSD). PTSD has a lifetime prevalence of 4% (1) and is characterized by intrusive memories of the traumatic event, avoidance of trauma-related triggers, negative alterations in cognitions and mood, hyperarousal and in some people dissociation (2). Of all individuals with PTSD, around 22% has a comorbid borderline personality disorder (BPD) and 63% a comorbid cluster C personality disorder (CPD; 8-23% for a specific CPD 3). BPD is characterized by a pattern of unstable and intense interpersonal relationships, an unstable sense of self, impulsivity, emotion regulation problems and recurrent self-harm or suicidal behaviors (2). CPD includes avoidant, dependent and obsessive-compulsive personality disorders which share traits of fear and anxiety (2). A recent meta-analysis showed that individuals with PTSD and comorbid personality disorders profit from trauma-focused treatment, but with smaller effect sizes than individuals with PTSD without a comorbid personality disorder (4).

First line treatments for PTSD include trauma-focused cognitive behavioral therapy (CBT) and Eye Movement Desensitization and Reprocessing (EMDR; 5, 6). An emerging form of trauma-focused CBT is imaginary rescripting (IMRS; 7, 8). Trauma-focused treatment (TFT) is based on exposure to traumatic memories and principles of extinction learning and reconsolidation of the traumatic memories (6). In the brain, this relies on areas in the fear circuit and areas involved in emotional reactivity including the amygdala, dorsal anterior cingulate cortex (dACC), ventromedial prefrontal cortex (vmPFC) and insula. Specifically, a recent meta-analysis showed indications for decreased activation of the amygdala, insula and anterior cingulate cortex after treatment in individuals with PTSD (9).

For personality disorders, dialectical behavior therapy (DBT) and schema therapy (ST) are first line treatments and both aim to improve emotion regulation although the conceptual models of these treatments are different (10). Brain areas involved in emotion regulation are the dorsolateral and ventrolateral prefrontal cortex (dlPFC/vlPFC; 11). There are only a few neuroimaging studies on treatment-related changes in brain activation in individuals with BPD. One study observed that individuals with BPD responding to DBT treatment showed decreased activation post-treatment in the emotional reactivity areas (amygdala, dorsal anterior cingulate cortex; dACC) and emotion regulation areas (orbitofrontal and dlPFC) during a reappraisal task compared to pre-treatment (12). Other studies in BPD reported mixed findings, showing increased dACC, dlPFC and frontopolar activation and decreased vlPFC and hippocampal activation during an emotional go/no-go task after transference-focused therapy (13) and increased dlPFC activation during a go/no-go task after seven months of DBT (14).

To our knowledge, there are no studies about the effect of treatment on brain activation in people with CPD and very few papers about imaging in CPD in general (15).

Imaging studies on PTSD with comorbid BPD/CPD are even more scarce and it is yet unclear what the additional effect of personality focused treatment is on TFT, both on a clinical and neurobiological level. The PROSPER trials (Prediction and outcome study in PTSD and personality disorders) were designed to bridge this knowledge gap and study treatment effects in individuals with PTSD and comorbid BPD/CPD on clinical symptoms and brain activation (16-18). In the current study, we investigated changes in brain activation during an emotional face task in participants with PTSD and comorbid CPD and/or BPD after either TFT or integrated TFT + personality treatment (PT). The main research questions were: Does TFT with or without PT affect brain activity? And: is TFT versus integrated TFT+PT treatment associated with differential changes in brain activation during an emotional faces task?

Because of advances in Bayesian analytical techniques and new insights based on our previous analyses, we have chosen to adapt the regions of interest in our hypotheses and analyses for this paper relative to our previously published design paper (16). This imaging study and the hypotheses were preregistered on the Open Science Framework (https://osf.io/9be67) prior to analyses. We hypothesized that 1) task-related activation of the amygdala, dorsal ACC, insula and vmPFC during the emotional faces task would decrease after both TFT and TFT+PT, 2) that participants in the TFT+PT condition would show a larger change in activation of the above-mentioned brain areas as compared to those in the TFT only condition, with an expected additional decrease in activation in vlPFC and increase in activation in the dlPFC, and 3) that change in task-related brain activation is related to improvement in PTSD symptoms, emotion regulation and depression and dissociation severity.

Methods

Sample

The sample consists of participants from two randomized controlled trials (RCTs) in the PROSPER study. Baseline data from these participants is described in (19). Inclusion criteria were: a diagnosis of PTSD; at least three traits of avoidant or obsessive-compulsive personality disorder, and/or four traits of dependent or borderline personality disorder (i.e., one less than required for the DSM-5 diagnosis); age 18-65 years, sufficient understanding of the Dutch language for participation in group therapy and ability to provide written informed consent. Exclusion criteria were severe outward aggression, current psychosis, mental retardation, addiction or eating disorder interfering with

treatment and/or randomization, a primary personality disorder other than BPD or CPD and benzodiazepine use more than three times 10mg oxazepam (or equivalent) daily. Medication needed to be stable for at least three months. This study was approved by the ethics committee of the VU Medical Centre and conducted in accordance with the Declaration of Helsinki.

Study design

The design of the PROSPER RCTs is described in detail elsewhere (17, 18), and see (16) for a schematic overview of the trials. Briefly, participants with PTSD and comorbid BPD as assessed by the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD; 20, 21) were randomly assigned to either EMDR or EMDR+DBT (https://ClinicalTrials.gov NCT03833453). Participants with PTSD and comorbid CPD as assessed by the SCID-5-PD were randomly assigned to either IMRS or IMRS+ST (https://ClinicalTrials.gov NCT03833531). To increase statistical power, we will compare all participants in the TFT conditions together (i.e., EMDR and IMRS) with all participants in the TFT+PT conditions together (i.e., EMDR+DBT and IMRS+ST), across borderline and cluster C personality disorder diagnoses.

All participants of the two PROSPER RCT samples (17, 18) were asked if they also wanted to participate in the MRI study, until the required number of participants was achieved (see (16) for a justification of the sample size). All participants were screened for MRI eligibility (e.g., metal implants). This subset of the PROSPER participants were scanned before start of the treatment and after completing their TFT (defined as attending at least 75% of the sessions, i.e. > 8 sessions). Prior to the scan, participants filled out a questionnaire about medication and psychoactive substances they had used in the last 24 hours. In addition to the scanning session, PTSD symptoms were assessed with a clinical interview by a trained researcher and participants filled out questionnaires online.

Treatments

The treatments are described in more detail elsewhere (17, 18). Briefly, in the TFT condition, participants underwent 12 to 18 sessions of either EMDR or IMRS. Sessions took place weekly, for 60-75 minutes. Therapists were urged to deliver the first 12 sessions within 14 weeks and if indicated, a maximum of six additional sessions within six months after the start of treatment.

In the integrated TFT+PT condition, participants started with group PT, either DBT or ST. For DBT, treatment started with six weekly individual pretreatment sessions, followed by 48 weekly group therapy sessions with concurrent biweekly individual coaching sessions. ST started with four individual pretreatment sessions, followed by 40 weekly

group therapy sessions and additionally 18 sessions of schema-focused psychomotor therapy with an explicit focus on experiential schema therapy techniques delivered in three blocks during the ST. After ST, participants received three individual booster sessions of either IMRS, ST or schema-focused psychomotor therapy. TFT started after approximately 12 weeks of pretreatment and group therapy.

Measures

MRI measures

The primary outcome is brain activation, measured with functional MRI (fMRI) during an emotional face task, based on (22). The task consisted of four conditions: scrambled, fearful, angry and neutral faces. Participants saw three pictures at the same time, one on top and two below. Participants had to match the sex of the top picture to one of the bottom two pictures by pressing a button with either their left or right hand. For the scrambled condition, they had to match the orientation (horizontal or vertical) of the pictures. There were five pseudo-randomized blocks of four trials for angry and fearful faces, and six blocks for scrambled and neutral faces. The contrast of interest was fearful faces versus scrambled faces. Task performance was calculated as the proportion of correct responses.

Clinical measures

The main clinical outcome measure was change in PTSD severity, measured with the Clinician-Administered PTSD scale for DSM-5 (CAPS-5, range 0-80). The CAPS-5 is a semi-structured interview that is designed to measure the presence and severity of PTSD (23, 24). We measured problems with emotion regulation with the Difficulties in Emotion Regulation Scale (DERS, range 36-180; 25), trait dissociation with the Dissociative Experiences Scale (DES, range 0-100; 26), depression severity with the Beck Depression Inventory (BDI, range 0-60; 27) and borderline symptom severity with the Personality Assessment Inventory – Borderline features (PAI-BOR; Range 0-72; 28). Before and after the emotional face task, participants rated their tension level on a scale from 0 to 100.

MRI acquisition and preprocessing

Scans were acquired on a 3T MRI scanner (GE Discovery MR750; General Electric, Milwauki, WI, USA) using a 32-channel head coil. Participants were scanned before and after TFT. Full imaging parameters of the scans are described in (16). First, we acquired anatomical T1 scans (TR = 6.9ms, TI = 900ms, TE = 3ms, flip angle = 9°, 168 slices, slice thickness 1 mm, matrix size 256x256). For the functional MRI scans, blip-up/down scans with opposite phase encoding directions with the same field-of-view were acquired to correct for susceptibility induced distortions and we performed high order shimming to homogenize the B0 magnetic field during the functional scans. We acquired 205 volumes (TR = 2200ms, TE=26ms, flip angle = 80°, 42 slices, slice thickness = 3mm, matrix

size = 64x64, 3.3 x 3.3 in plane resolution). Participants saw the task (programmed in E-prime version 2.0.10.353; Psychology Software Tools, Pittsburgh, PA) on a projector screen through a mirror mounted on the head coil.

Analyses

Preprocessing

Functional images were processed through the 'fmriprep' pipeline (29) and smoothed by applying an 8mm full-width half-maximum smoothing kernel, see supplements for the full boilerplate. First level analyses were performed in Statistical Parametric Mapping 12 (SPM 12; Wellcome Trust Centre for Neuroimaging, London, UK). Contrast estimates from the regions of interest (ROIs) were extracted using Marsbar.

For the first hypothesis, ROIs were the amygdala, dACC, insula and vmPFC. The amygdala was defined through the Automated Anatomical Labeling (AAL) atlas. The left and right insula (±36,-4,8; (30)), vmPFC (±4,41,-8; (31)), and dorsal ACC (±18,40,17; (31)) were built with 5mm spherical ROIs around the mentioned x,y,z coordinates in MNI space. ROIs were based on previous meta-analyses that found case-control differences between individuals with PTSD and/or a personality disorder relative control subjects on emotional processing tasks.

For the second and third hypotheses, additional ROIs were the bilateral dlPFC (±36,40,24; (30)) and vlPFC (±56,2,12; 9), again based on meta-analyses that studied changes in activation after treatment.

Statistical analyses

Primary analyses. To test our hypotheses, we used the Region-Based Analysis Program through Bayesian multilevel modeling (RBA, v1.0.10; 32). Age, sex and time between scans were added to all analyses as covariates. In RBA, the outcome is not a significance level but a Bayesian P+ value, which represents the area under the curve of the positive posterior distribution. The further away the median of the distribution is from zero, the larger the effect. P+ values are a measure for strength of support for the effect. P+ values >.975 and <.025 provide very strong (or credible) support, values >.95 or <.05 strong support and values >.90 or <.10 provide moderate support. To test hypothesis 1), we compared pre-post treatment change in task-induced activation across all treatment groups. For hypothesis 2), we compared pre-post change in activation in participants in the TFT condition to participants in the TFT+PT condition. Finally, for hypothesis 3), we correlated change in brain activation to change in PTSD symptoms (CAPS-5 T0-T2), change in emotion regulation (DERS T0-T2), change in depression severity (BDI T0-T2) and change in dissociation severity (DES T0-T2), while correcting for baseline severity of that measure. As post-hoc analyses, we analyzed the association between change

in PTSD severity and change in brain activation for both conditions separately. We also reran the analyses for hypothesis 3 with imputed data for missing questionnaire data, through multiple imputation in SPSS (IBM SPSS Statistics 28).

After visually inspection of the data, the MRI Quality Control Tool (33) and reports from fmriprep were used to assess the quality of the data. We checked quality parameters such as framewise displacement and signal to noise ratio. Scans with a mean framewise displacement of >0.5mm were excluded (34). Outliers on clinical measurements were only removed in case of an invalid value.

Secondary analyses. As sensitivity analysis, we added medication status as an additional covariate and as post-hoc analysis, we reran the main analysis without participants who switched medication during the intervention phase. Different than described in the preregistration, we compared neural response in treatment responders versus non-responders through Bayesian analyses instead of through an independent samples t-test, to be more in line with the other analyses. In line with (18), we defined treatment response as a CAPS-5 PTSD severity reduction of $SD_{pooled} \geq 1$compared to baseline. Finally, we performed an exploratory whole-brain analysis for the difference in activation after therapy with age and sex added as covariates. We ran the whole-brain analyses with a family-wise error (FWE) correction. For purposes of possible future meta-analyses, we also ran the analyses uncorrected with $p < .001$ and a minimum extent cluster threshold of 5 voxels.

Results

Sample

Of the 89 included participants for a magnetic resonance imaging (MRI) scan (19), 41 returned for a posttreatment scan. The final analysis sample comprised 38 participants, 22 in the TFT condition and 16 in the TFT+PT condition, see Figure 1 for a flow chart and reasons for dropout. Table 1 shows demographic and clinical measures of the participants. Most of the participants identified as female (73.7%) and as of Dutch ethnicity (63.2%). Other ethnicities included Belgian, Surinam and Indonesian, see footnote under Table 1. The median education category was ISCED level 3, which is equivalent to finishing high school. A large proportion of participants used medication (44.4%), most commonly antidepressants and low dose antipsychotic medication (mostly off-label for sleeping problems in PTSD). Of the 17 participants who used medication, five switched during their treatment. Three (in the TFT condition) discontinued (part of) their medication and two (one in each condition) started using medication. Regarding comorbidity, almost half of the participants fulfilled criteria for a BPD (47.4%) and/or a depressive disorder

(47.4%). Around 10% fulfilled criteria for a substance use disorder and 10-25% for an anxiety disorder. See Supplementary Table 1 for a full list of comorbid disorders. The groups differed significantly on weeks between scans, with more time between scans for the TFT+PT condition which is in line with the design of the study (with TFT starting later in this group). Mean scores for all clinical measures decreased from T0 to T2 (see Table 1). Pre- to posttreatment change in PTSD severity was significant: $t(37) = 8.609$, $p < .001$. In the full sample, 65.8% of participants were classified as responders. For the trauma-focused treatment, this was 72.7%; for the combined treatment, 56.3%.

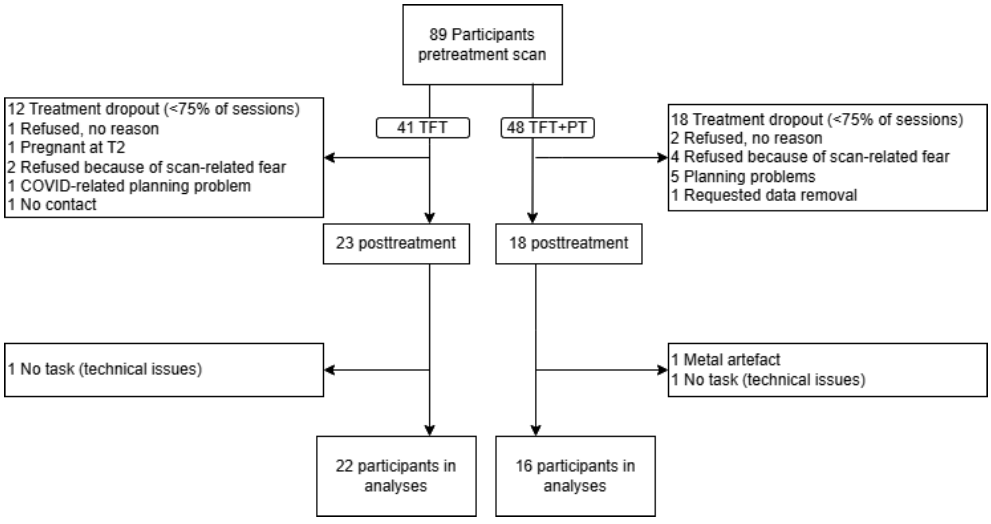

Figure 1. Flow chart of participants

Table 1. Demographic and clinical measures

	Full sample (n=38)	Trauma-focused treatment (n=22)	Trauma-focused + personality treatment (n=16)	Group comparisons
Age (years)	40.87 (10.65)	40.41 (11.64)	41.50 (9.45)	$t(36) = -0.308$, $p = .760$
Sex (f)	28 (73.7%)	17 (77.3%)	11 (68.8%)	$\chi^2(1, N=38)$, $p = .556$
Sex (m)	10 (26.3%)	5 (22.7%)	5 (31.3%)	
Ethnicity				$\chi^2(1, N=38)$, $p = .542$
Dutch	24 (63.2%)	13 (59.1%)	11 (68.8%)	
Other[a]	13 (34.2%)	8 (36.4%)	5 (31.2%)	
No information	1 (2.6%)	1 (4.5%)	0 (0%)	
Education	3 [4]	3 [1.75]	3 [3]	
Medication use T0 (Yes)	17 (44.4%)	11 (50%)	6 (37.5%)	$\chi^2(1, N=38)$, $p = .444$
Time between scans (weeks)	30.39 (13.26)	24.06 (9.49)	39.11 (12.94)	$t(36) = -4.141$, $p < .001$
Number of sessions	13.05 (3.42)	12.50 (3.07)	13.81 (3.82)	$t(36) = -1.175$, $p = .248$
PTSD severity T0	43.24 (11.38)	41.50 (11.31)	45.62 (11.40)	$t(36) = -1.106$, $p = .276$
PTSD severity T2	22.67 (15.91)	22.05 (17.15)	23.52 (14.53)	$t(36) = -0.275$, $p = .785$
Emotion regulation problems T0	120.75 (19.90)	117.10 (20.07)	125.31 (19.34)	$t(34) = -1.240$, $p = .223$
Emotion regulation problems T2	98.30 (26.57)	97.83 (27.71)	98.87 (26.09)	$t(31) = -0.110$, $p = .913$
Depression severity T0	34.32 (12.03)	31.05 (12.43)	38.63 (10.33)	$t(35) = -1.973$, $p = .056$
Depression severity T2	21.36 (14.89)	20.55 (14.26)	22.38 (16.05)	$t(34) = -0.361$, $p = .720$
Dissociation severity T0	24.47 (15.76)	23.50 (17.04)	25.69 (14.46)	$t(34) = -0.410$, $p = .685$
Dissociation severity T2	13.97 (11.51)	13.91 (13.00)	14.04 (9.75)	$t(34) = -0.033$, $p = .974$
Borderline symptom severity T0	37.89 (8.19)	37.90 (8.39)	37.88 (8.20)	$t(34) = 0.009$, $p = .993$
Borderline symptom severity T2	30.24 (10.30)	30.67 (10.43)	29.73 (10.48)	$t(31) = 0.255$, $p = .800$
Distress rating before task T0	37.45 (27.79)	34.29 (27.00)	41.92 (9.75)	$t(27) = -0.721$, $p = .477$
Distress rating after task T0	40.32 (26.31)	39.80 (27.47)	40.89 (26.59)	$t(17) = -0.088$, $p = .931$
Distress rating before task T2	26.40 (22.32)	21.88 (20.94)	32.31 (23.51)	$t(28) = -1.282$, $p = .210$
Distress rating after task T2	27.94 (19.26)	22.27 (16.94)	38.33 (22.29)	$t(15) = -1.675$, $p = .115$
Task performance T0 (proportion)	0.77 (0.30)	0.76 (0.33)	0.79 (0.25)	$t(36) = -0.291$, $p = .386$
Task performance T2 (proportion)	0.88 (0.17)	0.89 (0.20)	0.87 (0.10)	$t(36) = 0.493$, $p = .313$

Values are presented as mean (SD), median [inter-quartile range] or n (%). T0 = measurement before start of treatment. T2 = measurement after trauma-focused treatment. [a] Ethnicity is diverse and included Belgian, Moroccan, Turkish, Surinam, Indonesian, Antillean, French, Panaman, British Guyanan, Vietnamese, Iraqi and Afghan descent.

Primary analyses

Figure 2 and 3 show results from the primary analyses. For hypothesis 1) in the full sample, there was no credible evidence for change from pre- to post-treatment task-related brain activation in any of the ROIs (all P+ values between .20 and .80, see Figure 2 for a ridge plot). For hypothesis 2) there was also no credible support for a difference in change in activation between the treatment groups (Figure 2).

For hypothesis 3) none of the analyses between change in brain activation and change in clinical symptoms after treatment provided credible support (all P+ values between .10 and .90; see Figure 3). The strongest (non-credible) evidence was for a positive association between a decrease in bilateral dlPFC activation after treatment and a decrease in borderline severity symptoms (P+ .84/.85), and between a decrease in bilateral vmPFC activation and decrease in borderline (P+ .84/.85) and PTSD severity symptoms (P+ .86/.86). The post-hoc analysis for the separate treatment conditions, showed moderate support for a positive association between decrease in bilateral vmPFC activation and decrease in PTSD symptoms (P+ .92/.93) in the TFT but not TFT+PT condition (Supplementary Figure 1). With imputed data for missing questionnaire data, results were similar to the original analysis.

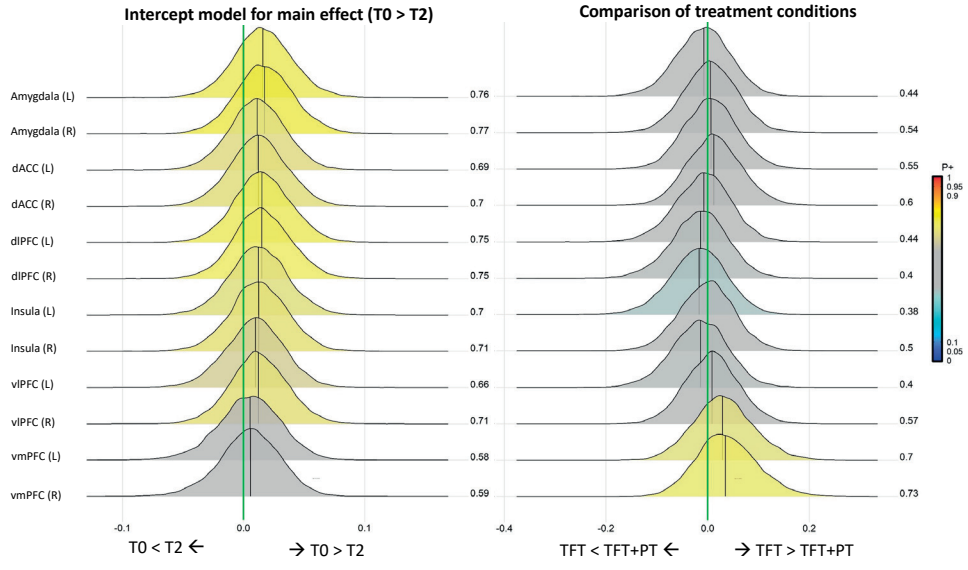

Figure 2. Ridge plot for main effect of treatment in the whole group and comparison between treatment conditions on change in task-induced brain activation

T0 = measurement before start of treatment. T2 = measurement after trauma-focused treatment. TFT = trauma-focused treatment. PT = personality treatment. P+ = posterior distribution. Values of < .10 or > .90 indicate credible support for an effect. L/R = left/right. dACC = dorsal ACC. dlPFC = dorsolateral prefrontal cortex. vlPFC = ventrolateral prefrontal cortex. vmPFC = ventromedial prefrontal cortex.

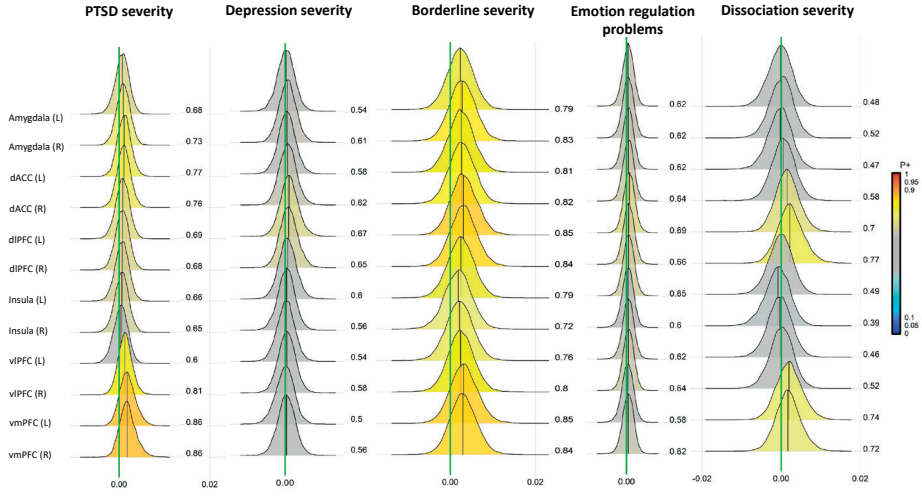

Figure 3. Ridge plots for association between change in brain activation and change in clinical measures from T0 to T2

PTSD = posttraumatic stress disorder. P+ = posterior distribution. Values of < .10 or > .90 indicate credible support for an effect. L/R = left/right. dACC = dorsal ACC. dlPFC = dorsolateral prefrontal cortex. vlPFC = ventrolateral prefrontal cortex. vmPFC = ventromedial prefrontal cortex.

Secondary analyses

With medication status at baseline as a covariate, there was no credible evidence for difference between treatment conditions (all P+ values between .20 and .30). Results remained similar when all participants who switched medication (n = 5) were removed from the analysis (P+ values between .20 and .40). See Supplementary Figure 2 for ridge plots.

There was very strong to strong support that responders show a larger decrease in pre-post change in brain activation in the right (P+ = .020) and left vmPFC (P+ = .059) compared to non-responders (see Figure 4 for the ridge plot and Supplementary Figure 3 for raincloud plots). Non-responders had significantly higher depression scores at baseline than responders ($t(34) = 2.351$, $p = .025$) and responders were more likely to use medication ($\chi^2(1, N=38)$, p = .038; see Supplementary Table 2 for a comparison of all clinical measures).

For the whole-brain analyses, see Supplementary Table 3 for all uncorrected results. With FWE correction, none of the whole-brain contrast were statistically significant.

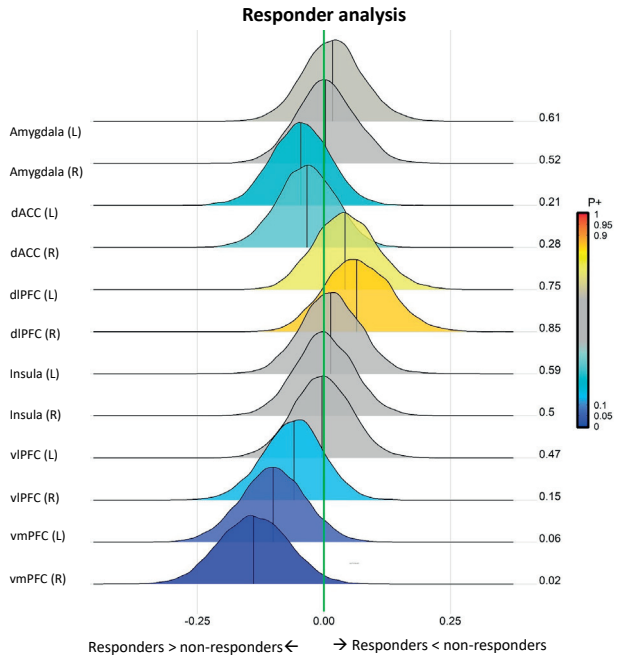

Figure 4. Ridge plot for treatment induced decrease in task-related brain activation in all ROIs, responders vs. non-responders

P+ = posterior distribution. Values of < .10 or > .90 indicate credible support for an effect. L/R = left/right. dACC = dorsal ACC. dlPFC = dorsolateral prefrontal cortex. vlPFC = ventrolateral prefrontal cortex. vmPFC = ventromedial prefrontal cortex.

Discussion

In this study, we used imaging data from the PROSPER clinical trials to compare change in brain activation after either TFT or combined TFT+PT in participants with PTSD and comorbid personality disorders. Contrary to our hypotheses, we found no credible evidence for a change in brain activation after TFT, nor for a difference between participants who received TFT treatment or TFT+PT or associations with clinical improvement. Sensitivity analyses for medication status or when accounting for missing data did not change these findings. There was, however, credible support for a more pronounced decrease in activation in the bilateral vmPFC in treatment responders, compared to non-responders.

Even though our findings are contrary to our hypotheses, they are in line with several other studies. In a baseline study on the same sample, we found no reliable case-control differences between participants with PTSD and control subjects (19). Because there were

little to no differences relative to healthy controls at baseline, it may be that the task we used was not sensitive enough to measure dysfunction and change in brain activation. A recent meta-analysis also showed – if multiple comparison corrected – no statistically significant change after psychotherapy for PTSD, although there were some indications for a decrease in activation in areas from the fear and cognitive control network (9). The high prevalence of comorbidities in our sample may also be an explanatory factor. Borderline severity scores were around the cutoff for borderline personality disorder (35). Apart from personality disorders, around 50% of the sample had also comorbid depressive disorders, with mean depression severity scores indicating severe depression at baseline (27). Since both depression and borderline personality disorders can have profound and sometimes opposite effects on brain activation compared to PTSD, this could have influenced our results. Depression and BPD, and dissociation as well, have been found to be related to lower amygdala activation, compared to higher amygdala activation in PTSD (30, 36)

There is a discrepancy between the clinical findings (with a large decrease in all measures) and the imaging measures. We used an emotional face task to measure brain activation and elicit a fear response. Although previous research showed some baseline activation differences between control participants, PTSD (22, 37) and BPD (38) participants, respectively, it is possible that the current task is not sensitive for measuring treatment induced change in participants with PTSD and comorbid personality disorders. In future studies, it could be interesting to use a task more specifically designed to evoke PTSD specific (and individualized) symptoms or emotion regulation during scanning, to get more insight into the possible mechanism of treatment, such as a personalized script-driven imagery paradigm or a reappraisal task.

An interesting finding is the strong support for a larger pre- to posttreatment decrease in vmPFC activation in responders compared to non-responders. The vmPFC is involved in the regulation of (negative) emotions (39), which can be improved through treatment. This fits with our finding that decrease in vmPFC activation was related to decrease of PTSD severity in the TFT condition. It is also possible that less top-down vmPFC regulation of limbic areas is necessary after successful treatment, although change in limbic activation was not visible in our results. Clinically, responders used more medication than non-responders, and had lower depression scores, which is in line with a meta-analysis that shows that depression is related to attenuated treatment response in PTSD (40). Research shows that PTSD treatment in individuals with PTSD and comorbid major depressive disorder is effective and also leads to lower depression scores (41). Conversely, starting with depression treatment does not decrease PTSD symptoms. It is important to notice the relatively small size of the non-responder group in interpreting these results.

There are some limitations to consider. First, the time between scans is highly variable with a range of more than a year. A possible contributing factor to this range were COVID-19 restrictions. We used time between scans as a covariate to limit this effect, but this cannot correct for the systematic difference between conditions since participants in the combined condition started their TFT later (a mean difference of 15 weeks). Second, medication use was not stable between measurements. Even though participants and therapists were asked to refrain from changes in medication during treatment, part of the sample (13.2%) did start or stop taking medication. This means that treatment effects cannot be wholly attributed to psychotherapy alone. It is however representative for clinical practice, as individuals with PTSD often receive both pharmacotherapy and psychotherapy concurrently or medications are discontinued during treatment. Furthermore, removing participants who switched medication during treatment from the analysis did not change the results indicating that a medication switch did not contribute to the results. Third, we did not have a control group that did not receive treatment to account for the passing of time.

Strengths of this study are the relatively large sample size compared to other PTSD pre-post treatment studies, see (9) for a meta-analysis where the largest sample sizes were 36 and 21 participants. There are also very few studies with participants with comorbid personality disorders, especially with cluster C personality disorders. Another strength of our approach is the use of Bayesian analyses, which allows for incorporating shared information between ROIs and can be more sensitive to detect effects than frequentist methods (32). Furthermore, Bayesian analyses fit within recent recommendations to show all results and not only arbitrarily thresholded results (42).

This is one of the first studies to analyze changes in brain activation after psychotherapy for participants with PTSD and comorbid borderline and/or personality disorders. Despite a large change in clinical symptoms, we did not find credible support for change in brain activation after TFT. We did find support for a decrease in vmPFC activation in treatment responders, possibly reflecting improved emotion regulation or less top-down regulation. Possibly, the paradigm used in this study was not sensitive to measure change in this sample.

Acknowledgements

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Supplementary materials

The supplementary materials for this chapter can be accessed through https://surfdrive.surf.nl/files/index.php/s/Pufgdt0eTPz2VWs.

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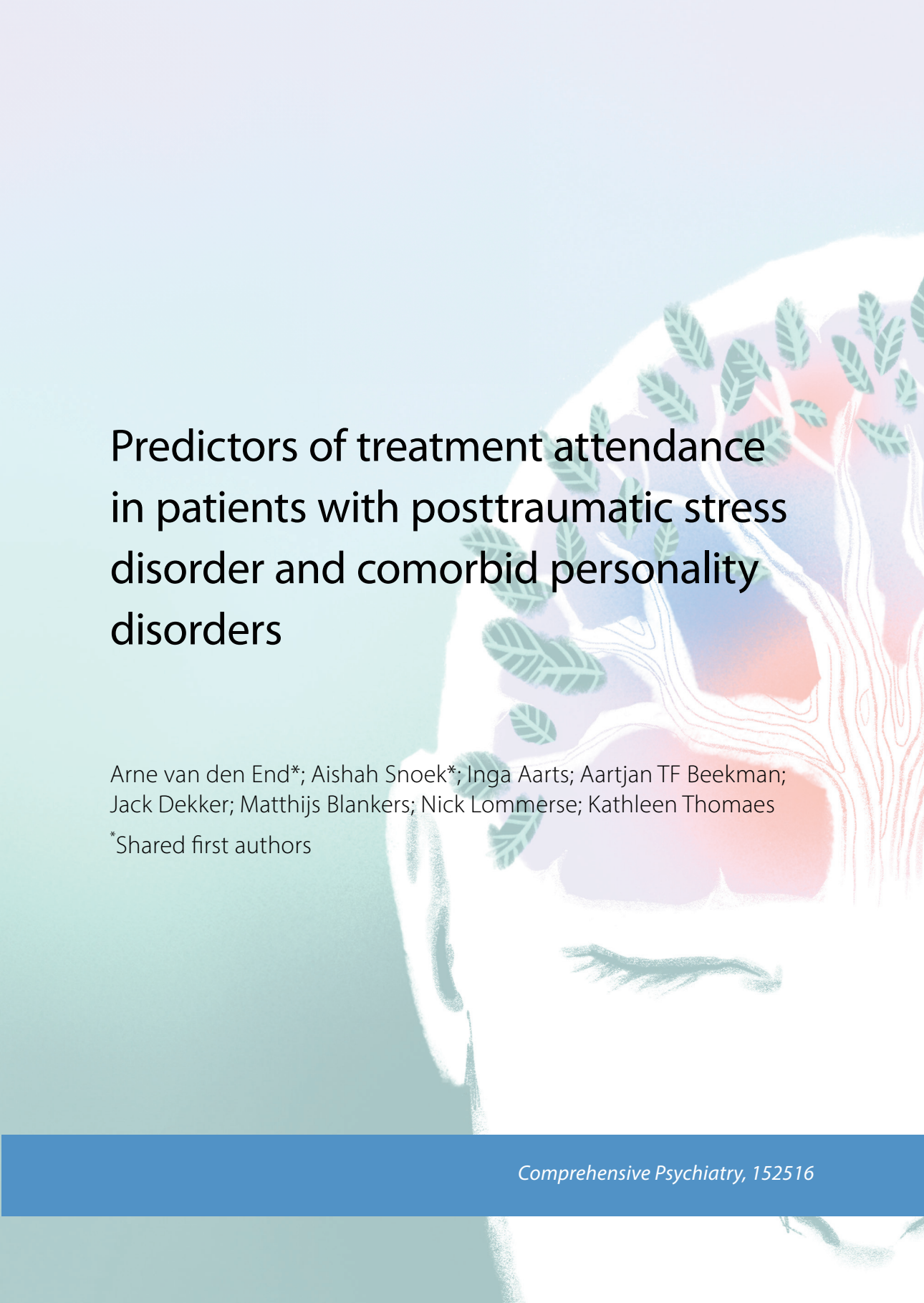
CHAPTER 6



Predictors of treatment attendance in patients with posttraumatic stress disorder and comorbid personality disorders

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Abstract

Introduction: High dropout rates among patients with posttraumatic stress disorder (PTSD) and personality disorders (PDs) continue to pose a significant challenge. Despite numerous studies focusing on enhancing treatment attendance, the identification of consistent and reliable predictors in patients with PTSD and comorbid PDs remains limited.

Objectives: This study aims to investigate a wide range of potential predictors of treatment attendance, encompassing demographic, patient-severity, treatment, and therapist-related variables in patients with PTSD and comorbid borderline and/or cluster C PDs.

Methods: Utilizing data from 255 patients, candidate predictors were individually analyzed in univariate regression models. Significant predictors were then combined in a multiple ordinal regression model.

Results: In total, 40 percent of patients attended fewer trauma-focused treatment sessions than the minimum recommended in treatment guidelines. Out of the 38 candidate predictors examined, five significant, independent predictors of treatment attendance emerged in a multiple ordinal regression model. Higher baseline PTSD severity ($OR = 1.04$, $p = .036$), higher education level ($OR = 1.22$, $p = .009$) and a stronger patient-rated working alliance ($OR = 1.72$, $p = .047$) with the therapist predicted higher treatment attendance. Conversely, inadequate social support from friends (OR = 0.90, p = .042) and concurrent PD treatment and trauma-focused treatment (OR = 0.52, p = .022) were associated with lower treatment attendance.

Conclusions: In conclusion, this constitutes the first study investigating predictors of treatment attendance in patients with PTSD and comorbid PDs. The results highlight the complexity of pinpointing reliable predictors. Nevertheless, the identification of five predictors provides valuable insights, aiding clinicians in customizing treatment strategies for individual patients and enhancing overall treatment attendance.

Keywords: PTSD, personality disorder, treatment attendance

Introduction

Dropout from psychological treatment is a serious concern in mental health care (Wells et al., 2018) since patients may continue to suffer from mental health problems when they do not receive a sufficient dosage of evidence-based psychological treatment. A specific subgroup facing a heightened risk of treatment dropout comprises patients suffering from posttraumatic stress disorder (PTSD) and comorbid personality disorders (PDs). PTSD and PDs often co-occur (1). A recent meta-analysis estimates an overall dropout rate of 18 percent for trauma-focused treatment, yet substantial heterogeneity exists among studies, with dropout rates ranging from 0 to 65 percent (k = 116) (2). Dropout rates in PD treatments are also substantial. Arntz and colleagues (3) reported an unweighted mean dropout rate of 43 percent for borderline PD after one year of treatment. Furthermore, patients with PTSD and comorbid PDs may face an elevated risk of dropout compared to those without comorbid PDs, although research in this domain is limited. A recent meta-analysis found no statistically significant increase in dropout rates for patients with comorbid PTSD and PDs, but the findings were based on a restricted number of studies with moderate between-study heterogeneity (4).

As emphasized by Schottenbauer and colleagues (5), systematically assessing predictors of dropout is imperative for a comprehensive understanding and improvement of dropout rates. However, the literature on predictors of dropout in PTSD and PD treatments presents a highly mixed picture. Variables identified as predictive of dropout in one study often yield null findings in others; a pattern observed in multiple meta-analyses. Lewis and colleagues (2) examined various psychotherapy modalities and found that therapies for PTSD with a trauma focus were associated with higher dropout rates compared to those without a trauma focus. Varker and colleagues (6) compared dropout proportions in guideline-recommended PTSD treatments, revealing a higher dropout proportion in military versus civilian samples, particularly in treatments with a trauma-focus. Furthermore, Mitchell and colleagues (7) explored the impact of baseline symptom severity on dropout and found that higher clinician-rated PTSD symptom severity predicted dropout. In the context of borderline PD (BPD), a recent meta-analysis studied the impact of treatment type, setting, format and demographic features on dropout (3). Results indicated higher treatment retention in schema therapy and mentalization based treatment, with increased dropout observed in group treatment compared to other formats. The authors also noted that the majority of dropout occurred in the first quarter of treatment and that demographic characteristics of patients were not related to dropout. In sum, these meta-analyses identified some predictors of treatment dropout, but results were not consistent between the studies. Moreover, no consistent predictors of dropout have been identified for patients with PTSD-PD comorbidity.

Hence, our study delved into an extensive array of potentially relevant predictors of treatment attendance among patients with PTSD and comorbid PDs receiving trauma-focused treatment with and without concurrent PD treatment. We chose to conceptualize the outcome as treatment attendance and not dropout, since no uniform definition of dropout exists and a dichotomous value (yes/no) does not adequately reflect clinical practice. We pooled data from two recent randomized controlled trials (RCTs). These RCTs aimed to investigate whether treatment outcomes could be enhanced by concurrently treating PTSD and PDs rather than solely focusing on PTSD. In the first RCT, trauma-focused treatment with and without concurrent PD treatment were compared in patients with PTSD and comorbid BPD (8). The second RCT compared trauma-focused treatment with and without concurrent PD treatment in patients with PTSD and comorbid cluster C PDs (9).

Based on theoretical and clinical reasoning, several hypotheses can be construed. First, we anticipate that overall patient severity will be associated with lower treatment attendance. Elevated symptom severity may complicate the implementation of manualized trauma-focused treatments, reduce tolerability for both patients and clinicians and hinder attendance due to persistent avoidance, passivity, or paranoid ideation symptoms common in PTSD and PD comorbidity. Second, we hypothesize that therapist and therapist-patient variables will predict treatment attendance. Specifically, patients perceiving their therapist as active, committed, collaborative, respectful, caring and understanding (indicating high therapeutic alliance) are expected to be more likely to remain in treatment. Additionally, therapist experience is anticipated to positively predict treatment attendance, with more experienced therapists possessing a broader range of skills to adapt to individual patient needs. Third, despite inconsistent findings in earlier studies regarding demographic factors predicting dropout, it is consistently shown that certain patients are more challenging to engage and retain in treatment. For example, studies on Improving Access to Psychological Therapies program in the UK show that retention and recovery rates are negatively correlated with, for example, socioeconomic deprivation and waiting times (10,11). Thus, we expect sociodemographic variables such as waiting times, distance from the treatment center, education level, social support, and work status to positively predict treatment attendance. Fourth, we anticipate that treatment attendance will be predicted by the type of treatment received. Our sample was randomized to either stand-alone trauma-focused treatment or a combination of trauma-focused treatment concurrent with PD treatment. Aligning with recommendations by Lewis and colleagues (2), we expect that an intervention targeting the specific PTSD-PD subgroup will result in higher treatment attendance. Lastly, we will explore whether any significant association between predictor variables and treatment attendance is moderated by treatment condition.

Methods

Study design

Data was utilized from patients who were enrolled in the Prediction and Outcome Study on PTSD and Personality Disorders (PROSPER; $n_{enrolled} = 255$). The PROSPER study consists of two RCTs (8,9) comparing the effectiveness of trauma-focused treatment with and without concurrent PD treatment in patients with PTSD and comorbid PD. The first RCT compared eye movement desensitization and reprocessing (EMDR) with and without concurrent dialectical behavior therapy (DBT) in patients with PTSD and comorbid BPD (n = 125) (8). The second RCT compared imagery rescripting (ImRs) with and without concurrent schema therapy (ST) in patients with PTSD and cluster C PD (n = 130) (9). Both trials were identical in terms of design, measurements, and number of trauma-focused sessions. A detailed study design has been published elsewhere (8,9). Analyses were preregistered at the Open Science Framework (https://osf.io/2axd6). All participants provided written informed consent and approval for the study protocol (case number A2018.428, version 7) has been obtained from the Medical Ethics Committee Amsterdam University Medical Center, number 2017.335.

Sample

Patients were between 18 and 65 years old and sought PTSD treatment at a mental health care institution in the Netherlands specialized in the treatment of PTSD. To be included in the PROSPER study, patients had to meet the following inclusion criteria: (1) a primary diagnosis of PTSD according to DSM-5 as measured by the Clinician Administered PTSD Scale for DSM-5 (CAPS-5); (2) at least four BPD symptoms and/or three avoidant PD symptoms and/or four dependent PD symptoms and/or three obsessive-compulsive PD symptoms (i.e. the required number of DSM-5 criteria minus one) as measured by the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD); (3) a stable medication regimen for at least three weeks prior to starting treatment. Patients were excluded in case of (1) current psychosis; (2) IQ < 70; (3) comorbidity interfering with (group) treatment or randomization, such as severe outward aggression, treatment interfering substance and eating disorders, or treatment interfering somatic problems; (4) a primary diagnosis of paranoid, schizoid, schizotypal, narcissistic, histrionic, or antisocial PDs; (d) insufficient mastery of the Dutch language for participation in group therapy.

Measurements

Outcome variable

The outcome variable treatment attendance was defined using the last attended trauma-focused treatment session (EMDR or ImRs). Any cut-off point for treatment dropout or completion is arbitrary and there is no consensus in the literature on the use

of one definition. Moreover, dichotomizing leads to loss of information, as we assumed that more than two meaningful categories of treatment attendance existed. On the other hand, a continuous analysis of treatment attendance would be less pertinent to clinicians compared to an examination of clinically meaningful categories. In our endeavor to maximize the clinical relevance of our study, we asserted that meaningful clinical categories should serve as the outcome variable, supplemented by a secondary analysis of the continuous outcome (see section 2.6 for further details). For instance, we assumed that patients who attended no sessions constitute a distinct group from those who attended some treatment sessions but fewer than recommended (1-7 sessions in our operationalization). Moreover, we identified differences between patients who attended several sessions and those who completed at least the recommended number of sessions (8-11 sessions). Finally, we inferred that the group who completed treatment per protocol represented yet another distinct category. Therefore, we chose to group our outcome variable in four clinically meaningful categories based on PTSD treatment guidelines: attending zero sessions; attending fewer than the prescribed minimum number of sessions (1-7), attending the minimum recommended number of sessions in PTSD treatment (8-11) (12,13) and attending the number of sessions prescribed in the previously published study designs (12-18 sessions).

Predictor variables

Predictors were selected based on the extant literature and clinical reasoning and were divided into demographic, patient severity, treatment, patient-therapist, and therapist related variables. See table 1 for the selected predictors, their grouping and the instruments used to measure the variable. Gender was self-report and included response categories *male*, *female* and *other, namely*. See van den End and colleagues (9), Snoek and colleagues (8) and the preregistration of the current study for a complete overview of all study variables.

Treatments

A detailed description of all treatments can be found in the previously published study protocols (8,9). The EMDR and ImRs protocols both comprised a minimum of 12 and a maximum of 18 weekly sessions. The DBT protocol consisted of six individual pre-treatment sessions, 40 group sessions and 20 biweekly individual sessions. The schema therapy protocol consisted of four individual pre-treatment sessions, 40 group sessions, 18 group psychomotor therapy sessions and four optional booster treatment sessions of individual ImRs or ST.

Therapists

A total of 21 therapists performed the EMDR treatments, 21 therapists the ImRs treatments and 7 therapists performed both treatments. All therapists held a master's

degree in clinical psychology, completed certified training for the relevant interventions and received biweekly supervision sessions.

Data analysis

To enhance generalizability and bolster the statistical power required for prediction analyses, the data from both trials were pooled. The trials were identical in terms of their design, measurements, and the recommended minimum number of trauma-focused sessions. The trials further shared considerable overlap in PD symptoms, and both included an evidence-based trauma-focused treatment method (ImRs or EMDR) and an evidence-based personality disorder treatment method (ST or DBT). Thus, ImRs and EMDR were pooled as trauma-focused treatment, and ST and DBT were pooled as personality disorder treatments. The variable 'trial' (distinguishing between the EMDR-DBT trial with PTSD and BPD patients, and the ImRs-ST trial with PTSD and cluster C PD patients) was included as a covariate in all analyses to account for differences between the trials and to control for their potential impact on the results.

The statistical method was based on Hosmer and Lemeshow's method of purposeful selection (14). Bursac and colleagues (15) found that the purposeful selection method retained significant covariates and cofounders of other model covariates "in a manner superior to stepwise selection" (Hosmer and Lemeshow, p. 93). First, the association between each candidate predictor variable and the number of attended trauma-focused sessions was assessed by a univariate ordinal regression analysis, while controlling for trial. Each predictor variable demonstrating an above threshold association ($p < .10$) with treatment attendance was subsequently entered into the multiple ordinal regression model. In this final model, an association between the predictor variable and treatment attendance of $p < .05$ was deemed significant. Model fit was assessed by comparing the final model to the covariate-only model, utilizing the -2-log likelihood statistic by inspecting its chi-square values and significance, together with the pseudo-R^2 statistic (Nagelkerke R^2). Additionally, exploratory moderator analyses were performed with treatment condition and the significant predictors as two-way interactions. Finally, to test the stability of the findings we reanalyzed the data following the same analysis procedure, but with multiple regression and a continuous outcome (number of attended sessions).

All analyses were conducted using SPSS version 29 (16). To address missing data, a multiple imputation approach was employed, specifically the fully conditional specification method with 50 imputations (17). The R-squared statistics and chi-square statistics were pooled through averaging (18). Model assumptions were met, unless explicitly stated otherwise.

Results

Sample characteristics

Table 1 provides descriptive statistics for the total sample (N = 255) and for those who attended zero (n = 42), one to seven (n = 59), eight to eleven (n = 45), and twelve to eighteen trauma-focused sessions (n = 109). One patient received 19 sessions and one patient received 20 sessions and were classified as belonging to the upper category (12-18 sessions). Notably, 40 percent of all patients attended fewer than the recommended eight sessions. Most participants identified as female, with a mean age of 28.2 years (SD = 11.11). The median education level was ISCED level 3 (upper secondary). The mean CAPS-5 score, indicative of PTSD severity, was 41.38 (SD = 10.73) with a range from 17 to 68, which is similar to other studies on complex presentations of PTSD (19).

Initial predictors of treatment attendance

A total of ten predictor variables showed an above threshold association ($p < .10$) with the number of attended trauma-focused sessions.

Demographic variables

Patients with a higher education level (OR = 1.20, 95%CI [1.05, 1.37], p = .007) attended more sessions, while more days between randomization and start of treatment was associated with attending fewer sessions (OR = 0.99, 95%CI [0.99, 1.00], p = .005). The remaining demographic variables were not significantly ($p < .10$) associated with the number of attended treatment sessions.

Patient-severity variables

Patients with higher PTSD severity according to CAPS-5 (OR = 1.03, 95%CI [1.00, 1.05], p = .038) and PCL-5 (OR = 1.04, 95%CI [1.02, 1.06], $p < .001$), higher general symptom severity (OR = 1.01, 95%CI [1.00, 1.03], p = .052) and those reporting more difficulties in emotion regulation (OR = 1.02, 95%CI [1.01, 1.03], p = .009) attended more sessions, while patients with a higher number of friends (OR = 0.73, 95%CI [0.51, 1.04], p = .079) and higher levels of experienced inadequacy of social support from friends (OR = 0.90, 95%CI [0.82, 0.97], p = .009) attended fewer sessions. The remaining patient-severity variables were not significantly associated with the number of attended treatment sessions.

Treatment variables

Patients who received trauma-concurrent PD treatment attended fewer trauma-focused sessions than patients who did not receive concurrent PD treatment (OR = 0.53, 95%CI [0.34, 0.84], p = .006).

Therapist variables

Working alliance was positively associated with the number of attended treatment sessions (OR = 1.64, 95%CI [1.01, 2.67], p = .048), whereas therapist experience and gender were not significantly associated with the number of attended treatment sessions.

Final model

The final model, including the ten predictor variables mentioned earlier, demonstrated a good fit to the data after comparing -2 log likelihood and pooled chi-square values (F(11, 218.25) = 3.55, p < .001), compared to the intercept-only model. Furthermore, pooled Nagelkerke R^2 = .29 indicated that the final model was significantly better than the intercept-only model in predicting the outcome variable. Higher education level (OR = 1.22, 95%CI [1.05, 1.42], p = .009), self-rated PTSD severity (OR = 1.04, 95%CI [1.00, 1.08], p = .036) and working alliance (OR = 1.72, 95%CI [1.01, 2.93], p = .047) were significantly (p < .05) associated with a larger number of attended sessions. Inadequate social support from a friend was associated with a smaller number of attended sessions (OR = 0.90, 95%CI [0.80, 1.00], p = .042). Finally, treatment condition was significantly associated with the number of attended sessions such that patients receiving trauma-focused treatment with concurrent PD treatment attended fewer trauma-focused treatment sessions compared to those receiving trauma-focused treatment without concurrent PD treatment (OR = 0.52, 95%CI [0.30, 0.91], p = .022). The model correctly classified 51.5% of the cases (which is above 25%, the chance level with four categories). The model performed best in predicting 12-18 sessions class membership (86.7%), followed by 1-7 sessions (38.5%), 0 sessions (33.8%) and 8-11 sessions (0%). None of the interaction terms between the significantly associated variables (working alliance, inadequate social support, self-report PTSD severity, education level) and treatment condition was significant in predicting treatment attendance.

Sensitivity analysis

First, results of the non-imputed versus imputed separate ordinal regression analyses were compared. Most variables yielded similar results in terms of p-value thresholds and parameter estimates, except for trait anger (nonimputed p = .058, imputed p = .109), number of friends (nonimputed p = .372, imputed p = .079), and inadequate social support (nonimputed p = .718, imputed p = .009).

Further, multiple regression analysis with the number of attended sessions as a continuous outcome variable were comparable to the results from the ordinal regression analyses. In the first step, all ten relevant variables that emerged from the ordinal analysis were significant at the p < .10 level. Additionally, substance use disorder (p = .072) and trait anger (p = .087) were identified as significant in the first step. In the

final model with 12 variables, education level (p = .006), inadequate social support (p = .035), and working alliance (p = .031), but not self-rated PTSD severity (p = .302), and condition (p = .078) significantly predicted treatment attendance. The pooled explained variance for the final model was 23.9%.

We also tested whether the education level variable remained a stable predictor after recoding the ISCED levels into three commonly used levels: low, middle, and higher education. The results were similar to those using the original ISCED coding.

Furthermore, our pre-registered analysis protocol was based on the Hosmer and Lemeshow method of purposeful selection. However, we used a slightly more conservative selection criterion for step 1 ($p < .10$ instead of $p < .20$) and retained non-significant variables in the final model instead of further simplifying the model by removing non-significant variables. As a sensitivity analysis, we employed the full protocol (step 1 through 7) of Hosmer and Lemeshow, using a $p < .20$ as criterion in step 1 and following a backward elimination approach for the final model while retaining good model fit (by checking model fit parameters, p-values and estimate changes at every model simplification step and finally, checking whether non-included variables at step 1 modified the coefficients of the final model when included one by one in the final model). We found the same significant predictors as with our, pre-registered, analysis protocol. These analyses are available from the corresponding author upon request.

Finally, the proportion of treatment responders in each category was explored, since lower treatment attendance does not necessarily mean worse treatment effects. To do this, treatment response was defined as one standard deviation below the baseline CAPS-5 mean (in accordance with the definition used in the primary RCT analyses). However, these data were highly associated with measurement completion, such that treatment response data was only available for 3 (7.14%) participants in the 0 sessions category, 29 (49.15%) in the 1-7 sessions category, 37 (82.2%) in the 8-11 sessions category and 95 (87.15%) in the 12-18 sessions category. Therefore, we did not re-analyze the final model with treatment response as a covariate. Interestingly, though, of the available data, 19 out of 29 (65.52%) in the 1-7 sessions category, 27 out of 37 (72.97%) in the 8-11 sessions category, and 57 out of 95 (60%) in the 12-18 sessions category were classified as treatment responder.

Table 1. Descriptive statistics for demographic and clinical variables for the whole sample and per category of number of treatment sessions

Predictor	Whole sample			0 sessions			1-7 sessions			8-11 sessions			12-18 sessions		
	N	M	SD	n	M	SD	n	M	SD	n	M	SD	n	M	SD
Demographic variables															
Age (years)	255	38.29	11.11	42	40.24	11.02	59	35.88	11.52	45	38.69	11.66	109	38.68	10.60
Gender (%F)	255	82.4%		42	78.6%		59	83.1%		45	80.0%		109	84.4%	
Education level	239	3[&]	3[#]	34	3	4	53	3	1	43	3	3	109	3	3
Employment status (%unemployed)	250	57.3%		42	66.7%		56	50.8%		45	55.6%		109	57.8%	
Distance between home and treatment center (km)	255	18.08	14.77	42	19.31	13.43	59	14.64	9.65	45	19.03	16.84	109	19.08	16.45
Time between randomization and start of treatment (days)	235	80.40	61.09	24[a]	93	69.75	59	91.17	75.57	45	90.64	62.41	107	67.33	45.18
Patient severity variables															
PTSD symptom severity (CAPS-5)	230	41.38	10.73	23	39.78	12.48	56	40.34	10.69	44	38.95	11.00	107	43.26	10.04
PTSD symptom severity (PCL-5)	194	56.33	13.01	17	48.10	12.19	42	55.25	13.54	39	53.53	13.78	96	59.39	11.77
Childhood trauma	201	70.39	20.10	19	70.37	21.96	42	72.40	18.81	40	64.30	18.42	100	72.98	20.70
Substance use disorder	193	4.19	5.56	14	4.29	4.92	41	4.66	6.20	39	4.26	5.94	99	3.95	5.28
Comorbid psychiatric disorders	254	3.56	2.30	41	3.78	1.97	59	3.51	2.32	45	3.38	2.73	109	3.58	2.22
Depression severity	200	33.72	12.10	18	33.22	11.02	42	33.74	11.68	40	30.10	12.04	100	35.24	12.33
Borderline personality disorder severity	193	38.01	10.47	14	35.14	8.84	41	40.15	9.16	39	37.28	10.80	99	37.81	11.03
General psychiatric symptom severity	201	104.84	21.60	19	99.89	19.99	42	103.10	18.12	40	101.30	21.21	100	107.92	23.16
Hospitalization history (% no)	212	72.2%		42	42.9%		59	66.1%		45	82.2%		109	82.6%	
Anger	193	21.31	7.22	14	20.43	5.46	41	20.15	7.49	39	20.85	7.56	99	22.09	7.19
Emotion dysregulation	193	119.93	22.12	14	106.50	21.06	41	117.56	21.53	39	120.59	22.33	99	112.55	21.96
Social support															
Number of friends	191	1.97	0.83	13	2.00	0.577	40	2.08	0.730	39	2.00	0.973	99	1.91	0.846
Partner: emotional support	191	8.61	7.36	13	5.31	6.36	40	6.50	6.36	39	11.13	6.35	99	8.91	7345
Partner: practical support	191	3.98	3.66	13	4.79	3.47	40	2.80	3.49	39	5.36	3.43	99	4.08	3.68

Table 1. Continued

Predictor	Whole sample			0 sessions			1-7 sessions			8-11 sessions			12-18 sessions		
	N	M	SD	n	M	SD	n	M	SD	n	M	SD	n	M	SD
Partner: negative experiences	191	3.43	3.10	13	2.69	3.28	40	2.58	3.13	39	4.67	2.88	99	3.39	3.04
Partner: inadequacy of social support	191	3.68	3.32	13	3.00	3.63	40	2.95	3.50	39	4.56	2.84	99	3.71	3.34
Friend: emotional support	191	8.90	7.71	13	7.85	7.71	40	7.83	7.43	39	10.28	7.99	99	8.92	7.74
Friend: practical support	191	3.06	3.26	13	2.38	2.66	40	2.63	3.03	39	3.41	3.34	99	3.19	3.39
Friend: negative experiences	191	2.42	2.59	13	2.08	2.29	40	2.25	2.58	39	2.23	1.90	99	2.61	2.86
Friend: inadequacy of social support	191	3.18	3.10	13	3.31	3.52	40	3.20	3.28	39	3.33	3.09	99	3.10	3.03
Health and disability status	191	2.66	0.73	13	2.38	0.82	40	2.54	0.63	39	2.81	0.73	99	2.70	0.75
Quality of Life	191	52.36	20.24	13	60.77	20.60	40	51.50	18.33	39	54.10	21.85	99	50.91	20.26
Self-harm (# days in past 3 months)	199	2.07	2.28	17	1.59	1.97	42	2.52	2.61	40	1.90	2.16	100	2.02	2.23
Dissociation	195	22.67	16.59	15	16.90	8.61	41	24.20	19.48	40	22.12	14.91	99	23.13	16.87
Sleep Quality	193	11.84	4.14	14	9.43	4.75	41	12.51	3.91	39	11.85	3.52	99	11.90	4.30
Cumulative Trauma Exposure	209	5.08	2.09	21	5.52	1.63	44	5.05	2.24	40	4.58	1.82	104	5.19	2.19
Response inhibition	129	233.01	85.16	11	229.92	88.33	32	235.00	77.18	29	234.79	61.08	55	231.66	100.47
Working memory	128	61.22	20.74	11	56.52	16.21	31	62.02	21.16	27	61.88	22.28	59	61.37	20.93
Patient-therapist variable															
Working alliance	122	3.68	0.93	42	No data	No data	13	3.33	.92	29	3.48	1.05	80	3.81	0.87
Treatment variable															
Treatment condition (%TFT only)	255	50.6%		42	38.1%		59	40.7%		45	55.6%		109	58.7%	
Therapist variables															
Therapist experience (years)	211	7.73	5.27	16	5.38	4.40	54	8.04	5.69	43	6.91	5.33	98	8.30	5.05
Therapist gender (%F)	233[a]	80.7%		20[a]	60%		59	86.4%		45	82.2%		109	80.7%	

[a] Patients who dropped out before they were assigned a therapist are not recorded here. & Median value # Interquartile range

Table 2. Results of the simple ordinal regression analyses with potential predictors of treatment attendance

Predictor	Instrument	OR	95%CI	p
Demographic variables				
Age (years)	Demographic questionnaire	1.00	1.00, 1.00	.904
Gender	Demographic questionnaire	1.23	0.69, 2.22	.483
Education level	Demographic questionnaire	1.20	1.05, 1.37	.007*
Employment status	Demographic questionnaire	1.13	0.72, 1.79	.593
Distance between home and treatment center (km)	Demographic questionnaire	1.01	0.99, 1.02	.369
Time between randomization and start of treatment (days)	NA	0.99	0.99, 1.00	.005*
Patient severity variables				
PTSD symptom severity	Clinician Administered PTSD Scale – DSM-5 (20)	1.03	1.00, 1.05	.038*
PTSD symptom severity self-rated	PTSD Symptom Checklist – DSM-5 (21)	1.04	1.02, 1.06	.001*
Childhood trauma	Childhood Trauma Questionnaire (22)	1.00	0.99, 1.02	.614
Substance use disorder	Alcohol Use Disorder Identification Test (23)	0.96	0.92, 1.01	.117
Comorbid psychiatric disorders	Structured Clinical Interview for DSM-5 (24)	1.00	0.90, 1.10	.949
Depression severity	Beck Depression Inventory-II (25)	1.02	0.99, 1.04	.207
Borderline personality disorder severity	Personality Assessment Interview – Borderline Scale (26)	1.00	0.97, 1.03	.769
General psychiatric symptom severity	Outcome Questionnaire – 45 (27)	1.01	1.00, 1.03	.052*
Hospitalization history	Demographic questionnaire	0.78	0.36, 1.68	.518
Anger	State-Trait Anger Scale (trait anger only) (28)	1.03	0.99, 1.08	.109
Emotion dysregulation	Difficulties in Emotion Regulation Scale (29)	1.02	1.01, 1.03	.009*
Social support				
Number of friends	Close Person Questionnaire (30)	0.73	0.51, 1.04	.079*
Partner: emotional support	Close Person Questionnaire	1.01	0.97, 1.05	.717
Partner: practical support	Close Person Questionnaire	0.98	0.91, 1.06	.618
Partner: negative experiences	Close Person Questionnaire	0.95	0.86, 1.03	.220
Partner: inadequacy of social support	Close Person Questionnaire	0.96	0.89, 1.04	.355
Friend: emotional support	Close Person Questionnaire	0.98	0.95, 1.02	.255
Friend: practical support	Close Person Questionnaire	0.96	0.89, 1.05	.372
Friend: negative experiences	Close Person Questionnaire	0.95	0.86, 1.05	.272
Friend: inadequacy of social support	Close Person Questionnaire	0.90	0.82, 0.97	.009*
Health and disability status	World Health Organization Disability Assessment Scale (31)	1.24	0.81, 1.90	.314
Quality of Life	EuroQol visual analog scale (32)	1.00	0.98, 1.01	.528
Self-harm	Nonsuicidal Self-Injury Screener (33)	0.91	0.82, 1.02	.112

Table 2. Continued

Predictor	Instrument	OR	95%CI	p
Dissociation	Dissociative Experiences Scale – II (34)	1.01	0.99, 1.03	.498
Sleep Quality	Pittsburgh Sleep Quality Index (35)	1.02	0.95, 1.10	.574
Cumulative Trauma Exposure	Life-Events Checklist (36)	0.98	0.86, 1.12	.803
Response inhibition	Stop-signal task (37)	1.00	1.00, 1.00	.572
Working memory	n-back task (38)	1.00	0.99, 1.02	.819
Patient-therapist variable				
Working alliance	WAI – 12 (39)	1.64	1.01, 2.67	.048*
Treatment variable				
Treatment condition	NA	0.53	0.34, 0.84	.006*
Therapist variables				
Therapist experience	Years experience in mental health care	1.04	0.98, 1.10	.187
Therapist gender		1.33	0.71, 2.49	.371

Table 3. Results of the final multiple ordinal regression analysis for predictors of treatment attendance

Predictor	OR	95%CI	p
Trial	1.20	0.70, 2.04	.512
Education level	1.22	1.05, 1.42	.009
Time between randomization and start of treatment (days)	1.00	0.99, 1.00	.122
PCL-5	1.04	1.00, 1.08	.036
CAPS-5	1.00	0.97, 1.03	.955
OQ-45	0.99	0.97, 1.01	.358
DERS	1.01	0.99, 1.03	.380
Number of friends	0.75	0.50, 1.10	.142
Friend: Inadequacy of social support	0.90	0.80, 1.00	.042
Working alliance	1.72	1.01, 2.93	.047
Condition	0.52	0.30, 0.91	.022

Discussion

The current study examined a broad range of potential predictors of treatment attendance in patients with PTSD and comorbid PDs. We hypothesized that a) patient severity variables, such as symptom severity, b) patient-therapist and therapist variables, such as working alliance and therapist experience, c) sociodemographic factors, such as waiting times, distance from the treatment center, education level, social support, and work status, and d) treatment type would predict treatment attendance.

Among all patients, 40 percent attended fewer trauma-focused treatment sessions than the minimum recommended in treatment guidelines (12,13). While this percentage may appear high in comparison to the pooled dropout rate of 18 percent for trauma-focused

treatment reported in the meta-analysis by Lewis and colleagues (2), it is important to acknowledge the substantial variability in dropout rates across individual studies (2,5). Notably, the dropout rate found in the present study aligns with the dropout rate of 41.5 percent found by Mitchell and colleagues in a recent meta-analysis (7). Additionally, the patients in our sample have undergone substantial trauma and suffer from PDs; a comorbidity associated with elevated rates of treatment discontinuation (3). Since all patients have comorbid PDs, this comorbidity could not be explored as a predictor in the current sample.

Five independent and consistent predictors of treatment attendance were identified in the present study. Firstly, and contrary to our hypothesis, individuals with higher baseline PTSD severity were more likely to attend a larger number of trauma-focused sessions. This finding diverges from the findings in the meta-analysis by Mitchell and colleagues (7), who found that higher baseline PTSD severity is associated with higher treatment dropout, albeit with considerable variability between studies. The positive relationship between PTSD severity and treatment attendance observed in our study may be attributed to the heightened need for additional trauma-focused sessions among patients with more severe PTSD symptoms. Second and consistent with our hypothesis, lower education emerged as a significant predictor of lower treatment attendance. This corresponds with several individual studies indicating that lower education predicts treatment dropout in PTSD (40,41). However, educational level did not emerge as a significant predictor in the meta-analysis conducted by Lewis and colleagues (2). In that meta-analysis, the education of participants was unknown for a considerable number of studies, which might explain the divergent findings. Notably, childhood abuse and neglect have been associated with lower educational attainment in adulthood (42), making lower education a prevalent risk factor in patients with PTSD and PDs. Third, and consistent with our hypothesis, patients with a stronger working alliance with their therapists attended more trauma-focused sessions. Consistent with multiple studies, a positive treatment alliance has been found to predict both symptom reduction (43–45) and lower dropout rates in PTSD (46). Fourth and in line with our hypothesis, patients who reported inadequate social support from a friend attended fewer treatment sessions. Fredette and colleagues (47) conducted a systematic review on social support in cognitive behavioral therapy (CBT) for PTSD, highlighting the importance of both social and marital support for treatment efficacy. In our study, solely inadequate social support from friends was predictive of treatment attendance. It is important to note that the clinical relevance of this finding may be low, given that none of the other social support scales of the Close Persons Questionnaire were significant, and that the statistical significance of the inadequate social support subscale did not survive Bonferroni correction for multiple testing in the first step. Fifth and contrary to our hypothesis, patients receiving trauma-focused treatment in conjunction with PD

treatment attended fewer trauma-focused sessions compared to those solely receiving trauma-focused treatment. Our original reasoning was that additional psychological treatment focusing on comorbid pathology would enable patients to stay in treatment. This finding may be explained by anecdotal patients reports indicating that undergoing two therapies concurrently is too demanding. Sequential treatment of PTSD and PDs, integrated into a predetermined plan, might be more feasible. An alternative explanation is that treatment attendance was defined based on the number of trauma-focused sessions. The possibility that some patients discontinued trauma-focused treatment, but continued PD treatment is theoretically plausible, though not explicitly allowed in the study protocol. Moreover, PTSD is characterized by pervasive avoidance of trauma-related stimuli. The continuation of any form of treatment following the termination of trauma-focused therapy has the potential to selectively reinforce avoidance behavior, thereby possibly leading to lower treatment attendance in the concurrent treatment arm.

Finally, and importantly, it should be noted that among the 38 candidate predictors examined in the current study, only five were identified as significant predictors of treatment attendance. It is striking that some of the other predictors were non-significant. For example, based on previous research, we expected demographic factors such as distance from the treatment center and waiting times to be related to treatment attendance (10,11). It is unknown why these factors are not associated with treatment attendance in this study. Possibly, there was not a lot of variation in these variables or other variables (such as PTSD severity) were more important as an explanatory factor. Our findings align with prior research, which similarly observed that only a minority of examined variables exhibited a significant association with treatment attendance and these results were not consistent across studies (2,7). The issue of low treatment attendance thus persists as a complex challenge without a systematic solution and clinical judgment remains an important decision tool in predicting treatment outcome.

Several limitations should be considered. First, data were obtained from two randomized controlled trials conducted in real-worlds treatment settings, potentially introducing bias due to factors like imprecise measurements (e.g., self-report questionnaires), and inconsistent intervention implementation. However, the treatments were compared under controlled conditions, incorporating protocol adherence and measurement checks. Hence, it is unlikely different effects would be observed outside a research setting. Second, there was a significant amount of missing data on various predictors, which may introduce bias to the model. Although largely similar, the results from the main analysis with multiple imputed data differed somewhat from those from the sensitivity analysis with the non-imputed dataset for trait anger, number of friends, and inadequate social support. Future studies and further aggregation of existing data

may further enhance the robustness of these findings. Third, measurement of working alliance occurred after the trauma-focused treatment. Averaging working alliance ratings over several measurement points during treatment may enhance the validity of this variable (43). Moreover, the absence of working alliance measure completion by patients who discontinued treatment without receiving any trauma-focused sessions may introduce bias to the results. Fourth, our definition of treatment attendance did not differentiate between responders and non-responders. Low treatment attendance does not necessarily imply a poorer treatment outcome (48). In fact, early treatment response may well predict early treatment termination. This is supported by our finding that higher PTSD severity was associated with higher treatment attendance. Due to missing data in the treatment response variable, we did not explore the effect of treatment response status on the other predictors in a regression model, although we did find that treatment response was not uncommon in patients who attended fewer sessions. Future studies with larger samples could examine the relationship between early treatment response and termination, considering factors such as PTSD severity. Additionally, larger studies could investigate therapist effects using mixed model approaches, incorporating a random effect for therapist. Finally, our study mainly comprised female patients diagnosed with PTSD due to childhood trauma and with comorbid personality disorders. Therefore, the generalizability of our findings to male patients with different trauma etiologies or without comorbid personality disorders may be limited. Expanding the study sample to encompass diverse demographic and clinical characteristics is therefore suggested.

The current study is noteworthy for its comprehensive inclusion of various potential predictors, aligning with recent studies (41). Notably, we employed a clinically driven categorization of the treatment attendance variable, allowing the examination of a wide range of factors closely reflecting actual treatment outcomes. Moreover, our study stands out as the first to explore the prediction of treatment attendance in individuals with PTSD and comorbid PDs, providing valuable insights for enhancing treatment attendance rates in this sample.

Our findings carry several implications for enhancing treatment attendance. First, therapists should be mindful of the potential for lower treatment attendance in individuals with a lower educational background. To address this, therapists may need to allocate more time to psychoeducation, elucidating the treatment rationale and fostering commitment to prevent premature dropout and enhance treatment outcome (49,50). Adjusting education materials to enhance accessibility may also be necessary. Secondly, placing emphasis on establishing a strong working alliance at the commencement of treatment and consistently monitoring it throughout could enhance overall attendance (51). While the patient does play a role in establishing a

strong working alliance, the predominant benefits of the alliance have been identified as stemming from the therapist's contributions. Specifically, these contributions include facilitative interpersonal skills such as verbal fluency and conveying hope, warmth, empathy, and responsiveness in repairing alliance ruptures (52), which may be challenging in a therapy where therapists are also expected to address avoidance behavior and stimulate patients to confront their fears. Third, therapists are encouraged to actively involve relatives of the patient in the treatment process. This collaborative approach seeks to augment social support as suggested by Fredette and colleagues (47), potentially leading to enhanced treatment attendance. Future research could further investigate the impact of social support on dropout rates. This could entail minor strategies like directly involving a relative in treatment or more significant adjustments such as integrating interventions aimed at enhancing social support. Finally, therapists should be mindful of the increased demand of simultaneously treating PTSD and PDs, which may elevate the risk of treatment dropout. Hence, it is crucial to transparently explain the requirements and practical implications of concurrent treatment to the patient, enabling them to assess their capacity to commit to therapy.

In conclusion, this is the first study investigating a wide range of variables potentially associated with treatment attendance in patients with PTSD and comorbid PDs. Findings underscore the challenging nature of identifying reliable predictors of treatment attendance. Nonetheless, the identification of five predictors offers valuable insights that can assist clinicians in tailoring their treatment strategies for specific patients, with the goal of improving overall treatment attendance.

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CHAPTER 7

General discussion

Summary of results

In this thesis I described four chapters on participants with posttraumatic stress disorder (PTSD) and comorbid personality disorders (PDs), and neurobiological correlates associated with these disorders.

In **Chapter 2** we described the design of a neuroimaging study on a subsample of two PROSPER randomized clinical trials (RCTs). For this imaging study we acquired magnetic resonance imaging (MRI) scans on participants with PTSD and comorbid borderline PD (BPD) and/or cluster C PD (CPD), plus control subjects. We collected both resting-state and task-based functional and structural imaging data. The other chapters in this thesis are about task-based functional imaging data.

In **Chapter 3**, using the pre-treatment data from the PROSPER samples, we studied whether the type of comorbid personality disorder (borderline PD (BPD), cluster C PD (CPD) or BPD+CPD) had an effect on brain response to an emotional face task in participants with PTSD and comorbid BPD/CPD (N=76 PTSD+PD, N=30 controls). With traditional frequentist analyses, we found no consistent differences in brain activation between different personality disorder comorbidities in our regions of interest (ROIs; bilateral amygdala, right dorsolateral prefrontal cortex (dlPFC), right dorsomedial PFC (dmPFC) and right insula). These ROIs were chosen mainly from the fronto-limbic or salience and central executive networks. With Bayesian analyses, we found strong credible evidence for higher activation in most of the ROIs (bilateral amygdala, dmPFC, dlPFC, insula, hippocampus, dorsal anterior cingulate cortex (dACC) and superior occipital gyrus) in participants with PTSD+BPD+CPD compared to participants with PTSD+BPD or PTSD+CPD; no differences have been found between PTSD+BPD and PTSD+CPD. Across all comorbidity groups, we also found a negative association between dissociation severity and right dmPFC and right insula activation, and between the level of emotion regulation problems and right dmPFC activation. The absence of case-control differences in our main analyses may be related to opposite effect of comorbidity and medication compared to the effect of PTSD on the brain. The result that severity of dissociation and level of emotion regulation problems were related to activity in certain brain regions and that PTSD+BPD+CPD showed higher activation than BPD or CPD only, is in line with a more dimensional approach to personality disorders.

In **Chapter 4** we conducted a meta-analysis of 12 studies (total N=191) on psychotherapy-induced change in brain activation during negative emotional processing in individuals with PTSD. We found evidence for a decrease in activation in areas of the fear and cognitive control networks after psychotherapy, including the left amygdala, (para) hippocampus, putamen insula and ventrolateral PFC (vlPFC). A sensitivity analysis with

only whole-brain studies included showed a decrease in the left vlPFC and left amygdala. Nevertheless, when correcting for multiple testing, these findings were no longer significant. The non-corrected results are partly in line with previous studies, but fail to show the increased prefrontal activation found in the separate studies. Importantly, only 12 studies could be included which limits the interpretability of our findings.

Chapter 5 described the findings from pre- to post-treatment change in brain activity in the PROSPER samples using an emotional face task (N=38). In this study, we found no credible support for a change in brain activation from pre- to post-treatment or for differences between treatment conditions (trauma-focused treatment or concurrent trauma-focused and personality treatment), despite a large decrease of clinical symptoms after treatment. In addition, there was no credible evidence for an association between change in task-induced brain activation and change in symptom severity. A possible explanation might be that the emotional face task was not sensitive enough to detect activation changes. However, treatment responders (65.8%, defined as a PTSD severity reduction $SD_{pooled} \geq 1$) showed a larger increase in vmPFC activation after treatment than non-responders. And this might indicate improved emotion regulation after successful treatment.

In **Chapter 6** we used clinical data from both PROSPER trials to study predictors of treatment attendance. Forty percent of participants attended less treatment sessions than recommended. We found five consistent predictors of treatment attendance (out of 32 potential predictors). Lower dropout was related to higher baseline PTSD severity and stronger patient-rated working alliance, while higher dropout was related to lower educational status, inadequate social support from friends and following combined treatment. Clinicians could use this information to help guide their treatment. For example, it might be necessary to invest more time in the preparation of treatment for individuals with lower educational background. Furthermore, clinicians can invest in the therapeutic relationship and involve the network of the individual in treatment.

Interpretation of main findings

A dimensional approach to diagnosing personality disorders

Based on our findings in **Chapter 3**, especially the relationship between severity of dissociation and emotion regulation problems and brain activation, it seems fitting to adopt a dimensional approach to personality disorders in contrast to the more traditional categorical approach. In a dimensional approach, symptoms are placed on a severity spectrum instead of grouping them into separate categories as is done in the DSM-5. We found no clear distinction between BPD and CPD based on imaging

measures, although participants with both comorbid BPD and CPD showed more aberrant functioning than participants with BPD or CPD only. In the Netherlands, the Diagnostic and Statistical Manual (DSM-5; 1) is most commonly used for diagnosis and this gives separate classification criteria for every personality disorder. The latest version of the International Classification of Diseases (ICD-11, World Health Organization, however, already adopts a more dimensional approach. In the development of the ICD-11 personality disorder classification, there has been a lot of debate about whether it was necessary to have a separate borderline personality disorder classification, eventually leading to a system wherein a personality disorder is rated on its level of severity of intrapersonal and interpersonal functioning, with trait domain specifiers and an optional 'Borderline pattern' specifier (3, 4). This also fits within a broader trend of dimensional approaches to diagnosing psychopathology. A common criticism is that categorical diagnostic approaches unjustly suggest a homogeneous symptom pattern, which is not representative of the heterogeneity of a disorder. Rief, Hofmann (5) discuss of existing and novel frameworks such as the Hierarchal Taxonomy of Psychopathology (HiTOP), Research Domain Criteria (RDoC) and systems approaches. They argue that a synergy between models can lead to interesting new insights.

To better understand the underlying structure of personality disorders and to test the validity of the current categorical grouping of personality disorder symptoms, Sharp, Wright (6) used a factor analyses; it was based on the previous version of the DSM, DSM-IV. In a large sample of participants (N = 966) from an inpatient setting who were interviewed with a structured interview for personality disorder symptoms, the confirmatory factor analysis showed that the DSM classification was largely replicated. The factors however showed a high correlation, indicating overlap in symptom profiles. When they made a two-factor model for each PD with a general and specific factor, BPD items loaded only on the general factor. This means that there was no specific BPD factor. For other PDs, symptoms loaded either on both factors or mostly on the personality disorder specific factor. Sharp, Wright (6) theorize that the BPD general factor represents a general severity factor of PDs and that BPD symptoms are therefore indicative of overall PD severity.

There are a few neuroimaging studies focused on the difference between BPD and CPD whose results point in a similar direction as ours, which is no discernable neural differences between those groups. In a machine learning classification analysis, Cremers, van Zutphen (7) tried to classify BPD versus CPD and controls without a personality disorder based on brain activation during an emotion regulation task. Their classification accuracy for BPD versus controls was 55%, which is near to a chance rate, and statistically non-significant. Another study applying an affective go/no-go task to measure impulsivity, there were no activation differences between BPD and CPD (8).

There was an indication for a linear relationship, where the brain response of the CPD group was in between that of BPD and controls, supporting a dimensional model where BPD is representative of more severe symptoms. Our findings in **Chapter 3** indicate that BPD+CPD is more severe than BPD or CPD only.

Clinically, Massaal-van der Ree, Eikelenboom (9) compared psychiatric comorbidity between individuals with BPD, CPD or BPD+CPD. They found no differences between the groups on comorbid mood disorders, total number of comorbid axis-I disorders, trauma experience, PTSD or global functioning. They did find more anxiety disorders in the BPD+CPD group compared to the BPD group, and more substance dependence and lifetime suicide attempts in the BPD compared to CPD group. This shows that the type of personality disorder (at least BPD/CPD) is mostly unrelated to severity and type of comorbid problems. Although comorbidity may not be different between BPD and CPD groups, it can make interpretation of imaging results more difficult because of contradictory effects on brain activation (see discussion section of **Chapter 3)**.

All in all, both imaging and clinical results point to a dimensional model of borderline and cluster C personality disorders. In a dimensional model, overall severity level is influenced by comorbidity. Instead of rating symptoms as they fit within a certain category (as in the DSM-5), we would rate different dysfunctions on a severity scale (i.e. high impulsivity, low anxiety, high suicidal thoughts etc), which might show a better relation with results from brain imaging.

Pre- to posttreatment change in brain activation

Both our meta-analysis (**Chapter 4**) and our own pre- to posttreatment activation study (**Chapter 5**), show no reliable change in brain activation from pre- to posttreatment. This is contrary to the clinical findings from the trials, which show large effect sizes of treatment on clinical measures (Van Den End et al., under review; Snoek et al., in preparation). This discrepancy between imaging and clinical outcomes is possibly related to the choice of imaging modality and task. PTSD (and PD) treatment generally aim to improve emotion regulation (10, 11), which is maybe not conceptualized well with a face task (see below, 'Emotional Face Task' under Methodological considerations for a more extensive discussion of the task).

The meta-analysis (**Chapter 4**) showed some uncorrected findings in line with existing models of PTSD treatment, although there was no relationship with PTSD symptom improvement. It is possible that the meta-analysis was not adequately powered since we were only able to include 12 fairly small studies. On the other hand, the included studies were also small and might therefore be more liable to inflated findings (12), especially by using a region of interest approach. Our final sample of 38 participants

in **Chapter 5** is still a relatively small sample to detect treatment-induced changes in brain activation patterns. This is further complicated by the heterogeneity of the psychopathology and comorbidity. Both PTSD and PD are characterized by a broad range of possible symptoms (4, 13), which can mean that two people with PTSD have completely different sets of symptoms. Furthermore, comorbidity can confound the effects. As described in the discussion section of **Chapter 4**, most studies did not report on comorbidity (such as depressive disorder or dissociation). Both depressive disorders and dissociation can be related to blunted limbic activation, while PTSD and BPD are related to heightened limbic activation (14-16). However, we would not necessarily expect comorbidity to change during treatment (except for a decrease of symptoms), which therefore cannot fully explain the lack of change from pre- to posttreatment. In line with the previous discussion on a dimensional approach to psychopathology, we would expect a decrease in symptom severity to be reflected in the brain. A possible solution to overcome the problems of low power, high heterogeneity and comorbidity might be to conduct a mega-analysis where different samples are combined, such as in the ENIGMA approach (see https://enigma.ini.usc.edu/ongoing/enigma-ptsd-working-group/ for an overview of the ENIGMA PTSD working group)

Imaging measures have previously been used in models to predict treatment response. As an example, two studies have used imaging data to predict individual treatment response in individuals with PTSD (17, 18). In **Chapter 6** we described predictors of treatment dropout. Because imaging data was only available for a subset of participants, it was unfortunately not possible to add imaging measures to these prediction models. Our results in **Chapter 5** show a relation between both imaging measures (change in the vmPFC) and clinical measures (depression severity) and treatment response, indicating that focusing on successful treatment might help to shed more light on understanding the treatment mechanism.

Methodological considerations

Sample

A strength of the research in this thesis is the unique sample; as described in **Chapter 1**, imaging literature on PDs is scarce, especially on CPD (19, 20), just as literature on PTSD and comorbid PD. This means our research sheds light on a group that is clinically relevant considering the high comorbidity of PTSD and PDs in clinical practice. The sample is also representative of treatment-seeking individuals with PTSD, more so since a majority of other RCTs excludes suicidal ideations, which is one of the symptoms of BPD (21). Furthermore, compared to other PTSD treatment studies on neurobiological outcomes, our sample for pre- posttreatment change was relatively large. Still,

considering the heterogeneity of symptoms and comorbidity, quite a large sample is necessary to make reliable symptom profiles and our sample might not be large enough to detect subtle differences.

We did have quite some dropout in the study. From the baseline analyses (N=76) to pre-post analyses (N=38), there was an almost 50% dropout. This dropout consisted of both treatment and study dropout. As presented in the flow chart in **Chapter 5**, two thirds of the dropout from T0 to T2 was treatment dropout. Some participants who opted out of a second MRI scan did so because of scan-related fear; this selective dropout may have led to less limbic activity in the sample at T2. As described in **Chapter 6**, treatment dropout was more likely in the TFT+PT condition, which could have impacted our results. COVID restrictions could also have played a role in treatment and/or study dropout. Compared to other PTSD studies (without comorbid personality disorder), dropout was quite high. In a meta-analysis, Lewis, Roberts (22) found a pooled dropout of 16% in PTSD studies, although the range was 0 to 65%. Our dropout rate was comparable to the rate found in BPD (23). See also **Chapter 6** for a more extensive discussion of dropout both in literature and in our sample.

We were unfortunately unable to add control groups beside a baseline 'healthy' group: we did not have a PTSD-only or PD-only group or a group without treatment. The PTSD- and PD-only groups could have helped to clarify our findings by disentangling the effects of the specific disorders, although the effect of comorbid depression, anxiety disorders, medication use and dissociation would be more difficult to eliminate. By scanning all groups on the same scanner with the same task, the separate biotypes of PTSD, CPD and BPD could become clearer. Since the clinical effect of treatment was generally large, it might have been difficult to show a difference between treatment groups. Scanning a group without treatment could potentially make the treatment effect clearer. Finally, adding a follow-up scan later could have shown some more effect; it is possible that durable change takes longer to manifest in the brain and could therefore not been shown on a scan shortly after treatment.

Emotional Face task

We used an emotional face task to measure (negative) emotional processing. Specifically, our task used implicit emotional processing since participants were asked to focus on the perceived sex of the depicted faces and not on the emotions (see Chapter 2 and 24 for a more detailed description of the task). As a main contrast, we focused on fearful vs scrambled faces. Fusar-Poli, Placentino (25) meta-analyzed 105 studies that used an emotional face task and found some differences in activation dependent on the type of emotional face. For example, they found heightened activation in the amygdala in neutral, happy, disgusted and fearful faces but not sad or angry faces. They also

showed activation in different areas depending on whether the processing of emotions was implicit or explicit. For example, there was more amygdala activation in explicit processing and more insula activation in implicit activation (25). Meta-analyses have shown a robust amygdala activation in response to negative emotional faces in both control subjects (25) and BPD (26). Brain activation in the brain in response to emotional faces may be a general effect, rather than disease-specific.

It is not yet clear what task is most sensitive to study treatment effect in PTSD and personality disorders: to the best of our knowledge there are no studies available that directly compare the effect of different tasks in PTSD or PD. There is some data on participants without psychiatric disorders. Riedel, Yanes (27) clustered activation maps from the BrainMap database into meta-analytic groupings of types of experiments. As an example, one of their groupings yielded activation mostly in the amygdala, parahippocampal gyrus and fusiform gyrus. Task paradigms associated with these areas were affective pictures and words, and emotion indication. They found five such groups that all map onto slightly different brain areas and task paradigms, although there were also common factors. Finally, Hartling, Metz (28) directly compared four types of emotional tasks (emotional faces, emotional n-back, two types of emotional scenes) in 45 healthy participants. They used four ROIs (amygdala, dlPFC, anterior insula and pregenual ACC) and found increased amygdala activation in all tasks, but varying activation of the other ROIs across tasks. The faces task only showed amygdala activation. Unfortunately, Hartling, Metz (28) did not include a whole-brain analysis.

Contrary to our expectations, the emotional face tasks appeared not to be sensitive to measure change in brain activation in PTSD and comorbid PD. In PTSD studies, a PTSD-specific symptom provocation task where participants listen to a script of their trauma or watch trauma-related pictures is also common. Such a task can be used to elicit PTSD symptoms such as re-experiencing or dissociation (29, 30). It is possible that using such a task could have tapped more directly into the mechanism that is disturbed in PTSD and therefore have shown more change through treatment. Another type of task that could have been more sensitive to change through treatment could be a cognitive reappraisal task. In treatment, people learn how to better regulate their emotions and control their responses, something that is conceptualized in a reappraisal task. Research in both healthy populations and populations with a psychiatric diagnosis has shown that this type of task shows recruitment of cognitive control areas and modulation of the amygdala (31, 32).

Bayesian versus frequentist analyses

In **Chapter 3**, we used both frequentist and Bayesian analysis methods, to compare the methods and because it is possible to simultaneously investigate multiple regions of interest in one model with Bayesian analyses. Where the frequentist analysis did not show difference between the groups, the Bayesian analyses did show credible support for differences in the same ROIs (i.e. amygdala, dl/dmPFC, insula) between PTSD+BPD+CPD. This is in line with results from other studies (33, 34). Sensitivity is higher in Bayesian analysis because it can better incorporate information across ROIs (that are derived from the same brain and therefore not independent) and participants. In traditional frequentist analyses, analyses have to be run separately and then combined and corrected for multiple testing for all ROIs. Employing Bayesian testing also fits within recent recommendations for transparent reporting of all research findings instead of only focusing on significance (35).

Based on our findings, it would be interesting to see a broader application of Bayesian analysis methods in neuroimaging research. As described above, Bayesian analysis can be more sensitive than 'traditional' analysis and more representative of how the brain works, with ROIs that are not independent. There is a growing body of research that uses Bayesian methods of neuroimaging analyses. Using Bayesian methods on larger pooled datasets or in meta-analyses could give more nuanced insight into subtle effects.

Bayesian analyses are still limited by the quality of the data. As in 'traditional analyses', a challenge in Bayesian analyses is that it is dependent on the definition of the ROIs (34). In literature, there is a lot of diversity in the coordinates and definition of ROIs, which makes direct comparison harder. Studies using both frequentist and Bayesian methods could give more insight into the strengths and weaknesses of the Bayesian approach.

Clinical implications

One important clinical implication of our research is the use of a dimensional versus categorical model of personality disorders, as already advocated for by the ICD-11 (WHO, 2019/2021). Currently, there is still a lot of debate about the conceptualization of the BPD diagnosis (4) and the distinction between the complex PTSD diagnosis from the ICD-11 and having PTSD with comorbid BPD (36, 37). As a diagnosis is important for deciding on the course of treatment, the implications of a diagnostic system are far reaching.

The clinical results from both PROSPER trials show a large improvement in PTSD symptoms (Snoek et al., in preparation; Van Den End et al., under review). In the

PTSD+CPD trial, there was no difference between treatment conditions on any of the outcome measures, such as PTSD symptom severity, PD severity, wellbeing and dropout (Van Den End et al., under review). In the PTSD+BPD trial, there was no difference between treatment conditions on PTSD and BPD symptom severity and quality of life. The TFT-only condition but not TFT+PT condition showed moderate improvement in global functioning, and dropout was twice as high in the TFT+PT condition (Snoek et al., in preparation). Based on these findings and our own findings in **Chapter** 5, it seems advisable to start with a trauma-focused approach in individuals with PTSD and comorbid PD. Furthermore, based on these findings and the suggestion for a dimensional diagnostic approach, it might not be necessary or reliable to diagnose a personality disorder before commencing trauma-focused treatment.

Another result that is important for clinical practice concerns dropout. Dropout was quite high in our trials, compared to the overall dropout in other PTSD studies, but not compared to BPD studies (22, 23). Our results and discussion sections in **Chapter 6** give some tools for clinicians to possibly help treatment retention. The expectation that adding PD treatment to PTSD treatment would lead to better treatment retention was unmet; following both treatments was associated with more dropout. We also see from our results that treatment is quite effective in participants who completed treatment. To improve treatment outcome in PTSD, it might therefore be more impactful to focus on preventing dropout and reach more individuals than to adapt and improve the existing treatments further (38, 39).

Future directions

The studies I have described here provide some starting points for future research. There is still a lot unclear about PTSD and comorbid PD, especially CPD. Because of the high comorbidity between PTSD and PD, and high dropout rates, better understanding the neurobiological mechanisms and the mechanism of change through treatment can improve treatment outcome.

One possible way to better understand the treatment mechanism is by focusing on treatment responders, or by comparing data from responders to non-responders. For example, in **Chapter 5**, there was no overall change in brain activation after treatment, but responders did show a larger decrease in vmPFC activation than non-responders, pointing to a potential role for the vmPFC and its connected regions in effective treatment. Furthermore, combining data from different scan modalities can further improve our understanding. In the PROSPER study, we have also collected resting state functional data and diffusion-based data (see **Chapter 2** for a more extensive

description), but the results are beyond the scope of this thesis. This data can provide more insights into both functional and structural networks in the brain and how these change through therapy. Finally, this data can be used to predict treatment outcome. An example of this are the studies by Zhutovsky, Thomas (17) and Zhutovsky, Zantvoord (18) used functional connectivity measures to individually predict treatment outcome in adults and children with PTSD.

As Neria (13) describes, better understanding biotypes can lead to improved treatment and novel targets for treatment. Combining information from immunology, behavior, brain, genes and other sources can lead to advances in personalized psychiatry (e.g. 40). Because of the heterogeneity in the symptom profile and comorbidity, it is important that future imaging research focuses on underlying dysfunctions and symptom dimensions such as a depression severity scale, an impulsivity measure etc. One such approach that is used in neuroscience is the Research Domain Criteria (RDoC) framework, proposed by the National Institute of Mental Health (NIMH) in the United States. In RDoC, mental illnesses are conceptualized as disorders of brain circuits and it aims to identify these circuits by using a diverse range of tools from clinical neuroscience (41). The RDoC framework can be used as a starting point for future research (5, 42). For individuals with PTSD, a focus on the research domains 'negative valence', 'cognitive systems' and 'arousal systems' (43) seems fitting. Additionally for PD, the 'social processes' seem especially relevant. The hypothesized working mechanism of treatment for both PD and PTSD is through improving emotion regulation/cognitive control (10, 11), which could be reflected in the 'cognitive systems' domain. Furthermore, within the RDoC framework it is encouraged to combine sources of data (e.g. imaging modalities, genetics, behavioural data), which could lead to a more detailed and rich understanding of treatment processes (42)

In line with the discussion on methodological considerations, it would be interesting to compare brain activation through different types of emotion processing tasks in participants with PTSD/PD directly, by comparing different tasks such as an emotional face task, an individualized symptom provocation paradigm and reappraisal paradigm in one sample (conform the study by Hartling, Metz (28) in participants without psychiatric disorders). This could give us more information about the brain processes associated with the different tasks and where individuals with PTSD or PD show differential activation.

Conclusion

There is a large knowledge gap about individuals with PTSD and comorbid PDs, especially CPD. This thesis aimed to bridge part of this gap. Our data show support for a dimensional model of personality psychopathology and the use of Bayesian statistics on imaging data. Our studies did not show support for change in brain activation after treatment. More data on imaging paradigms and what neurobiological circuits they activate is necessary.

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APPENDIX

A

Nederlandse samenvatting

Ongeveer 70% van de mensen maakt één of meer traumatische gebeurtenissen mee tijdens hun leven, en ongeveer 4% van de volwassenen ontwikkelt een posttraumatische stressstoornis (PTSS). De PTSS diagnose omvat vier symptoomclusters: herbelevingen/ intrusies, vermijding, negatieve veranderingen in cognities en stemming en ten slotte veranderingen in reactiviteit en arousal. Dissociatieve symptomen komen ook regelmatig voor bij PTSS. Ongeveer 35% van de mensen met een diagnose PTSS heeft een comorbide diagnose persoonlijkheidsstoornis, waarbij paranoïde, borderline en cluster C (vermijdend, dwangmatig en afhankelijke) persoonlijkheidsstoornissen het meest voorkomen.

Psychotherapie is de eerste keuze voor behandeling voor zowel PTSS als borderline persoonlijkheidsstoornis (BPS). Voor cluster C persoonlijkheidsstoornissen (CPS) bestaat (nog) geen behandelrichtlijn. Bij mensen met comorbide PTSS en persoonlijheidsstoornissen is behandeling minder effectief en BPS is geassocieerd met een hoge behandeldropout. Het is nog onduidelijk of PTSS symptomen eerst behandeld moeten worden, of tegelijkertijd met persoonlijkheidsstoornissen. Om deze reden is het PROSPER (PRediction and Outcome Study in PTSD and PERsonality disorders) onderzoek in het leven geroepen. Dit zijn twee gerandomiseerde klinische trials waarbij deelnemers gerandomiseerd werden naar ofwel traumabehandeling (12-18 sessies), ofwel traumabehandeling (12-18 sessies) plus een groepsbehandeling gericht op de persoonlijkheidsstoornis van een jaar. Mensen met PTSS en BPS kregen EMDR (eye-movement desensitization and reprocessing) of EMDR + DGT (dialectische gedragstherapie), mensen met PTSS en CPS IMRS (imaginaire rescripting) of IMRS+ST (schematherapie). In totaal deden er 254 deelnemers mee, waarvan 89 ook een MRI scan hebben ondergaan.

Er is al veel onderzoek gedaan naar de neurobiologische correlaten van PTSS. Er zijn twee neurobiologische subtypen beschreven: een herbelevings/hyperarousal subtype en een dissociatief subtype. In het hyperarousal subtype is er vooral hoge activatie in limbische gebieden als de amygdala, met beperkte top-down regulatie door prefrontale gebieden. In het dissociatieve subtype is juist 'te veel' controle door prefrontale gebieden, wat zorgt voor verlaagde activiteit in limbische gebieden. Latere modellen beschrijven andere activatie in mensen met PTSS dan mensen zonder PTSS in verschillende netwerken zoals het fronto-limbische circuit.

In persoonlijkheidsstoornissen zijn enkele neurobiologische studies gedaan, die zich vooral focussen op BPS. Hierbij zijn nog geen eenduidige resultaten gevonden, zo vinden sommige studies een verhoogde activatie van de amygdala terwijl anderen een

verlaging van activatie vinden. Dissociatieve symptomen, medicatiegebruik en de keuze voor contrast van de scantaak spelen hierbij mogelijk een rol. Voor PTSS en comorbide persoonlijkheidsstoornissen zijn pas enkele (kleine) studies gedaan.

In dit proefschrift beschrijven we resultaten van vooral neurobiologische onderzoeken die uitgevoerd zijn binnen de PROSPER studie bij mensen met PTSS en comorbide persoonlijkheidsstoornissen.

Hoofdstuk 2 bevat de opzet van een studie op een subgroep van de twee PROSPER trials. Voor deze beeldvormingsstudie maakten we MRI-scans van deelnemers met PTSS en comorbide BPS en/of CPS, plus een controlegroep zonder psychiatrische diagnose. We verzamelden functionele scans zowel tijdens rust als tijdens een taak, naast structurele scans. De andere hoofdstukken in dit proefschrift gaan vooral over de taakgerelateerde functionele scans.

In **hoofdstuk 3** onderzochten we, met behulp van de gegevens van vóór de behandeling uit de PROSPER dataset, of het type comorbide persoonlijkheidsstoornis (BPS, CPS of BPS+CPD) een effect had op de hersenreactie tijdens een emotionele gezichtentaak bij deelnemers met PTSS en comorbide BPS/CPS (N=76 PTSS+PS, N=30 controles). Met traditionele frequentistische analyses vonden we geen consistente verschillen in hersenactivatie tussen verschillende persoonlijkheidsstoorniscomorbiditeiten in onze interessegebieden (bilaterale amygdala, rechter dorsolaterale prefrontale cortex (dlPFC), rechter dorsomediale PFC (dmPFC) en rechter insula). Deze gebieden werden voornamelijk gekozen uit de fronto-limbische, salience en centrale executieve netwerken. Met aanvullende Bayesiaanse analyses vonden we sterk overtuigend bewijs voor hogere activatie in de meeste gebieden (bilaterale amygdala, dmPFC, dlPFC, insula, hippocampus, dorsale anterieure cingulate cortex (dACC) en superieure occipitale gyrus) bij deelnemers met PTSS+BPS+CPS vergeleken met deelnemers met PTSS+BPS of PTSS+CPS; we vonden geen betrouwbare verschillen tussen PTSS+BPS en PTSS+CPS. Over alle PTSS-groepen heen vonden we ook een negatieve associatie tussen de ernst van dissociatie en de activatie in de rechter dmPFC en rechter insula, en tussen het niveau van emotieregulatieproblemen en de activatie van de rechter dmPFC. Het ontbreken van verschillen met de controles in onze hoofdanalyses kan gerelateerd zijn aan het tegenovergestelde effect van comorbiditeit en medicatie vergeleken met het effect van PTSS op de hersenen. Het resultaat dat de ernst van dissociatie en het niveau van emotie-regulatieproblemen gerelateerd waren aan activiteit in bepaalde hersengebieden en dat PTSS+BPS+CPS hogere activatie vertoonde dan BPS of CPS alleen, was in lijn met een meer dimensionele benadering van persoonlijkheidsstoornissen.

In **hoofdstuk 4** voerden we een meta-analyse uit van 12 studies (totaal N=191) over door psychotherapie geïnduceerde verandering in hersenactivatie tijdens negatieve emotieverwerking bij mensen met PTSS. We vonden aanwijzingen voor een afname van activatie in gebieden van de angst- en cognitieve controlenetwerken na psychotherapie, inclusief de linker amygdala, (para)hippocampus, putamen, insula en ventrolaterale PFC (vlPFC). Een sensitiviteitsanalyse met alleen whole-brain studies toonde een afname in de linker vlPFC en linker amygdala. Desalniettemin waren deze bevindingen niet langer significant na correctie voor multiple toetsing. De niet-gecorrigeerde resultaten zijn gedeeltelijk in lijn met eerdere studies, maar tonen niet de verhoogde prefrontale activatie die in de afzonderlijke studies is gevonden. Belangrijk is dat slechts 12 studies konden worden meegenomen in de analyses, wat de interpretatie van onze bevindingen belemmert.

In **hoofdstuk 5** beschreven we de bevindingen van verandering door therapie in hersenactiviteit in de PROSPER deelnemers, met behulp van een emotionele gezichtentaak (N=38). In deze studie vonden we geen geloofwaardig bewijs voor een verandering in hersenactivatie van pre- tot post-behandeling of voor verschillen tussen behandelcondities (traumabehandeling of gelijktijdige trauma- en persoonlijkheidsbehandeling), ondanks een grote afname van klinische symptomen. Bovendien was er geen geloofwaardig bewijs voor een associatie tussen verandering in taakgeïnduceerde hersenactivatie en verandering in symptoomernst. Een mogelijke verklaring zou kunnen zijn dat de emotionele gezichtentaak niet gevoelig genoeg was om veranderingen in activatie te detecteren. Deelnemers die goed reageerden op behandeling (65.8%, gedefinieerd als een PTSS ernstreductie SDpooled ≥ 1) vertoonden een grotere toename in vmPFC activatie na behandeling dan niet-responders. Dit zou kunnen wijzen op verbeterde emotie-regulatie na succesvolle behandeling.

In **hoofdstuk 6** gebruikten we klinische gegevens van beide PROSPER onderzoeken om voorspellers van behandeluitval te bestuderen. Van de deelnemers voltooide 40% minder behandelsessies dan aanbevolen in de richtlijnen. We vonden vijf consistente voorspellers van deelname aan behandelsessies (van de 32 potentiële voorspellers). Lagere uitval was gerelateerd aan hogere PTSS ernst bij start van de behandeling en sterkere door de cliënt beoordeelde werkalliantie, terwijl hogere uitval gerelateerd was aan een lager opleidingsniveau, inadequate sociale steun van vrienden en het volgen van de gecombineerde behandeling. Clinici zouden deze informatie kunnen gebruiken om hun behandeling te ondersteunen. Het zou bijvoorbeeld nodig kunnen zijn om meer tijd te investeren in de voorbereiding van de behandeling voor individuen met een lagere opleidingsachtergrond. Bovendien kunnen clinici investeren in de therapeutische relatie en het netwerk van het mensen betrekken bij de behandeling.

In de discussie van het proefschrift **(hoofdstuk 7)** werden de resultaten samengebracht en geef ik een interpretatie. Daarnaast beschreef ik sterke en zwakkere kanten en suggesties voor vervolgonderzoek. Ik beschreef hoe, gebaseerd op onze resultaten en nieuwe modellen van psychopathologie, een dimensionele benadering van persoonlijkheidsstoornissen passend lijkt. Ook beschreef ik mogelijke verklaringen voor waarom we weinig effect vinden van de behandeling op hersenactivatie, terwijl de klinische verandering groot is. Mogelijk speelde de grootte van de steekproef of comorbiditeit hier een rol in. Methodologische overwegingen die besproken werden in de discussie zijn de steekproef en de dropout hiervan, de gebruikte gezichtentaak en het gebruik van frequentistische versus Bayesiaanse analyses. Klinische implicaties van dit proefschrift zijn onder andere het gebruik van dimensionele modellen van persoonlijkheidsstoornissen. Daarnaast lieten de resultaten van de klinische trials zien dat traumabehandeling+groepsbehandeling niet effectiever is dan traumabehandeling alleen. Op basis hiervan bevelen we aan om te starten met traumabehandeling bij mensen met PTSS en comorbide persoonlijkheidsstoornissen. Voor toekomstige onderzoeken beveel ik aan om specifieke analyses te richten op mensen die goed reageren op behandeling ('responders'), om zo de mechanismen van behandeling beter te leren begrijpen. Daarnaast kan het goed zijn om zogenaamde 'biotypes' te onderzoeken en ik suggereerde frameworks die hiervoor gebruikt kunnen worden. Ook zou het interessant kunnen zijn om verschillende taken met elkaar te vergelijken, zodat we beter begrijpen wat de taken precies meten.

Concluderend is er nog weinig bekend over mensen met PTSS en comorbide persoonlijkheidsstoornissen, vooral CPS. Het doel van dit proefschrift was om een deel van dit informatiegat te vullen. Op basis van onze resultaten werd geen bewijs gevonden voor verandering van hersenactivatie na psychotherapie. Onze data ondersteunen een dimensioneel model van persoonlijkheidspathologie en het gebruik van Bayesiaanse statistiek.

Curriculum vitae

Inga studied Bèta-gamma with a major in psychobiology and minors in Religious studies and Pedagogy at the University of Amsterdam. For her master's degree, she did both a clinical master ('orthopedagogiek') and a research master (Child Development and Education). She did her master's internship at the department of 'child & family' (Kind & Gezin) of the Bascule (now Levvel).

In June 2017, Inga started her PhD trajectory on the PROSPER trials at the Sinai Centre (part of Arkin) and was also embedded in Team Neuropsychiatry of the Amsterdam UMC (location VUmc). The PhD trajectory was supervised by Kathleen Thomaes, Odile van den Heuvel and Chris Vriend.

During her PhD trajectory, Inga has also worked as a psychologist at the Sinai Centre. In April 2024, she started her residency in health care psychology (GZ-opleiding) at Arkin, with her first internship at the Jellinek outpatient clinic.

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Aarts, I., Vriend, C., Van den End, A., Snoek, A., Blankers, M., Beekman, A.T.F., Dekker, J., Van den Heuvel, O.A., & Thomaes, K. (under review). Treatment effect of posttraumatic stress disorder treatment with or without concurrent personality disorder treatment on brain activation during an emotional face task.

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