DISSERTATION

Structural and functional neuroplasticity in posttraumatic stress disorder: fear learning and context processing

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“Anxiety is out of place in the present moment.

It depends on the past and the future for its existence.”

Kelly Wilson (2010),

“Things might go terribly, horribly wrong: A guide to life liberated from Anxiety”

Dedicated to Marianne Bichler

who taught me to live the here and now

Table of Contents

Abstract

Trauma exposure can lead to the development of posttraumatic stress disorder (PTSD), a mental disorder characterized by re-experience of the traumatic event, avoidance behavior, negative alterations in cognitions and mood and heightened arousal and reactivity. Fear learning and context processing are two psychological processes which have been highlighted by psychobiological models of PTSD. In this thesis, structural and functional brain differences are investigated in three studies between patients with PTSD and healthy trauma (TC) or non-trauma exposed (HC) control subjects and results are discussed within a common psychobiological model of PTSD.

In the first study, we provide a systematic review and meta-analysis including 30 studies with 1,700 participants on structural white matter differences. In the second study, we build upon our findings and investigate both white and gray matter alterations in PTSD in a cross-sectional study design consisting of 154 subjects. In the third study, we examine behavioral and psychophysiological alterations in patients with PTSD during uncued and cued contextual fear processing using virtual reality in a cross-sectional-, functional magnetic resonance imaging study, including 63 subjects.

Our results from the first two studies suggest that patients with PTSD show structural differences in a wide range of white matter tracts most prominently including tracts connecting the prefrontal cortices inter-hemispherically (e.g. forceps minor) as well as with more posterior brain regions like the parietal lobe (e.g. superior longitudinal fasciculus). White matter alterations in these regions of the brain can be associated with processing contexts, regulating emotions and guiding attention. Furthermore, our results suggest lower gray matter volumes in patients with PTSD in comparison to TC subjects in the anterior insulae, a region critical for processing fear and threat related information. The results of our third study show that patients with PTSD in comparison to HC but not TC showed lower functional activity in the ventromedial prefrontal cortex during uncued contextual fear learning and higher functional activity in the hippocampi during cued contextual fear learning. Patients with PTSD did show however similar behavioral ratings of arousal, valence and contingency as well as skin conductance responses during both conditions than both control groups.

In summary, this work suggests that patients with PTSD show alterations in structural and functional brain activity that can both be associated to fear learning and context processing. Our work proposes above all that lower volume and activity within the prefrontal cortex in combination with functional alterations in the hippocampi can be associated with deficient contextual fear processing. Structural and functional alterations in PTSD are mutually dependent and future work will benefit from discussing results of both branches within a common psychobiological model of PTSD. Targeting contextual fear processing in PTSD will help the overarching goal of translating the results from the lab into clinical practice.

1 Introduction

Psychological trauma (from τραύμα, the Greek word for wound) is characterized by a complex emotional response following the experience of an extremely aversive event (Forbes et al., 2020). The experience of such an event can lead to the development of posttraumatic stress disorder (PTSD), which is characterized by symptoms of re-experiencing, avoidance, heightened arousal and reactivity and alterations in cognition and mood. The past two decades of research have seen an immense effort in understanding the psychopathological mechanisms underlying PTSD. In particular, novel paradigms in combination with advanced neuroimaging techniques have led to a refined psychobiological model of PTSD. Here, fear learning and context processing have taken the center stage suggesting that patients with PTSD have difficulties in discriminating safe from dangerous contexts and in forming accurate expectancies about a potential threat within the respective context. Neurobiological findings support this hypothesis by showing functional differences in brain regions associated to fear learning and context processing. However, there is a gap in the literature on a) structural brain differences and their integration into a common psychobiological model of PTSD and b) functional brain activity during contextual fear conditioning in patients with PTSD in comparison to healthy control subjects with (TC) or without (HC) trauma experience. The goal of this dissertation was to investigate structural and functional brain differences associated to fear learning and context processing, between patients with PTSD and TC and HC subjects and to discuss the results within a shared psychobiological model of PTSD.

This cumulative thesis is based on the following three manuscripts:

Siehl, S., King, J. A., Burgess, N., Flor, H., & Nees, F. (2018). Structural white matter changes in adults and children with posttraumatic stress disorder: A systematic review and meta-analysis. *NeuroImage: Clinical*, *19*, 581-598. doi: 10.1016/j.nicl.2018.05.013

Siehl, S., Wicking, M., Pohlack, S., Winkelmann, T., Zidda, F., Steiger-White, F., King, J., Burgess, N., Flor, H., & Nees, F. (2020). Structural white and gray matter differences in a large sample of patients with Posttraumatic Stress Disorder and a healthy and trauma-exposed control group: Diffusion tensor imaging and region-based morphometry. *NeuroImage: Clinical*, *28,* 102424. doi: 10.1016/j.nicl.2020.102424

Siehl, S., Wicking, M., Pohlack, S., Winkelmann, T., Zidda, F., Steiger-White, F., Nees, F., & Flor, H. (2020). *Cued and contextual conditioning in patients with posttraumatic stress disorder and a healthy and trauma-exposed control group: A functional magnetic resonance imaging study using virtual reality.* Manuscript in preparation.

1.1 Posttraumatic stress disorder

According to the fifth edition of the Diagnostic and Statistical Manual (DSM-5; American Psychiatric Association, 2013), a diagnostic requirement for being diagnosed with PTSD is that an individual has either been directly or indirectly exposed or has learned about a close person being exposed to a traumatic event. In addition, the following four symptom clusters have to be fulfilled, having been present for the past four weeks: a) the re-experience of the traumatic event in form of intrusions or flashbacks; b) avoidance behavior around thoughts, emotions or reminders of the event; c) negative alterations in cognitions and mood; d) heightened arousal and reactivity. Often these key symptoms are accompanied by symptoms such as impaired social cognition (Couette, Mouchabac, Bourla, Nuss, & Ferreri, 2020) and somatic pain or disfigurements (Morina et al., 2018; Siqveland, Ruud, & Hauff, 2017), such as physical scars or amputations. An estimated seven out of ten adults worldwide experience at least one traumatic event in their lifetime with approximately every third adult experiencing four or more events (Benjet et al., 2016). This means that a majority of people worldwide experience at least one traumatic event during their lifetime. The lifetime prevalence of PTSD is about seven percent (Kessler et al., 2005) with significantly higher prevalence rates in conflict and post-conflict regions (Ng et al., 2020; Onyut et al., 2009). The probability to develop PTSD is increased by a variety of factors including female sex, childhood trauma or a higher number of traumatic events experienced (Shalev, Liberzon, & Marmar, 2017). Furthermore, the probability increases with an increased intensity (e.g., exposure to death) and unpredictability (e.g., torture) of the traumatic event as well as specific types of trauma, with interpersonal or voluntarily caused types (e.g., rape) resulting in higher probability rates than non-personal or involuntarily caused events (e.g., car accident; Kessler et al., 2017; Shalev, Liberzon, & Marmar, 2017). The comorbidity of PTSD is high with approximately every second individual being also diagnosed with a mood-, anxiety or substance abuse disorder (Antonacci & de Groot, 2000; Pietrzak, Goldstein, Southwick, & Grant, 2011). In the following sections, we will discuss psychological processes involved in the development and maintenance of PTSD, followed by the introduction of a novel psychobiological model of PTSD.

1.2 Psychological processes involved in posttraumatic stress disorder

A traumatic event can be defined as an extremely aversive, often life-threatening, learning experience. As such, learning processes, studied primarily through classical pavlovian fear conditioning, have been the natural starting point to investigate mechanisms in anxiety

disorders (Jacobs & Nadel, 1985; Rosen & Schulkin, 1998). In PTSD, a particular focus was placed on context conditioning (Maren, Phan, & Liberzon, 2013) in recent years. In the following, we discuss fear learning and context processing in more detail using the model of PTSD proposed by Shalev et al. (2017) and briefly touch upon related processes like threat detection, emotion processing and aspects of executive functions.

1.2.1 Fear learning

Fear learning, the process of learning to predict the occurrence of an unpleasant stimulus and changing one's behavior accordingly, is a central survival skill. Fear learning can be studied using classical pavlovian fear conditioning (Pavlov, 1927). In classical fear conditioning, an originally neutral stimulus (the conditioned stimulus, CS) is presented together with an aversive (e.g. tone, shock), unconditioned stimulus (US). During acquisition, the CS acquires aversive characteristics similar to the one of the US and the CS starts to elicit a conditioned response (CR). In the extinction phase, the CR can be overwritten when the CS is repeatedly presented without the US (for a review see Lonsdorf et al., 2017). In a differential fear conditioning paradigm, a modification of classical fear conditioning, there are multiple CSs, which are either paired with a US to become a danger (CS+) or safety signal (CS-). Earlier studies investigating differential fear conditioning (Lissek et al., 2005) found that patients with PTSD show difficulties in discriminating safety from danger cues (Grillon, 2002; Grillon, Morgan, Davis, & Southwick, 1998). Patients with PTSD were reported to show higher physiological reactions, measured via startle or skin conductance response (SCR), to safety cues than healthy control subjects (Jovanovic, Kazama, Bachevalier, & Davis, 2012; Jovanovic et al., 2010). An impaired safety signal learning was even suggested as a possible biomarker for PTSD (Jovanovic et al., 2012). The results on physiological responses during cued fear acquisition have been mixed, however, with some authors reporting an elevated startle or SCRs (Orr et al., 2000; Peri, Ben-Shakhar, Orr, & Shalev, 1999), while others did not find any differences (Milad et al., 2009; Nees, Heinrich, & Flor, 2014).

In the previous examples, the CS was a single item or cue (cue conditioning). In the absence of a specific cue that is predictive for the occurrence of the US, the entire context can become the CS (context conditioning; Maren, Phan, & Liberzon, 2013). Now, extreme stress leads to an ambiguity in the evaluation of contexts. Originally safe contexts are encoded as potentially dangerous. Different ways to study context conditioning have been developed, operationalizing "context" differently (for a review: Glenn, Risbrough, Simmons, Acheson, &

Stout, 2017). Early studies used distinct colored backgrounds (Armony & Dolan, 2001), transitioning colored backgrounds (Lang et al., 2009; Pohlack, Nees, Ruttorf, Schad, & Flor, 2012) or static background pictures (Marschner, Kalisch, Vervliet, Vansteenwegen, & Buchel, 2008; Steiger, Nees, Wicking, Lang, & Flor, 2015). More recent approaches include configural learning (Baeuchl, Hoppstädter, Meyer, & Flor, 2019; Baeuchl, Meyer, Hoppstädter, Diener, & Flor, 2015; Stout et al., 2018), in which the US can only be predicted by learning the configuration of multiple items, and virtual reality (Alvarez, Biggs, Chen, Pine, & Grillon, 2008; Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011; Andreatta et al., 2015; Baas, van Ooijen, Goudriaan, & Kenemans, 2008; Grillon, Baas, Cornwell, & Johnson, 2006; Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011). In PTSD, contextual fear learning was proposed to be a key mechanism around which the psychopathology evolves (for a review see Maren et al., 2013). In particular, an underlying inability to adequately form conjunctive context representations has been suggested (Stout et al., 2018), a process of binding single items into a unitary representation (Rudy & O'Reilly, 2001; Rudy & O'Reilly, 1999), and the inability to associate cues to the appropriate contexts (Acheson, Gresack, & Risbrough, 2012; Stout et al., 2018). In line with this, Steiger, Nees, Wicking, Lang, & Flor (2015) found that individuals with PTSD showed an impaired ability to discriminate safe and dangerous contexts as well as impaired contextual modulation of cue-related associations compared to healthy individuals with or without traumatic experience. For a better understanding of mechanisms behind context learning, we first have to define what we mean by context, and then look at the broader function of context processing in cognition.

1.2.2 Context processing

Context processing as a central psychological process involved in anxiety disorders has been on the radar of researchers for some time (Pitman et al., 2012) but recent theoretical work put it at the center of their models for the development and maintenance of PTSD (Brewin, Gregory, Lipton, & Burgess, 2010; Liberzon & Abelson, 2016; Robertson et al., 2017). Maren et al. (2013) define context very broadly "as the internal (cognitive and hormonal) and external (environmental and social) backdrop against which psychological processes operate" (p.417). In other words, an individual's appraisal of a context influences our internal and external responses to a given situation. In this work, we will mainly discuss external, and more specifically environmental, factors of context. *Figure 1a* shows elements of an office and their embedding into a context. Therein, context processing describes the embedding of cues in a common environmental space (single event), which is defined by its spatial borders

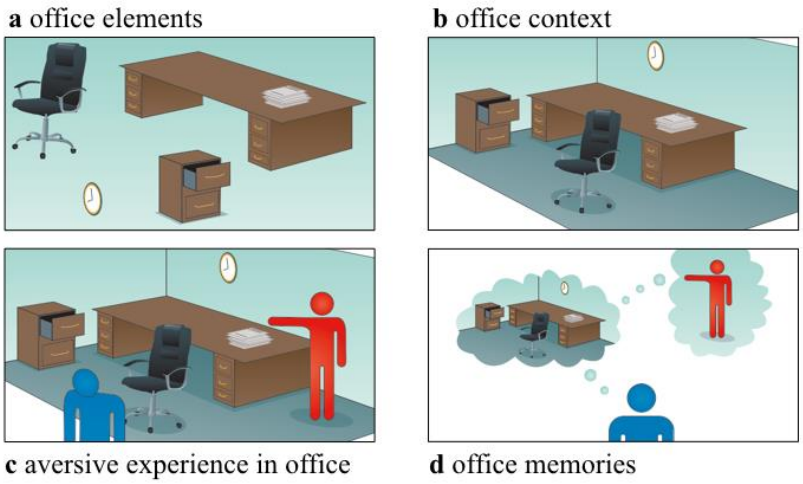

Figure 1. Context representation and the example of an aversive experience. **a)** Elements, in this case furniture, that are typically present in an office. **b)** Office context and particular spaces, in which the elements are placed in. **c)** Aversive experience in office, such as getting fired. An encoded context can be associated with a new event, such as this aversive experience. **d)** Office memories, which are associated to the event of getting fired, might provoke stress and anxiety and might generalize to similar context settings. [adapted from Maren, Phan, & Liberzon, 2013, without permission]

(e.g. wall), its complexity (e.g. high amount of interactions of objects/ people in environment) and its possible courses of action (e.g. control taking within a single event; see Figure 1a and b). Along these lines, combined cue-context conditioning paradigms have used predictable contexts, in which a single cue within the context predicts the US (CS; e.g. person in red in *Figure 1c*), in comparison to unpredictable contexts, in which no single cue but the context itself predicts the occurrence of a US (CTX+; Grillon, Baas, Lissek, Smith, & Milstein, 2004; Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011; Schmitz & Grillon, 2012). A combined cue-context study design allows studying the main effects of a conditioned cue and a conditioned context as well as their interaction simultaneously. To the best of our knowledge, no study has assessed this in patients with PTSD. We would hypothesize that patients with PTSD in comparison to TC and HC subjects show higher arousal, valence and contingency ratings as well as SCRs when the US occurs in an unpredictable context but not in the predictable context.

In addition, just remembering the office might elicit a fear response with the possibility of being generalized over time to similar environments (*Figure 1d*). This is in line with multiple lines of research, including fear conditioning, imagery and memory research, that found alterations in context processing in patients with PTSD (Brewin & Burgess, 2014; Brewin et al., 2010; Ehlers & Clark, 2000; Jacobs, Brown, & Nadel, 2017; Kheirbek et al., 2012; Levy-gigi, Richter-levin, Levy-gigi, & Richter-levin, 2016; Liberzon & Abelson, 2016;

Maren et al., 2013; Nadel & Willner, 1980). Using fear conditioning paradigms, patients with PTSD showed stronger fear generalization (Dunsmoor & Paz, 2015; Kheirbek et al., 2012; Lissek et al., 2005; Lissek & van Meurs, 2015; Morey et al., 2020), weaker context representations (Acheson et al., 2012; Flor & Nees, 2014; Lang et al., 2009; Maren et al., 2013; Steiger et al., 2015), deficient fear extinction and renewal with heightened levels of fear (Garfinkel et al., 2014; Maren & Holmes, 2016; Wicking et al., 2016). Similar results come from research on the development of intrusions and flashbacks (Bird et al., 2012; Brewin & Burgess, 2014; Brewin et al., 2010; Jacobs et al., 2017), showing alterations in processes associated to context processing, such as allocentric memory performance (Meyer et al., 2012; Smith, Burgess, Brewin, & King, 2015) and reduced accuracy in pattern separation (Liberzon, Duval, & Joshi, 2017). In addition, a reduced accuracy in temporal contextualization is discussed, measured via a reduced sense of 'nowness' (Brewin & Burgess, 2014; Glazer, Mason, King, & Brewin, 2013) and the effect of being 'frozen in time' (Ehlers & Clark, 2000). The representation of context is essential for detecting changes and predicting future events within the same map. Dysfunctional context processing is not an isolated process but accompanied by changes in attention, emotion processing and specific executive functions, which will be briefly discussed in the following section.

1.2.3 Threat and salience detection, emotion processing and executive functions in PTSD

The ability to detect or anticipate potential threats via guiding one's attention towards salient stimuli, like a snake lying in the grass, is a core survival mechanism in humans (Brewin et al., 2010; Eilam, Izhar, & Mort, 2011; Maren et al., 2013; Sripada et al., 2012). Patients with PTSD show exaggerated reactivity to salient stimuli (Fani et al., 2012), a stronger preferential attention to threatening stimuli (Buckley, 2000) and a heightened threat anticipation (Grillon et al., 2009). This constant alertness leads to increased levels of arousal and hypervigilance in patients with PTSD. At the same time, attentional inflexibility might underlie the difficulty in discriminating unpredictable and predictable contexts from their safe counterparts. Patients with PTSD also show alterations in emotion regulation, making it difficult to either downregulate very intense emotions or to match an emotional response to the situational demands (Gross, 2014; Gross, 1998). Here, an increased utilization of response-focused strategies was shown in patients with PTSD, in which the already evolved emotion is modulated (expressive suppression), and a decreased utilization of antecedent-focused strategies, in which one's thoughts are changed prior to the emotional response (cognitive reappraisal; Boden et al., 2013). Firefighters with low (but not high) emotion regulatory

flexibility showed a strong association between the number of traumatic events exposed to and symptom severity of PTSD (Levy-gigi et al., 2016; Polak et al., 2012). Higher flexibility in being able to choose between different emotion processing strategies seems to be a protective factor. Finally, Shalev et al. (2017) argue that a broader malfunctioning of key executive functions, such as the integrity of working memory or task-shifting components, underlie altered threat detection and emotion processing (Aupperle, Melrose, Stein, & Paulus, 2012; Polak et al., 2012). The malfunctioning of these necessary core processes in combination with increased levels of arousal and hypervigilance amplify the inflexibility in emotional processing and threat detection. These on the other hand create a context in which discrimination learning and predictability of threats are impeded. Abnormalities in the above discussed psychological processes are associated with and mediated by neurobiological processes. In the next section, common neuroimaging techniques shall be discussed to assess structural and functional brain differences. These will then be embedded in a psychobiological model of PTSD.

1.3 Neurobiological foundations of posttraumatic stress disorder

The human brain is a highly flexible organ adapting through growth and reorganization, a process termed neuroplasticity (Fuchs & Flügge, 2014). Neuroplasticity can be divided into structural and functional neuroplasticity (Sampaio-Baptista & Johansen-Berg, 2017; Zatorre, Fields, & Johansen-Berg, 2012). Structural plasticity can be further subdivided into gray and white matter plasticity (Zatorre et al., 2012) and both can be assesses with specialized magnetic resonance imaging (MRI) sequences. Furthermore, all types of analyses described in this section can be applied to all areas in the brain (so called whole-brain analysis) or to specific regions of interest (ROI analysis). Diffusion Tensor Imaging (DTI; Bihan & Johansen-Berg, 2012; Johansen-Berg & Behrens, 2014) is a commonly used imaging technique to assess white matter architecture, in which the directionality of diffusion of water molecules is estimated. It is assumed that the movement of water molecules in white matter is bound to the direction of the axons the water is dissolved in. The net directionality of water diffusion can be estimated with the so-called fractional anisotropy (FA), a measure ranging from 0 (isotropic; non-directional) to 1 (anisotropic diffusion; highly directional). FA values closer to 1 are associated with a higher streamline count of white matter tracts and are considered to be preferable over low values in areas in which a strong connectivity is assumed (Jones, Knösche, & Turner, 2013). In their systematic review and meta-analysis on differences in FA in patients with PTSD in comparison to either HC or TC subjects, Daniels

et al., (2013) found a variety of tracts differing significantly in the FA value. These tracts included bilaterally the cingulum and superior longitudinal fasciculus (SLF), the posterior limb of the internal capsule, the right anterior thalamic radiation and the right anterior corona radiate. More studies reported higher FA values in these tracts in patients with PTSD than in the respective control group, with only two studies reporting lower FA values. Differences in FA values seem to be found in large and long-reaching fiber tracts, connecting either anterior to posterior lobes (e.g. SLF) or in interhemispheric connections (e.g. cingulum). However, the results of the review and meta-analysis by Daniels et al. (2013) highlight a large heterogeneity in both the applied methodology and the included and compared samples. Thus, a systematic review and meta-analysis is needed with clearly defined groups, taking into consideration the age of participants (e.g. children vs. adulthood), the timing of trauma (e.g. childhood [<18 years of age] vs. adulthood [>18 years of age]) and the methodology of the assessment of white matter (whole brain vs. ROI). In addition, studies with larger sample sizes are needed comparing white matter in patients with PTSD with HC and TC subjects.

In respect to gray matter plasticity, volumes can be estimated with a technique called voxel-based morphometry (VBM; Ashburner & Friston, 2005), in which the volume of each voxel in the brain, after registration to a template brain, is estimated from a high-resolution MRI scan. Just like in DTI, VBM can be applied to the whole brain or to particular ROIs and group comparisons can then be calculated. In PTSD research, recent meta-analyses found smaller volumes in brain regions associated to all four psychological processes discussed in the previous section (Bromis, Calem, Reinders, Williams, & Kempton, 2018; Kühn & Gallinat, 2013). Interestingly, differences in volume were also found when TCs were compared to HC subjects, with lower volumes of the hippocampus bilaterally in TC subjects. Furthermore, patients with PTSD in comparison to patients with major depressive disorder (MDD) showed lower total brain volume, suggesting either a more generalized neuroplastic volume change in gray matter due to trauma experience or a pre-traumatic vulnerability factor for developing PTSD (Bromis et al., 2018). However, the number of studies is low for the majority of meta-analytical ROI analyses, with often only a handful of studies that could be included. Furthermore, it is not clear if and how gray and white matter differences are associated. The hen-and-egg problem in brain plasticity research in PTSD evolves around the question if these differences are the result of a simple trauma exposure or if trauma exposure is only the last straw that breaks the camel's back as the result of a pre-traumatic vulnerability. Zatorre et al. (2012) called this interaction between experience-based learning, mediated by

functional brain plasticity, and structural adaptation of the brain a dynamic loop. The challenge to study this loop and its various interacting mechanisms is further complicated by the fact that PTSD presents itself in a heterogeneous clinical picture (e.g. complex PTSD, dissociative subtype; Frewen, Zhu, & Lanius, 2019; Sierk, Manthey, Brakemeier, Walter, & Daniels, 2020) and can be the consequence of different kinds of events (e.g. involuntarily- or voluntarily caused events; Kessler et al., 2017) occurring at different points in life (e.g. childhood vs. adulthood; Alisic et al., 2014). To tackle this challenge, we need more well-powered studies on gray and white matter differences with strong study designs focusing on the various aspects mentioned above.

Finally, we can assess functional brain activity associated to specific tasks via a technique called blood-oxygenation-level-dependency (BOLD; Ogawa, Lee, Kay, & Tank, 1990). When a specific task is performed, the neurons involved in the computations are in need of more energy, reflected in oxygen. The latter is delivered by blood cells (bound to hemoglobin molecules) which are supplied via arteries in the brain. This consumption of oxygen leads to a change in the level of oxygenated (oxyhemoglobin) and deoxygenated (deoxyhemoglobin) blood, the so-called hemodynamic response. Differences in the magnetic susceptibility of oxy- and deoxygenated blood can be detected and are the basis for the BOLD signal, thus providing the underlying principle of functional MRI (fMRI). Using fMRI, we can study cognitive functions noninvasively, associate these functions to the activity in anatomically or functionally defined brain regions and compare the fMRI signal between groups (Logothetis, 2003, 2008). This can be done using task- or paradigm-based fMRI, in which a specific task is performed by participants in the MRI scanner, or using resting state fMRI (rs-fMRI), in which the brain activity is measured during the absence of any stimulus or task. The latter is often used to identify brain networks, which are brain areas whose BOLD activations are correlated over time. A large number of studies have investigated task-based and rs-fMRI group differences between patients with PTSD and HC and TC subjects across fear learning, context processing, threat detection and emotion processing. In the following section, we will discuss some of the findings within a novel psychobiological model of PTSD.

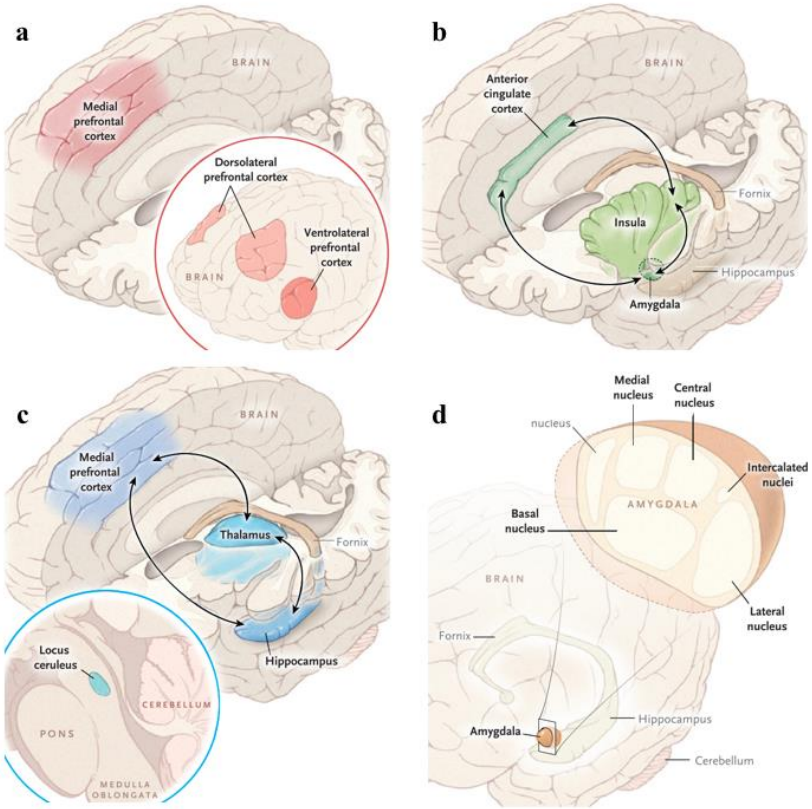

Figure 2. Psychobiological model of PTSD with brain regions and networks involved in the pathophysiology. **a)** Network involved in emotion regulation and executive function. **b)** Network involved in threat detection. **c)** Network involved in contextual processing. **d)** Network involved in fear learning. [adapted from Shalev, Liberzon, & Marmar, 2017, without permission]

1.4 Psychobiological model of posttraumatic stress disorder

The past two decades marked a major leap in the understanding of the neurobiology of PTSD. Shalev et al. (2017) proposed a psychobiological model associating the psychological processes with structural and functional differences in specific brain regions (*Figure 2*). The model is complemented by the psychobiological model by Maren et al. (2013; *Figure 3*) tackling specific neural mechanisms underlying cue and context conditioning in more detail.

Cue processing and context processing have been associated to different brain regions which are activated together, so-called circuits. The cue processing circuit consists of its most prominent candidate, the amygdala (*Figure 2;* Shalev et al., 2017), the thalamus, sensory cortices (such as primary visual or auditory cortex), the posterior insula and association areas (such as parietal and temporal lobe; Maren et al., 2013). The context conditioning circuit includes the hippocampus, the ventromedial prefrontal cortex (vmPFC), the anterior insula and the subgenual anterior cingulate cortex (sgACC; *Figure 3*; Maren et al., 2013). Patients

with PTSD showed alterations in the BOLD activity of the hippocampus during contextual fear acquisition (Lang et al., 2009; Lissek et al., 2005; for a review: Acheson, Gresack, & Risbrough, 2012b; Flor & Nees, 2014b) and impaired extinction recall associated with heightened amygdala activity (Garfinkel et al., 2014; Nees et al., 2015; VanElzakker, Kathryn Dahlgren, Caroline Davis, Dubois, & Shin, 2014). However, only very few neuroimaging studies have investigated cued fear learning in PTSD patients (for a review see Suarez-Jimenez et al., 2020), and even fewer have studied context conditioning and extinction in patients with PTSD (Rougemont-Bücking et al., 2011; Steiger et al., 2015). To study functional brain differences in fear learning and context processing in patients with PTSD in comparison to HC and TC subjects, a combined cue-context conditioning paradigm (Lonsdorf et al., 2017) would be desirable using virtual reality (Glenn et al., 2017).

The last four decades have shown that the hippocampus is more broadly involved in the representation of context as a spatial outline of the environment including objects and their spatial relation to each other (e.g. Nadel, Hoscheidt, & Ryan, 2013; Smith & Mizumori, 2006). This way of context mapping in the hippocampus is the prerequisite for learning and memory (Bird & Burgess, 2008; Burgess, Maguire, & O'Keefe, 2002; King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002) as well as imagery (Brewin, Gregory, Lipton, & Burgess, 2010; Zeidman & Maguire, 2016). Kheirbek et al. (2012) showed that extreme stress leads to a decrease in neurogenesis in the ventral and dorsal hippocampus of rats. Similar results were found in humans, linking neurogenesis in the anterior and posterior hippocampus to the formation of accurate pattern separation (Bakker, Kirwan, Miller, & Stark, 2008; Stark, Yassa, Lacy, & Stark, 2013; Yassa & Stark, 2011). This is in line with previously mentioned structural findings of hippocampus atrophy in patients with PTSD (Bromis et al., 2018). Besides the hippocampus, the mPFC supports maintaining context representations over time (Quinn, Ma, Tinsley, Koch, & Fanselow, 2008), shifting the perspective within scenes (Bird & Burgess, 2008) and incorporating novel into existing networks of memories (Preston & Eichenbaum, 2013). Eden et al. (2015) investigated the microstructural white matter in healthy individuals and different degrees of trait anxiety and found that individuals scoring higher on trait anxiety showed weaker connections, via tracts like the uncinate fasciculus, between the PFC and the amygdalae. Similarly, Nees et al., (2019) found a positive correlation in 93 healthy individuals between the microstructural white matter architecture in the hippocampal cingulum and skin conductance response during extinction of contextual conditioned responses. This effect was moderated by trait anxiety, suggesting an association

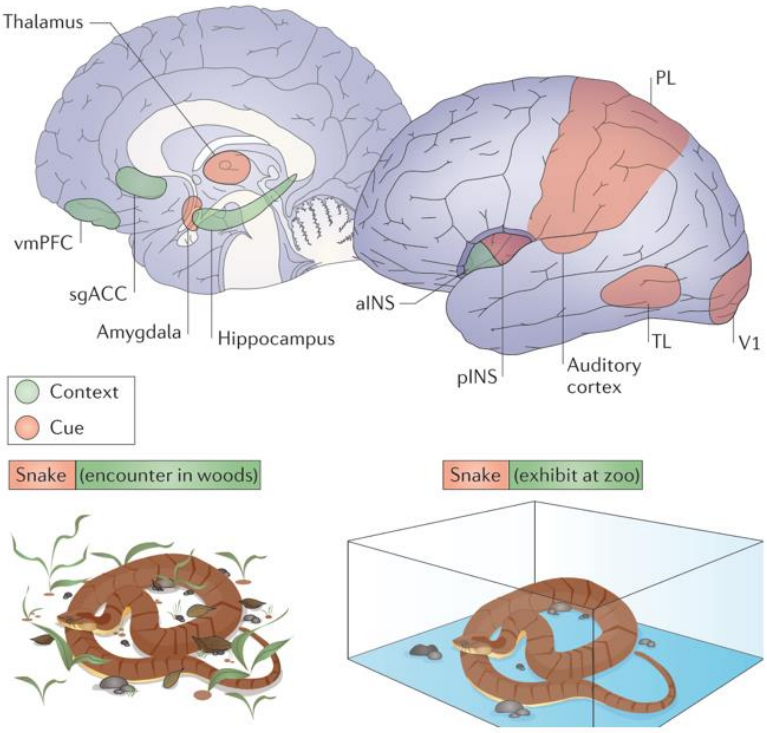

Figure 3. Brain regions and networks involved in cue and context processing. A cue, such as a poisonous snake, encountered in a context, such as in the wild, is appraised differently (potentially dangerous) than when it is exhibited in a zoo (safe or interesting). Two systems in the brain process cue- (in red) and context (in green) information. The cue processing system consists of the thalamus, amygdala, sensory cortices (e.g. V1 and auditory cortex), pINS and association areas (e.g. PL and TL). The context processing system consists of the vmPFC, hippocampus, aINS and sgACC. The cue and context processing systems interact, and learning about one of the two influences the processing of the other [adapted from Maren, Phan, & Liberzon, 2013, without permission].

[**Abbreviations:** aINS – anterior insula; pINS – posterior insula; PL – parietal lobe; sgACC – subgenual anterior cingulate cortex; TL – temporal lobe; V1 – primary visual cortex; vmPFC – ventromedial prefrontal cortex]

between emotion regulation, contextual learning and prefrontal and hippocampal white matter paths. Two other brain regions associated to context processing are the thalamus and the locus coeruleus (Shalev et al., 2017; *Figure 2c*). The thalamus on the one hand is involved in fear conditioning (LeDoux, Farb, & Ruggiero, 1990), consolidation of memories (Pereira de Vasconcelos & Cassel, 2015) and the recall and recognition of memories, likely in interaction with hippocampal activity (Aggleton & Brown, 1999). The hyperactive locus coeruleus on the other hand, as center of synthesis of the stress hormone and neurotransmitter norepinephrine, is argued to be a possible player in explaining difficulties in contextual memory consolidation due to the association between a hyperactive locus coeruleus and less rapid-eye movement sleep in patients with PTSD (Naegeli et al., 2018; Pietrzak et al., 2013; Shalev et al., 2017).

The ability to detect threats and process salience is associated to the activity in several brain areas such as the amygdalae, the insulae and the anterior cingulate cortices (ACC; Uddin, 2015). These regions are part of the salience network, a network of regions which was found to be simultaneously active during rs-fMRI. Patients with PTSD were repeatedly found to show alterations in the salience network with higher BOLD activities of the insula, amygdala and ACC (*Figure 2b*; Liberzon & Abelson, 2016; Shalev et al., 2017). Similar results were found in highly trauma-exposed populations without PTSD, such as firefighters, in comparison to non-exposed populations (Jeong et al., 2019). Differences were reported in the activity of and connectivity within the salience network and between the salience network and other brain networks such as the default mode network (DMN; Sripada et al., 2012). Lanius, Frewen, Tursich, Jetly, & McKinnon (2015) proposed a neuroscientifically-informed treatment intervention for traumatized individuals with clinical markers such as hyper-/ hypoarousal and treatments targeting the functional connectivity (FC) within the salience network via techniques such as mindfulness or neurofeedback. While we begin to understand that fMRI neurofeedback and mindfulness are powerful techniques that can be combined and used to enhance emotion regulation and reduce salience of aversive memories, the neuroscience behind it is still poorly understood (Lubianiker et al., 2019; Tang, Hölzel, & Posner, 2015). A more mechanism-based treatment approach in PTSD relies heavily on our understanding of the underlying structural white and gray matter regions that we aim to target and change. Goldin, McRae, Ramel, & Gross (2008) showed emotion-eliciting films to healthy women and found that the PFC responded within the first five seconds during cognitive reappraisal resulting in a decreased experience of negative emotion associated to decreased functional activation in the amygdalae and insulae. During suppression of negative emotions, the PFC responded after ten to 15 secs also leading to a decreased experience of negative emotion, which was associated with increased brain activity in the amygdalae and insulae. Interestingly, recent studies using Bayesian modelling of fMRI data showed that patients with PTSD display a downregulation of inhibitory connections from the vmPFC to the amygdala, while patients with PTSD and its dissociative subtype showed an upregulation of inhibitory connections from the vmPFC to the amygdala (Nicholson, Friston, et al., 2017). Central executive functions (Lanius et al., 2015), such as the inhibition of automatic responses and the regulation of attention, depend on the activity of several subregions of the prefrontal cortex (PFC) and its connectivity to other brain regions (Miyake et al., 2000). Patients with PTSD in comparison to healthy control subjects show a reduction of structural gray matter in the vmPFC and orbitofrontal cortex (Bromis et al., 2018; Kühn & Gallinat, 2013).

Furthermore, patients with PTSD show alterations in FA values (both lower and higher FA values) in white matter tracts in the frontal gyrus, when compared to HC (Sun et al., 2013; Zhang et al., 2011) and TC subjects (Fani et al., 2014; Li et al., 2016; Schuff et al., 2011). In addition, white matter alterations in interhemispheric connections within the PFC, like the forceps minor, have been found (Huang, Gundapuneedi, & Rao, 2012) between patients with PTSD and TCs.

1.5 Research questions

The aim of this dissertation is to study structural and functional brain differences in patients with PTSD in comparison to healthy control subjects with or without traumatic experiences within a shared model of psychobiology of PTSD. The current research on structural and functional neuroplasticity, fear learning and context processing discloses several gaps including the following:

1. a comprehensive systematic review and meta-analysis on white matter differences in patients with PTSD embedding findings in a common psychobiological model of PTSD

2. a well-powered study on structural white and gray matter differences embedding findings in a common psychobiological model of PTSD

3. an fMRI study using a combined cue-context fear learning paradigm, studying the discriminatory ability of patients with PTSD of safe and dangerous contexts.

Therefore, the first two studies presented here, focused on structural differences, with a particular focus on white matter differences, whereas the third study focused on contextual fear learning in a VR environment.

1.6.1 Hypotheses: Study 1

In the first study, a systematic review and meta-analysis on structural white matter differences in adults and children with PTSD was conducted. The main hypotheses of the study were:

a) *... lower FA values in the corpus callosum were expected in adults with PTSD and trauma experience in childhood in comparison to trauma control subjects.*
b) *... lower FA values in the cingulum, long-reaching white matter tracts like the inferior and superior longitudinal fasciculus (ILF and SLF) as well as in frontal white matter*

tracts such as the uncinate fasciculus (UF) and the forceps minor (FM) were expected in adults with PTSD in comparison to trauma control subjects.

c) *In the meta-analysis, significant clusters were expected in the above mentioned white matter tracts of the ILF, SLF, UF and FM, all associated to top-down control of emotion processing as well as visual spatial learning and attention.*

1.6.2 Hypotheses: Study 2

In the second study, structural white and gray matter differences in patients with PTSD using diffusion tensor imaging and voxel-based morphometry were examined. The following hypotheses were proposed:

Comparing patients with PTSD to healthy and trauma control subjects we expected …

a) *… higher FA values in frontal white matter tracts, such as the FM and UF in both control groups.*
b) *… higher gray matter volume of both hippocampi in both control groups.*
c) *… higher gray matter volume of both anterior insulae in both control groups.*
d) *… a positive correlation between differences in white and gray matter.*
e) *… negative correlations between symptom severity of PTSD, depression and trait anxiety and white and gray matter differences.*

1.6.3 Hypotheses: Study 3

In the third study, we investigated contextual fear learning in patients with PTSD in comparison to trauma and healthy control subjects using an immersive VR like environment during fMRI. For the different conditions, we expected the following:

For the uncued and therefore unpredictable context in comparison to a safe context, we hypothesized that patients with PTSD in comparison to HC and TC subjects …

a) *… report higher arousal, valence and contingency ratings.*
b) *… show an elevated skin conductance response.*
c) *… show smaller BOLD activities in the hippocampi, vmPFC and amygdalae.*

For the cued and therefore predictable context in comparison to the safe context, we expected higher BOLD activity in the amygdalae for patients with PTSD in comparison to HC and TC subjects. We also hypothesized that all three groups for the danger cue (CS+) in comparison to the safety cue (CS-)…

a) … report higher arousal, valence and contingency ratings and

b) … show an elevated skin conductance response.

2 Empirical Studies

2.1 Study 1:

Structural white matter changes in adults and children with posttraumatic stress disorder: A systematic review and meta-analysis[1]

[1] Publication:

Siehl, S., King, J. A., Burgess, N., Flor, H., & Nees, F. (2018). Structural white matter changes in adults and children with posttraumatic stress disorder: A systematic review and meta-analysis. *NeuroImage: Clinical*, *19*, 581–598. doi: 10.1016/j.nicl.2018.05.013

Structural white matter changes in adults and children with posttraumatic stress disorder: a systematic review and meta-analysis

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Abstract

White matter plasticity occurs throughout life due to learning and can be a protective factor against as well as a vulnerability factor for the development of mental disorders. In this systematic review we summarise findings on structural white matter changes in children and adults with posttraumatic stress disorder (PTSD) and relate them to theoretical accounts of the pathophysiology of PTSD with a focus on the disturbed processing of contexts and associated problems in emotional and cognitive processing and PTSD symptomatology. We particularly examine studies reporting fractional anisotropy (FA) measured with diffusion tensor imaging (DTI). We further subdivided the studies in adult-onset PTSD with traumatic experience in adulthood, adult-onset PTSD with traumatic experience in childhood and children with PTSD. We included 30 studies comprising almost 1700 participants with 450 adults and 300 children suffering from PTSD. Our systematic review showed that for children with PTSD and adult-onset PTSD with childhood trauma, a decrease in FA in the corpus collosum, most prominently in the anterior and posterior midbody, the isthmus and splenium were reported. For adult-onset PTSD with traumatic experience in adulthood, changes in FA in the anterior and posterior part of the cingulum, the superior longitudinal fasciculus and frontal regions were found. Using GingerAle, we also performed a coordinate-based meta-analysis of 14 studies of adult-onset PTSD with traumatic experience in adulthood and did not find any significant clusters. Our results suggest that changes in white matter microstructure vary depending on traumatic experience and are associated with changes in brain circuits related to the processing of contexts. Finally, we present methodological considerations for future studies.

Keywords: structural changes, PTSD, diffusion tensor imaging, systematic review, meta-analysis

1. Introduction

1.1 Structural changes in Posttraumatic Stress Disorder

A traumatic experience such as a life threatening event can lead to the development of posttraumatic stress disorder (PTSD). Structural changes in major white matter (WM) tracts have been reported in several studies in adult and juvenile patients suffering from PTSD (Fani et al., 2012a; Kennis et al., 2015). This is in line with recent work demonstrating that WM plasticity occurs in adults (Sampaio-Baptista & Johansen-Berg, 2017; Scholz, Klein, Behrens, & Johansen-Berg, 2009; Zatorre, Fields, & Johansen-Berg, 2012), suggesting a broader role of WM in learning and neural circuit formation. Traumatic experiences are an extremely aversive form of learning in a potentially life threatening situation. Changes inWM microarchitecture of certain tracts might also be a vulnerability factor similar to findings on smaller hippocampal volumes predicting susceptibility to posttraumatic symptoms (Gilbertson et al., 2002). Structural changes in major WM tracts have been reported in several studies in adult and juvenile patients suffering from PTSD. A recent review and meta-analysis (Daniels, Lamke, Gaebler, Walter, & Scheel, 2013) on WM changes using data from diffusion tensor imaging (DTI) focused on individuals with trauma exposure with or without the diagnosis of PTSD. The authors subdivided the reviewed articles in the following three populations: a) pediatric PTSD and trauma exposure in childhood, b) adults with childhood trauma exposure and c) adult-onset PTSD. However, the definition of childhood trauma is not clearly mentioned and can only be assumed to be below the age of 18 years. Daniels et al. (2013) included 25 studies in their review and found a heterogeneous picture with studies reporting an increase or decrease of white matter volume in PTSD. The majority of studies reported a significant reduction in WM volume of major fibre tracts including the corpus callosum, the cingulum bundle as well as the left posterior cingulate. Changes in the anterior and posterior parts of the corpus callosum were most prominently reported in trauma-exposed children with

or without the diagnosis of PTSD in comparison to healthy control subjects. Changes in WM volume in adult-onset PTSD in comparison to healthy control subjects with or without traumatic experience were found bilaterally in the cingulum and the left superior longitudinal fasciculus. The cingulum is one of the major fibre tracts for communication within the limbic system. The superior longitudinal fasciculus connects occipital, parietal and temporal regions to the frontal lobe and is involved in a wide range of functions including processing of visual spatial information. In addition, one longitudinal study observed a significant increase in the left posterior cingulate after remission of PTSD symptoms in adult-onset PTSD. The posterior cingulate is assumed to be a major hub for integrating information from different perspectives and feeding information into the precuneus for building up mental images (Burgess, Becker, King, & O'Keefe, 2001b; Burgess, Maguire, Spiers, & O'Keefe, 2001a; Vann, Aggleton, & Maguire, 2009). Due to the small number of studies included and the differences in comparison groups (trauma controls, healthy controls), it remains unclear whether trauma exposure, predisposition or the development of PTSD is the driving factor of structural changes. Except for two studies that reported on adult patients with PTSD in comparison to healthy controls and either trauma control subjects or patients with generalized anxiety disorder (GAD), none of the reviewed studies used more than one control group (Sun et al., 2013; Zhang et al., 2011). Furthermore, the majority of studies employed only healthy control subjects without any traumatic experience and no trauma control subjects with trauma experience. However, trauma control subjects are essential to determine whether these changes are the result of trauma exposure or are related to PTSD or based on pretraumatic vulnerability (for a summary Brewin, Andrews, & Valentine, 2000).

In this review, we focus on studies reporting DTI data in at least one population diagnosed with PTSD. We followed the subdivision by Daniels et al. (2013) in comparing adults with PTSD after traumatic experience in adulthood (aa-PTSD), adults with PTSD after

traumatic experience in childhood (ac-PTSD) and children with PTSD after traumatic experience in childhood (cc-PTSD). This subdivision was related to the fact that increases in WM volume are part of a natural maturation from birth to young adulthood (Giedd et al., 2015; Giedd & Rapoport, 2010). A traumatic experience during this vulnerable period might have a different effect on WM microstructure than after maturation of the core WM network in young adulthood. Trauma in childhood or adolescence is defined as any traumatic event experienced before the completion of the 18th birthday and was chosen rather as a legal than a biological boundary definition. While, we include all three age groups in our review of the literature, we will only include studies with aa-PTSD in our meta-analysis. The small number of studies available for ac-PTSD and cc-PTSD make a reliable interpretation of the findings difficult at this stage for these two groups. In addition, we will provide guidelines for future studies on white matter changes in trauma-exposed populations suffering from PTSD.

1.2 Theoretical considerations related to WM changes in PTSD

PTSD is characterized by symptom clusters such as re-experiencing the traumatic event, avoidance and numbing, hyperarousal and negative thought and mood changes (Diagnostic and Statistical Manual of Mental Disorders (DSM) 5; American Psychiatric Association, 2013). In the past decades, theoretical frameworks have identified several key brain circuits involved in different cognitive and emotional processes contributing to the development of PTSD with a focus on disturbed contextual processing, an inability to extinguish aversive memories and an increase in threat detection and arousal (Bisby & Burgess, 2017; Brewin, Gregory, Lipton, & Burgess, 2010; Ehlers & Clark, 2000; Flor & Nees, 2014; Jacobs & Nadel, 1985; Liberzon & Abelson, 2016; Maren, Phan, & Liberzon, 2013). Patients with PTSD have trouble to contextualize incoming visual-spatial information, which is associated with a functional down regulation in activity in the medial temporal lobe (MTL), most

prominently in the hippocampus, and the retrosplenial cortex (RSC), which translates this information into a coherent egocentric mental image in the precuneus (Bisby & Burgess, 2017). At the same time, the processing of salient emotional cues involves areas like the amygdala, the insula and the anterior cingulate cortex (ACC), which are up-regulated in PTSD (Bisby & Burgess, 2017; Brewin et al., 2010; Liberzon & Abelson, 2016). Finally, the prefrontal control of subcortical regions involved in fear learning and extinction such as the medial-, dorso- and ventrolateral prefrontal cortex (mPFC, dlPFC, vlPFC) is diminished (Bisby & Burgess, 2017; Brewin et al., 2010; Liberzon & Abelson, 2016). As a result, patients show increased levels of arousal and anxiety as well as hypervigilance and might have difficulties putting these negative emotions in context and thus successfully extinguish acquired fear responses. In line with this, several reviews and meta-analyses on volumetric gray matter (GM) changes reported significant differences in GM in the hippocampus, mPFC, superior frontal gyrus and the ACC (Kühn & Gallinat, 2013; Li et al., 2014) in PTSD patients compared to controls. These studies need to be complemented by research on WM changes because they might, similar to GM changes, directly reflect changes in connections between functionally distinct brain areas. In this review, we will mainly focus on changes WM microstructure after negative experiences early or late in white matter development due to its centrality and importance and the small number of existing reviews in this area.

1.2 Methods for measuring structural changes.

Changes in microstructural WM in individuals with adult-onset PTSD have been measured using manual tracing, volumetric morphometry and DTI. One of the earliest methods was manual tracing. In manual tracing, the corpus callosum is manually subdivided into seven parts (De Bellis et al., 2015). Manual tracing has particularly been used in underage populations suffering from traumatic experience and PTSD (Daniels et al., 2013), tracing mostly the corpus callosum. Here, differences in white matter are visible in a two dimensional

plane only. Voxel-based morphometry (VBM) was introduced as an approach to segment the brain into GM, WM and cerebrospinal fluid (CSF). Groups are contrasted using voxel-wise comparisons, which increase the accuracy of localization and permit a three-dimensional representation of the WM. However, the precise segmentation is error-prone and vulnerable to partial volume effects, which occur if more than one type of tissue occupies the same voxel and in consequence can cause loss of contrast (Smith et al., 2006). In DTI, the directionality of water molecules is calculated as they diffuse in a substance-dependent manner. This is achieved by fitting a voxel-wise ellipsoid tensor to the diffusion-weighted magnetic resonance images (MRI) in three dimensions (Bihan & Johansen-Berg, 2012; Le Bihan, 2014). Three eigenvectors (λ_1, λ_2, λ_3) of this tensor are obtained, which, in combinations with their lengths eigenvalues, allow to describe different measures of diffusivity, such as the mean diffusivity (MD; $(\lambda_1 + \lambda_2 + \lambda_3)/3$) assessing the total diffusion within one voxel, the axial diffusivity (AD, λ_1) assessing axonal injury or the radial diffusivity (RD; $(\lambda_2 + \lambda_3)/2$) assesses myelin injury. In addition, a fourth measurement can be obtained, the so called fractional anisotropy (FA; $\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_1-\lambda_3)^2}}{\sqrt{2(\lambda_1{}^2+\lambda_2{}^2+\lambda_3{}^2)}}$), which gives information about the shape of the diffusion tensor in each voxel. FA values range from 0 (isotropic; non-directional) to 1 (anisotropic diffusion; highly directional) and indicate the net directionality of water diffusion in the given tissue (Pierpaoli & Basser, 1996). Since the majority of diffusivity studies on PTSD report FA values we will focus on this measurement in this review. A decrease in FA or a more isotropic connection, is generally considered to lead to a decrease in structural connectivity and functionality of the tract (Zatorre et al., 2012; Hänggi, Koeneke, Bezzola, & Jäncke, 2010). An increase in FA or a more anisotropic connection, is considered to lead to an increase in structural connectivity and functionality of the tract (Scholz et al., 2009; Zatorre et al., 2012).

2. Aims

This paper seeks to systematically review the literature reporting structural changes using DTI in individuals with PTSD compared to healthy individuals with the experience of a traumatic event (trauma controls) and healthy individuals without the experience of a traumatic event (healthy controls). In the review part we subdivide three groups of studies: a) underage patients with PTSD after childhood/ adolescence trauma (cc-PTSD), b) adult-onset PTSD following childhood trauma (ac-PTSD) and c) adult-onset PTSD following trauma experience in adulthood (aa-PTSD). We suggest that traumatic experiences might interact with naturally occurring maturation processes during childhood and adolescence (Giedd et al., 2015; Giedd & Rapoport, 2010) and might therefore have a different impact on WM tracts than traumatization in adulthood. Early traumatization might therefore interfere more strongly in the development of the corpus callosum (Teicher et al., 2003). In the meta-analysis, we will investigate overlapping clusters of FA change. We will only include studies from adult-onset PTSD following trauma experience in adulthood, which used a whole brain analysis. See also Table 2a)

3. Methods

3.1 Literature search

PubMed, Web of Science, PSYNDEX and PsychINFO databases were searched to identify studies on the role of structural changes measured via DTI in patients with PTSD in comparison to healthy control subjects and/ or trauma-exposed control subjects. The systematic search was conducted with the following keywords: *structural changes* (OR diffusion tensor imaging OR DTI OR white matter integrity OR fractional anisotropy OR FA) AND *PTSD* (OR psychological trauma* OR posttraumatic stress* OR anxiety OR anxious* OR early life trauma OR childhood trauma OR childhood abuse OR childhood adversity OR childhood maltreatment).

3.2 Inclusion and Exclusion Criteria

Participants had to be clearly diagnosed with PTSD using the criteria of the fourth and fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2000; 2013) or the International Classification of Diseases (ICD 10; World Health Organization, 1992) available at the time of publication. We included all studies that examined structural changes using DTI. Studies on adult-onset PTSD were subdivided into studies with individuals suffering from PTSD after childhood trauma or trauma experienced in adulthood. In a third group, we included studies with children that suffered from PTSD. Studies were excluded, if no control group was included or if participants in the experimental group suffered from comorbid disorders such as substance abuse or psychotic symptoms.

3.3 Meta-Analysis using GingerAle

In our meta-analysis we included only DTI studies examining the whole brain, instead of specific predefined regions of interest (ROI). Although ROI-based analyses have several advantages such as theory guidance, a limited number of statistical tests performed on the ROIs and a definition of regions according to functional properties (Poldrack, 2007), the comparability between studies is impeded due to differences in the definition of ROIs and the masking of the same ROI. For studies using whole brain analysis, we included all coordinates in our meta-analysis, independent of the threshold applied to the p values or the cluster sizes used in the study. The small number of studies in the group of adults and children with trauma experience in childhood made it difficult to calculate any meaningful effects specific to this group Thus we only included DTI studies from the group of adult-onset PTSD with traumatic experience in adulthood. We further subdivided the findings in this group in studies reporting a significant decrease or a significant increase of FA in patients with PTSD in comparison to

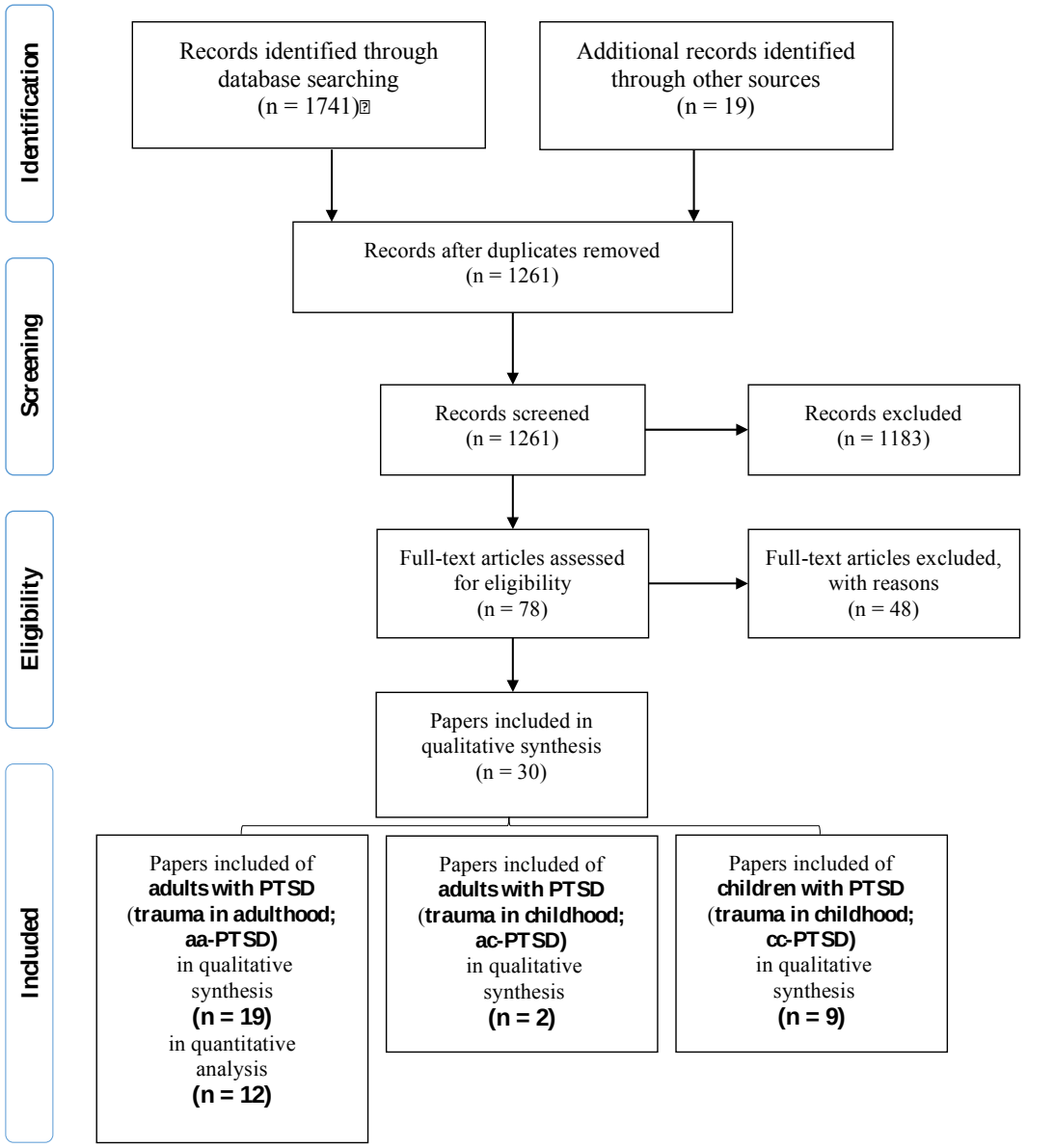

Figure 1. Flowchart of literature review. The total number of studies reviewed in this article is printed in bold letters (taken from the guidelines of the PRISMA group (Moher et al., 2009)).

at least one control group. The activation-likelihood (ALE) meta-analysis was computed separately for these two groups. The meta-analysis was carried out with the GingerAle software package (www.brainmap.org/ale/), a coordinate-based human brain mapping tool to perform meta-analyses of functional or structural datasets (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Eickhoff et al., 2009; Turkeltaub et al., 2012). All coordinates were either reported

	N (PTSD)	N (TC)	N (HC)	N (GAD)	**Total**	FA dec.	FA inc.	FA both	FA no ch.	**Total**
Adult onset PTSD (adulthood trauma)	431	422	101	20	974	10	6	3	0	19
Adult onset PTSD (childhood trauma)	21	0	19	-	40	1	0	0	1	2
Child onset PTSD (childhood trauma)	292	51	330	-	673	5	0	2	2	9
Total	744	473	450	20	**1687**	16	6	5	3	**30**

Table 1. Summary of reviewed articles with the number of individuals included in each subgroup (PTSD – Posttraumatic Stress Disorder; TC – Trauma Controls; HC – Healthy Controls; GAD – Generalized Anxiety Disorder) and number of studies reporting changes in fractional anisotrophy (FA; dec. – decrease; inc. – increase; both – decrease and increase; no ch. – no change).

in the Montreal Neurological Institute (MNI) space or transformed using the Bretts transformation algorithm in GingerAle. The meta-analysis was computed in four steps. For the calculations, GingerAle needs the following information of each study in a text file: the contrast (e.g. PTSD vs. TC), the mask (MNI), the subject size and the finding (e.g. decrease). First, an ALE score is calculated in a 3D image for each group of foci, using the information given above. Second, a Modelled Activation map (MA; Eickhoff et al., 2009) is constructed, finding in our case the maximum across the Gaussian distributions of the foci (Non-Additive; Turkeltaub et al., 2012). Third, All the MA are united to form an ALE image. We set the statistical threshold to a False Discovery Rate (FDR) of pN = .05 and the threshold of the cluster level analysis to p = .05 with 1000 threshold permutations. The FDR with pN thresholding is the more conservative option of two possible thresholdings, making no assumptions about correlations in the data. The cluster-level inference simulates random data sets based on the characteristics of our input data. Finally, GingerAle calculates the volumes which are above the threshold (clusters) and tracks the distribution of their volume. An output table is created indicating which clusters survived after applying the indicated threshold.

4. Results

Initially, 1741 articles were identified in the searched databases after applying the search terms. Of these, 1183 articles did not meet inclusion criteria, because they either did not specifically investigate PTSD, focused on different techniques or non-human samples. Further, we fully reviewed 78 articles, resulting in 30 studies that were ultimately included in the qualitative review. We included 19 papers in the group of aa-PTSD, two papers in the group of ac-PTSD and nine papers on cc-PTSD (see *Figure 1* for details). In total, the articles reviewed comprise a population of 1687 individuals, of whom 744 were diagnosed with PTSD, 473 were trauma-exposed control subjects, 450 were healthy control subjects and 20 were individuals with Generalized Anxiety Disorder (GAD). For the change in FA, 16 studies found a decrease, 6 found an increase and 5 reported both, a decrease and an increase in FA in patients with PTSD in comparison to at least one control group. In addition, two studies found no significant change in FA (see Table 1 for details).

In the systematic review, we further subdivided the identified regions depending on the comparison made between either PTSD patients and healthy or PTSD and trauma control subjects (see also Appendix Table 1, 2 and 3). In the group of aa-PTSD, studies predominantly used a whole brain approach and the majority of studies compared patients to trauma control subjects. In the group comparison between aa-PTSD patients and healthy control subjects, the most commonly mentioned regions were the cingulum, especially with its anterior and subgenual subparts (Abe et al., 2006; Kim et al., 2006) and the superior and orbital frontal gyrus (Sun et al., 2013; Zhang et al., 2011). In the cingulum, a significant increase, using whole brain (Abe et al., 2006), as well as decrease, using ROI analysis (Kim et al., 2006), was found. In the group comparison between aa-PTSD patients and trauma control subjects, a larger range of regions were found (detailed overview Appendix Table 1). Again, the most prominent regions included several subparts of the cingulum (Bierer et al., 2015;

Fani et al., 2012; Hu et al., 2016; Kennis et al., 2015; Kim, Shin, Kim, & Lee, 2016; Sun et al., 2013; Wang et al., 2010; Zhang et al., 2012), frontal gyrus (Li et al., 2016; Sun et al., 2015; Sun et al., 2013) and in addition the longitudinal fasciculus (Fani et al., 2012; Hu et al., 2016; Olson et al., 2017). In the cingulum, a significant decrease in FA was found, using whole brain (Fani et al., 2012; Hu et al., 2016; Kim, Shin, Kim, & Lee, 2016; Schuff et al., 2011; Sun et al., 2013) or ROI (Bierer et al., 2015; Wang et al., 2010) but also a significant increase in FA, using whole brain (Kennis et al., 2015; Zhang et al., 2012) or ROI (Kennis et al., 2015). In the frontal gyrus, all studies used whole brain analysis finding a decrease (Schuff et al., 2011; Sun et al., 2015; Sun et al., 2013) or increase (Li et al., 2016) in FA of several frontal areas. Within the inferior and superior longitudinal fasciculus, a decrease was found using whole brain analysis (Fani et al., 2012; Hu et al., 2016; Olson et al., 2017). In the group of ac-PTSD (detailed overview Appendix Table 2), both studies reviewed used ROI analysis of the corpus callosum, finding a decrease of the genu, mid-body and isthmus (Kitayama et al., 2007; Villarreal et al., 2004). Finally, in the group of cc-PTSD (detailed overview Appendix Table 3), the great majority studies focused on the corpus callosum and compared underage patients (< 18 years of age) with PTSD to healthy control subjects. Using ROI analysis, they found a decrease in FA, most prominently in the anterior and posterior midbody (De Bellis et al., 1999, 2002; De Bellis & Keshavan, 2003; Jackowski et al., 2008; Teicher et al., 2004) as well as the isthmus and splenium (De Bellis et al., 1999, 2002; De Bellis & Keshavan, 2003; Rinne-Albers et al., 2016; Teicher et al., 2004).

Table 2a. Diffusion tensor imaging studies in adult onset posttraumatic stress disorder after traumatic experience in adulthood

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), Race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood Trauma	Increase	Decreas	Key findings [Cohen's d]
[1] **Abe et al. (2006)**	36; **9 PTSD** vs. **16 HC**	21 to 69; PTSD M≈44	60% male; 100% Asian	CAPS	1.5T GE	**Whole brain/ ROI**	**DTI/FA**	**no**	**yes**	**no**	**Increase:** left anterior cingulum [d=1.63]
[2] Aschbacher et al. (2017)	57; **31 PTSD** vs. **26 TC**	22 to 55; M≈33	100% male; 54% Hispanic, 28% White, 23% African-American	CAPS; SCL-90-R; PDEQ;	3T Siemens	**ROI**	**DTI/FA**	**no**	**yes**	**no**	**Increase:** Superior fronto-occipital fasciculus [d=0.56]
[3] Bierer et al. (2015)	20; **12 PTSD** vs. **8 TC**	Range not specified; M≈43	100% male; 35% Latino, 30% White, 30% African-American	CAPS; SCID-I; CTQ; MS; BDI; STAI	3T Siemens	**ROI**	**DTI/FA and MD; TBSS**	**yes**	**yes**	**yes**	**Increase:** right cingulum (MD) **Decrease:** right cingulum (FA; p = .071) ROI: (bilateral anterior cingulum)
[4] **Fani et al. (2012)**	50; **25 PTSD** vs. **26 TC**	20 to 62; M≈36	100% female; 100% African-American	TEI; CTQ; PSS; BDI	3T Siemens	**Whole brain**	**DTI/FA; TBSS**	**yes**	**yes**	**yes**	**Increase:** right lateral occipital cortex [d=0.61] **Decrease:** left post. Cingulum [d=0.63] right post. Cingulum [d=0.85] left superior longitudinal fasciculus
[5] Fani et al. (2014)	82; **28 TC (CC)** vs. **34 TC (CT)** vs. **20 TC (TT)**	Range not specified; M≈39	100% female; 100%African American	TEI; PSS; CTQ	3T Siemens	**Whole brain**	**DTI/FA; TBSS**	**yes**	**no**	**yes**	**Decrease:** left posterior cingulum in carriers of two risk allele of type rs1360780

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), Race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood Trauma	Increase	Decrease	Key findings [Cohen's d]
[6] **Huang et al. (2012)**	34; **17 PTSD** vs. **17 TC**	18 to 60; M≈40	50% female; race not specified	CAPS; SCID-I; M.I.N.I; ASDI; BDI; PDI	3T GE	**Whole brain**	**DTI/FA; TBSS**	**no**	**no**	**yes**	**Decrease:** anterior thalamic radiation with 1. corticospinal tract, cingulum & inferior fronto-occipital fasciculus [d=1.46] 2. corticospinal tract, cingulum & superior fronto-occipital fasciculus [d=1.28] 3. forceps minor, inferior fronto-occipital fasciculus, superior longitudinal fasciculus [d=1.99]
[7] **Kennis et al. (2015)**	61; **39 PTSD** vs. **22 TC**	22 to 57; M≈36	100% male; race not specified	CAPS; SCID-I	3T Philips	**Whole brain/ ROI**	**DTI/FA**	**no**	**yes**	**no**	**Increase:** dorsal cingulum [d=0.53] ROI: dorsal and hippocampal cingulum bundle [d=0.57], stria terminalis [d=0.69] and fornix [d=0.53]
[8] **Kim et al. (2005)**	40; **20 PTSD** vs. **20 TC**	19 to 49; M≈28	40% males; race not specified	CAPS; SCID-I; PDQ-4; HDRS	3T GE	**Whole brain**	**DTI/FA**	**no**	**no**	**yes**	**Decrease:** Left anterior cingulate

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), Race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood Trauma	Increase	Decrease	Key findings [Cohen's d]
[9] Kim et al. (2006)	42; **21 PTSD** vs. **21 HC**	19 to 49; M≈28	38% male; race not specified	CAPS; SCID-I; PDQ-4; HDRS	3T GE	**ROI**	**DTI/FA**	**no**	**no**	**yes**	**Decrease:** left cingulum bundle - rostral anterior subregion [d=1.57] - subgenual anterior subregion [d=1.34] - dorsal anterior subregion [d=1.11] ROI: upper cingulate, rostral cingulate, dorsal cingulate, supragenual cingulum
[10] Koch et al. (2017)	77; **38 PTSD** vs. **39 TC**	Range not specified; M≈40	53% male; race not specified	CAPS; SCID; HADS-A; HADS-D; IES-R; AUDIT; ETI-SF; PLES	3T Philips	**Whole Brain**	**DTI/ FA, MD**	**yes**	**yes (only MD)**	**no**	**Increase:** right uncinated fasciculus (MD); - positively correlated with symptoms of anxiety in PTSD positively associated with amygdala activity and vmPFC activity in response to happy and neutral faces whereas FA remained unchanged

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), Race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood Trauma	Increase	Decrease	Key findings [Cohen's d]
[11] **Li et al. (2016)**	179; **88 PTSD** vs. **91 TC**	Range not specified; M≈43	30% male; race not specified	CAPS; PCL	3T GE	**Whole brain**	**DTI/FA (AD and RD)**	**no**	**yes**	**no**	**Increase:** left superior frontal gyrus [d=0.81] left middle frontal gyrus [d=0.70] left forceps major [d=0.71]
[12] **Olsen et al. (2017)**	37; **20 PTSD** vs. **17 TC**	21 to 56; M≈36	62% female; race not specified	CAPS; TLEQ	3T Siemens	**Whole brain**	**DTI/FA; TBSS**	**yes**	**no**	**yes**	**Decrease:** inferior longitudinal fasciculus [left: d=0.80; right d=0.17]
[13] Saar-Ashkenazy et al. (2016)	30; **16 PTSD** vs. **14 HC**	Range not specified; M≈35	67% male; race not specified	CAPS; STAI; PDS	1.5T Philips	**Whole brain**	**DTI/FA**	**no**	**no**	**yes**	**Decrease (only significant correlations):** total FA in corpus callosum (CC) correlated negatively with arousal, avoidance, re-experiencing and total symptom severity. Central CC correlated highest with symptoms of arousal, avoidance and re-experiencing
[14] **Schuff et al. (2011)**	38; **19 PTSD** vs. **19 TC (5 not exposed)**	Range not mentioned; M≈43	Not specified	CAPS; SCID-I; LSC-R	4T Siemens	**Whole brain**	**DTI/FA; TBSS, .001 uncorrected**	**Some not excluded**	**no**	**yes**	**Decrease:** anterior cingulate cortex prefrontal cortex precentral gyrus posterior internal capsule posterior angular gyrus

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), Race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood Trauma	Increase	Decrease	Key findings [Cohen's d]
[15] **Sun et al. (2013)**	60; **21 PTSD** vs. **22 HC** vs. **17 TC**	18 to 60; M≈38	45% male; race not specified	CAPS; M.I.N.I.; ASDI	3T GE	**Whole brain**	**DTI/FA**	**no**	**no**	**yes**	**Decrease PTSD< TC (FA):** right middle temporal gyrus WM [d=1.78] right anterior cingulate cortex WM [d=1.76] right midbrain WM [d=1.26] left gyrus rectus/ medial OFC WM [d=1.55] **Decrease PTSD< TC (MD):** right superior frontal gyrus WM left subcallosal gyrus WM **Decrease PTSD< HC (FA):** left superior frontal gyrus, orbital part WM [d=1.55] left superior temporal gyrus WM [d=1.51] right inferior occipital gyrus WM [d=1.51]
[16] **Sun et al. (2015)**	29; **15 PTSD** vs. **14 TC**	18 to 60; M≈39	52% male; race not specified	CAPS; M.I.N.I.; ASDI	3T GE	**Whole brain**	**DTI/FA;**	**No**	**no**	**yes**	**Decrease (FA):** commissural tract connecting bilateral superior/ middle frontal gyrus [d=0.84]

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), Race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood Trauma	Increase	Decrease	Key findings [Cohen's d]
[17] Wang et al. (2010)	20; **10 PTSD** vs. **10 TC**	17 to >40; not specified	Not specified	CAPS; PSQI; HDRS; SCL-90-R	3T Siemens	**Whole brain/ ROI**	**DTI/FA; manual tracing, p = .05 uncorrected**	**Some not excluded**	**no**	**yes**	**Decrease:** right posterior cingulum [d=1.14] hippocampus (body) [d=1.21] ROI: hippocampus and cingulum
[18] Zhang et al. (2011)	65; **17 PTSD** vs. **28 HC** vs. **20 GAD**	23 to 43; M≈32	66% male; race not specified	CAPS; PSWQ	1.5T GE	**Whole brain/ ROI**	**DTI/FA; whole brain: P = .001, uncorrected, ROIs: P = .05**	**No**	**yes**	**yes**	**Decrease (PTSD<GAD):** right anterior cingulate [d=2.91] **Increase (PTSD>HC):** left superior frontal gyrus [d=1.18]
[19] Zhang et al. (2012)	27; **13 PTSD** vs. **14 TC**	Not specified; M≈39	Gender not specified; race not specified	PCL-C; STAI; BDI	1.5T GE	**Whole brain**	**DTI/FA; p = .005, uncorrected**	**No**	**yes**	**no**	**Increase:** left posterior cingulate gyrus right posterior cingulate gyrus right precuneus right parietal sub-gyrus left middle temporal gyrus

Table 2b. Diffusion tensor imaging studies concerning adult onset posttraumatic stress disorder after traumatic experience in childhood

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), Race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood Trauma	Increase	Decrease	Key findings [Cohen's d]
[20] Kitayama et al. (2007)	18; **9 PTSD** vs. **9 HC** **Childhood Abuse**	Not mentioned; M≈37	100% female; not mentioned	CAPS; ETI; SCID	1.5T GE	**ROI**	**Manual Tracing**	**yes**	**no**	**no**	**No difference found in whole corpus callosum** ROI: corpus callosum
[21] Villarreal et al. (2004)	22; **12 PTSD** vs. **10 HC** **In most cases physical and sexual childhood abuse**	Not mentioned; M≈43	82% female; not mentioned	CAPS; SCID; BDI; BAI	1.5T GE	**ROI**	**Manual Tracing**	**Yes (50% of the sample)**	**no**	**yes**	**Decrease:** absolute and normalized corpus callosum; In subregions: 2 (genu) [d=1.03]; 4 (anterior mid-body; trend) [d=0.77]; 5 (mid-body) [d=1.32]; 6 (isthmus) [d=1.19] ROI: corpus callosum

Table 2c. Diffusion tensor imaging studies concerning childhood onset posttraumatic stress disorder after traumatic experience in childhood

[22] De Bellis et al. (1999)	105; **44 PTSD** vs. **61 HC**	7 to 17; M≈12	58% male; 75% white, 13% African American, 11% biracial	K-SADS-PL; CDI; CBCL; CDC; GAF; SES; WISC-R; PANESS	1.5T GE	**ROI (Corpus callosum)**	**Manual Tracing**	**yes**	**no**	**yes**	**Decrease:** corpus callosum (total size) [d=0.41] corpus callosum (genu) [d=0.31] corpus callosum (ant. midbody) [d=0.58] corpus callosum (post. midbody) [d=0.50] corpus callosum (isthmus) [d=0.39] corpus callosum (splenium) [d=0.48]

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), Race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood Trauma	Increase	Decrease	Key findings [Cohen's d]
[23] De Bellis & Keshavan (2002)	94; **28 PTSD** vs. **66 HC**	5 to 17; M≈12	58% male; 78% white, 7% African American, 15% biracial	K-SADS-PL; CDI; CBCL; CDC; GAF; SES; WISC-R; PANESS	1.5T GE	**ROI (Corpus callosum)**	**Manual Tracing**	**yes**	**no**	**yes**	**Decrease:** corpus callosum (ant. midbody) [d=0.56] corpus callosum (post. midbody) [d=0.55] corpus callosum (isthmus) [d=0.61] corpus callosum (splenium) [d=0.74]
[24] De Bellis & Keshavan (2003)	[183; **61 PTSD** vs. **122 HC]** **(pooled from studies 1999 and 2002 (see above))**	5 to 17; M≈12	51% male; Race not specified	K-SADS-PL; CDI; CBCL; CDC; GAF; SES; WISC-R; PANESS	1.5T GE	**ROI (Corpus callosum)**	**Manual Tracing**	**yes**	**no**	**yes**	**Decrease: (females > males)** corpus callosum (total size) corpus callosum (ant. midbody) corpus callosum (post. midbody) corpus callosum (isthmus) corpus callosum (splenium) Decrease in white matter volume higher in females with PTSD than in males with PTSD
[25] De Bellis & Hooper et al. (2015)	79; **23 PTSD** vs. **27 TC vs. 29 HC**	6.2 to 16.2; M≈10	54% female; 45% African American, 42% Caucasian, 13% Multi-racial	K-SADS-PL; WISC-R; CBCL; CGAS	3T Siemens	**ROI (Corpus callosum)**	**DTI/FA**	**yes**	**no**	**no**	**Decrease in AD: (PTSD<TC, HC)** corpus callosum (splenium)

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), Race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood Trauma	Increase	Decrease	Key findings [Cohen's d]
[26] Jackowski et al. (2008)	32; **17 PTSD** vs. **15 HC**	6.3 to 14.4; M≈11	56% female; 41% African American, 25% Caucasian, 18% Hispanic, 16% Biracial	K-SADS-PL; SCARD	1.5T GE	**ROI (Corpus callosum)**	**DTI/FA**	**yes**	**no**	**yes**	**Decrease:** corpus callosum (ant. midbody) [d=3.00] corpus callosum (post. midbody) [d=3.50]
[27] Lei et al. (2015)	51; **25 PTSD** vs. **24 TC**	Range not specified; M≈13	57% female; race not specified	CAPS; PCL	3T GE	**Whole brain**	**DTI/FA, MD, RD, AD**	**yes**	**yes**	**yes**	**Increase:** left angular gyrus (MD) left angular gyrus (AD) **Decrease:** right thalamus (MD)
[28] Richert et al. (2006)	47; **23 PTSD (52% full diagnosis)** vs. **24 HC**	7 to 14; PTSD M≈13	56% male in PTSD group; race not specified	CAPS-CA; K-SADS-PL	1.5T GE	**ROI**	**Volu-metric analysis**	**yes**	**no**	**no**	**No difference in white matter found** ROI: prefrontal cortex

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), Race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood Trauma	Increase	Decreas	Key findings [Cohen's d]
[29] Rinne-Albers et al. (2016)	40; **20 PTSD** vs. **20 HC**	Range not specified; M≈16	87.5% female; race not specified	ADIS-C/P; PDS; TSCC	3T Philips	**Whole brain/ ROI**	**DTI (threshold p<0.075) TBSS/ FA, AD, RD, MD**	**yes**	**yes**	**yes**	**Decrease:** left splenium of the corpus callosum (FA) **Increase:** left splenium of the corpus callosum (RD, MD) ROI: bilateral uncinated fasciculus, genu, splenium and body of the corpus callosum (RD, MD)
[30] Teicher et al. (2004)	166; **51 PTSD/TC (50% with diagnosis of PTSD)** vs. **115 HC**	Range not specified; M≈12	58% male; race not specified	DSM-III-R	1.5T GE	**ROI (Corpus callosum)**	**Volu-metric analysis**	**yes**	**no**	**yes**	**Decrease: [*detailed effect sizes in paper]** corpus callosum (total size) corpus callosum (rostral body) corpus callosum (ant. midbody) corpus callosum (cost. midbody) corpus callosum (isthmus) corpus callosum (splenium)

AD – Axial Diffusivity; ASDI – Acute Stress Disorder Inventory; ADIS-C/P – Anxiety Disorders Interview Schedule Child and Parent Versions; AUDIT – Alcohol Use Disorders Identification Test; BAI – Beck Anxiety Inventory; BDI – Becks' Depression Inventory; CAPS – Clinician-Administered PTSD Scale; CAPS-CA – Clinician-Administered PTSD Scale for Children and Adolescents; CBCL – Child Behaviour Checklist; CDC – Child Dissociative Checklist; CDI – Childhood Depression Inventory; CGAS – Children Global Assessment Score; CTQ – Childhood Trauma Questionnaire; DMN – Default Mode Network; DSM-III-R – Diagnostic and Statistical Manual of Mental Disorders (revised 3rd edition); DTI – Diffusion Tensor Imaging; ETI-SF – Early Trauma Inventory; GAD – Generalized Anxiety Disorder; GAF – Children's Global Assessment Scale; HADS-A – Hospital Anxiety and Depression Scale – Anxiety; HADS-D – Hospital Anxiety and Depression Scale – Depression; HC – Healthy Control; HDRS – Hamilton Depression Rating Scale; IES-R – Revised Impact of Events Scale; K-SADS-PL – Schedule for Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime; LSC-R – Life Stressor Checklist-Revised; M – Mean; M.I.N.I. – Mini-International Neuropsychiatric Interview; MS – Mississippi Scale; OFC – Orbitofrontal Cortex; PANESS – Revised Physical and Neurological Examination for Subtle Signs; PCL – PTSD Checklist; PCL-C – PTSD Checklist Civilian Version; PDEQ –

Peritraumatic dissociative experiences questionnaire; PDI – Peri-traumatic Distress Inventory; PDS – Puberty Development Scale; PDQ-4 – Personality Disorder Questionnaire-4; PLES – Police Life Events Scale; PSQI – Pittsburgh Sleep Quality Index; PSS – PTSD Symptom Scale; PSWQ – Penn State Worry Questionnaire; PTSD – Posttraumatic Stress Disorder; RD – Radial Diffusivity; ROI – Region of Interest; SCID-I – Structured Clinical Interview for DSM IV; SCARD – Screen for Child Anxiety and Related Disorders; SCID – Structured Clinical Interview for DSM-IV; SCL-90-R – Revised Symptom Checklist 90; SD – Standard Deviation; SES – Hollingshead four factor index of socioeconomic status; STAI – State-Trait Anxiety Inventory; TC – Trauma Control; TEI – Traumatic Events Inventory; TLEQ – Traumatic Life Events Questionnaire; TSCC – Trauma Symptom Checklist for Children; WISC-R – Wechsler Intelligence Scale for Children

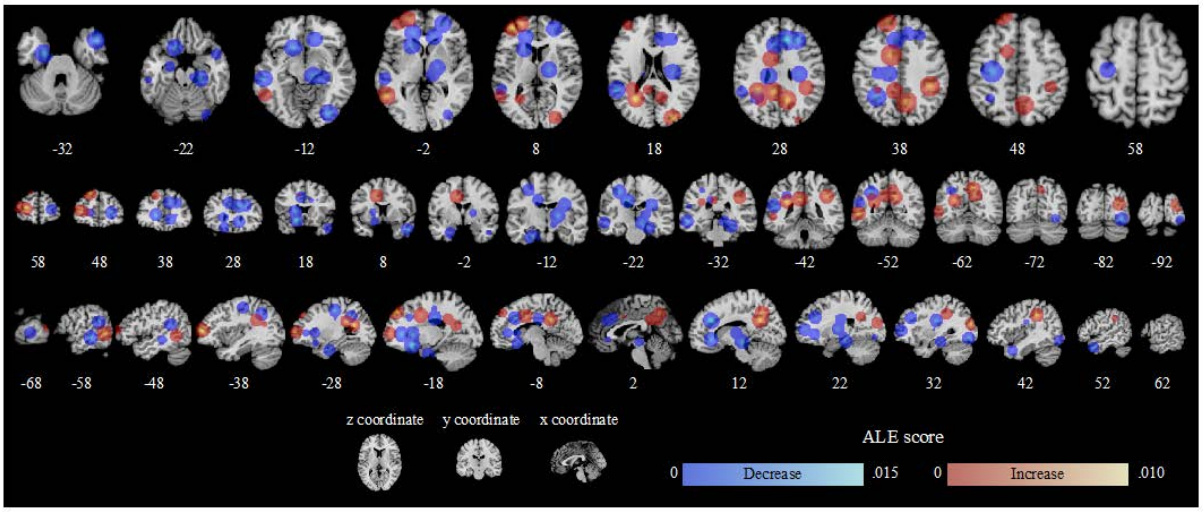

Figure 2. Overview of thirteen studies reporting coordinates in MNI space on changes in FA in adult-onset PTSD. The ALE scores are displayed in colour (blue spectrum for increase of FA, red spectrum for decrease of FA). Due to the choice of showing the Gaussian distribution of each foci, weighted by the number of subjects included in each study, foci might appear in several slices

5. Meta-Analysis

In the meta-analysis, we included only studies fulfilling the following five criteria: a) one group of adult patients (> 18 years of age) with PTSD and at least one control group; b) clearly stating if childhood trauma and comorbid disorders were present; c) using diffusion tensor imaging measuring fractional anisotropy; d) using whole brain analysis; e) reporting foci of significant cluster differences. In total, 14 DTI studies of patients with adult-onset PTSD were included in the meta-analysis. Seven studies reported a decrease of FA (Fani et al., 2012; Hu et al., 2016; Kim et al., 2005; Olson et al., 2017; Schuff et al., 2011; Sun et al., 2013; Sun et al., 2015; Zhang et al., 2011), including 9 contrasts with 22 foci. In this group of studies, 175 patients with PTSD, 130 trauma and 22 healthy control subjects and 20 subjects with GAD were included. In contrast, six studies reported an increase in FA (Abe et al., 2006; Fani et al., 2012; Kennis et al., 2015; Li et al., 2016; Zhang et al., 2011, 2012), including six

contrasts with twelve foci. In this second group of studies, 191 patients with PTSD, 153 trauma and 44 healthy control subjects are comprised in the analysis (see Figure 2).

6. Discussion

The aim of this systematic review was to provide a comprehensive evaluation of studies reporting structural WM changes in patients with PTSD. We identified 30 articles, including almost 1700 individuals comprising 450 adult patients and 300 children suffering from PTSD. Firstly, for aa-PTSD in comparison to trauma and healthy control subjects, the most common changes in white matter were reported in the cingulum (decrease and increase) and frontal regions (decrease and increase). Furthermore, changes in the longitudinal fasciculi (decrease) were shown in studies comparing adult patients with trauma control subjects. A meta-analysis using GingerAle, including 14 studies of adults with adult onset PTSD in comparison to trauma and healthy control subjects did not reveal any significant clusters. Secondly, for ac-PTSD in comparison to healthy control subjects, only two studies could be included both focusing on changes in the corpus callosum (decrease and no change). Thirdly, for children diagnosed with PTSD compared to healthy control subjects, all available studies found changes in the corpus callosum (decrease), most prominently in the anterior and posterior midbody, the isthmus and the splenium. Only one study in this subgroup also compared children suffering from chronic PTSD to trauma control subjects and found no change in FA in the corpus callosum. Our review revealed a high heterogeneity regarding significant changes of WM, measured via change in the FA, in patients with PTSD in comparison to trauma and healthy controls. The most prominent changes in fiber tracts included the corpus callosum (CC), the cingulum, the superior longitudinal fasciculus (SLF). Theses changes can be related to contextualization, the processing of emotionally salient cues and extinction of aversive memories. Changes in the white matter microarchitecture due to traumatic experiences could play an important role in the development of child- and adult onset PTSD.

Firstly, the corpus callosum, the largest connecting fiber bundle which facilitates inter-hemispheric communication, was reported to show a decreased FA mainly in patients with childhood trauma in comparison to healthy control subjects (see also Appendix Table 3; De Bellis et al., 1999, 2002; De Bellis & Keshavan, 2003; Jackowski et al., 2008; Kitayama et al., 2007; Lei et al., 2015; Richert, Carrion, Karchemskiy, & Reiss, 2006; Rinne-Albers et al., 2016; Teicher et al., 2004; Villarreal et al., 2004). Only one study with adult-onset PTSD with trauma experience in adulthood found a significant negative CC and symptoms like arousal, avoidance and re-experiencing (Saar-Ashkenazy et al., 2016). The CC has been reported to be important for encoding and retrieval of memories (Gazzaniga, 2000; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). A malfunctioning or reduction in volume was suggested to result in a lack of lateralization and specification in associative memory (Saar-Ashkenazy et al., 2014, 2016). These results point towards changes in WM maturation due to traumatic experiences rather than vulnerability. Interestingly, Saar-Ashkenazy et al. (2014, 2016) found a high negative correlation of 0.65 between WM in the mid-posterior, posterior and the total FA of the CC and associative memory encoding and retrieval of words in adult-onset PTSD. In addition, they found a strong negative correlation of 0.65 between WM in the anterior, central and total FA of the CC for the mean association reaction time for pictures. These findings indicate a deficit in associative encoding and memory, which is in line with the idea of a disturbance of brain circuits involved in contextual processing in PTSD (Bisby & Burgess, 2017; Brewin et al., 2010; Flor & Nees, 2014; Liberzon & Abelson, 2016). In their review, Daniels et al. (2013) observed a reduced volume of the CC in the majority of studies investigating trauma-exposed children. They found a similar amount of studies as in our review reporting volume loss in the CC in adult-onset PTSD. However, this is not surprising considering that the CC is developing most dramatically during childhood and adolescence, driven by additive genetic effects and environmental exposure (Giedd & Rapoport, 2010; Luders, Thompson, & Toga, 2010). Luders et al. (2010) found differences in males and

females in colossal maturation patterns and segments. The authors suggested that a decrease in the thickness of the CC may reflect axonal redirection or pruning. Alternating periods of growth and shrinkage of the CC during childhood and adolescence were found to be normal in healthy development of the human brain. Interestingly, the only study in the subgroup of children with PTSD including a healthy as well as a trauma control group, did not find any differences in FA in the corpus callosum (De Bellis et al., 2015). However, in their well-designed study De Bellis et al. (2015) found a decrease in axial diffusivity in childhood patients in comparison to trauma controls in the section of splenium projecting to occipital regions. Although the authors discuss reasons for an innate vulnerability, they also mention the limited inference one can make from a cross-sectional design. Future studies should include healthy and trauma control groups in their design and take into account sex- and age-specific differences in WM development of the corpus callosum. Overall, a decrease in FA in the CC is more prominent in children with PTSD than adults, suggesting a more drastic changes in white matter architecture given the central role of the CC in interhemispheric communication. However, in adults, a negative association between the decrease in FA in subparts of the CC and the performance in an association task with words and pictures was found, suggesting a role of the CC in associative encoding and processing.

Secondly, the cingulum was reported to show an alteration in FA in individuals with aa-PTSD (see also Appendix Table 1). Our findings rather support the hypotheses of the cingulum as a vulnerable WM tract, with several studies showing differences between patients with PTSD and trauma controls. Although the cingulum is the most frequently reported WM bundle to be affected by chronic stress besides the CC, the directionality of change in FA stays unclear with some studies reporting an increase (Kim et al., 2007; Schuff et al., 2011) and others a decrease (Abe et al., 2006; Zhang et al., 2013) in FA. In general, the cingulum has been associated with a variety of functions including the integration of negative affect and

pain (Shackman et al., 2011) and verbal and spatial short-term memory (Kalisch, Wiech, Critchley, & Dolan, 2006; Vytal, Cornwell, Arkin, & Grillon, 2012; Vytal, Cornwell, Letkiewicz, Arkin, & Grillon, 2013). Robinson et al. (2014) demonstrated over a series of experiments that individuals with anxiety disorder but without PTSD showed an increased circuit coupling during processing of fearful faces in the amygdala and the anterior cingulate cortex (ACC). An increased trait anxiety was thereby associated with an increased connectivity of the amygdala and the ACC. Fani et al. (2014) found that traumatized females without the diagnosis of PTSD carrying two risk alleles of the FKBP5 gene showed a decreased FA in the posterior cingulum, pointing towards WM changes as a vulnerability factor. The posterior cingulate cortex (PCC) is assumed to be a major region involved in the integration of information from an ego- and allocentric perspective into a cohesive whole (Aggleton & Vann, 2004; Burgess, Becker, King, & O'Keefe, 2001b; Burgess, Maguire, et al., 2001a; Hassabis, Kumaran, Vann, & Maguire, 2007; Vann et al., 2009). It is thought to play a part in combining spatial components to form mental images and episodic memories and was further found to be important for imagination and planning for the future (Vann et al., 2009). Recent findings found alterations in WM integrity in the PCC and dorsolateral PFC (dlPFC) in adults with PTSD and trauma experience in the adulthood (e.g. Kennis et al., 2015). Interestingly, individuals with PTSD showed similar WM alterations in the PCC and dlPFC during fear extinction (Li et al., 2016). In summary, mixed findings within the cingulum might be explained by the different functions of the ACC and PCC in human cognition and emotion. Whereas the ACC is important for the processing of negative emotions and spatial short-term memory (Brewin et al., 2010; Liberzon & Abelson, 2016), the PCC integrates and transforms information of different perspectives to create mental images and episodic memories. Furthermore, the PCC might play a role in contextualization as part of a salience, visual and default mode network, which was found to be distorted in individuals with PTSD (Liberzon & Abelson, 2016; Sripada et al., 2012) and has recently been associated

with symptoms like intrusions (Brewin & Burgess, 2014; Brewin et al., 2010) or overgeneralization (Kheirbek, Klemenhagen, Sahay, & Hen, 2012; Maren et al., 2013). More speculatively, changes in white matter in the ACC and connected areas such as the amygdala or insula could be associated with an up-regulation in sensory emotional processing of the experience of the traumatic event (Brewin et al., 2010). In contrast, changes in WM in the PCC and connected areas such as the hippocampus or precuneus could be associated with a down-regulation of contextualization of traumatic events. This imbalance in information processing with, for example, an up-regulation of object recognition and a down-regulation of spatial and temporal scene recognition could be associated with the development of intrusions (Brewin et al., 2010; Flor & Wessa, 2010). A recent study by Hermann, Stark, Blecker, Milad, & Merz (2017) showed a direct relationship between the hippocampal part of the cingulum, connecting the cingulate cortex and the hippocampus, and context dependent extinction recall. They found that healthy participants with a higher FA value in the hippocampal part of the cingulum showed higher renewal of conditioned skin conductance responses (SCRs). This is in line with research on adult-onset patients with PTSD after traumatic experience in adulthood, showing that they have an impaired extinction recall and fear renewal, making it difficult for them to distinguish safe and dangerous environments (Garfinkel et al., 2014; Milad et al., 2009; Steiger, Nees, Wicking, Lang, & Flor, 2015; Wicking et al., 2016). Further research is needed here to distinguish the role of different segments of the cingulum in contextualization and the role of distorted salience and contextual networks in adult-onset PTSD with trauma (see Figure 2).

Thirdly, the superior longitudinal fasciculus (SLF) was found to be altered in individuals with aa-PTSD (see also Appendix Table 1).Here, two studies found a decrease in WM integrity in the left SLF (Fani et al., 2012; Schuff et al., 2011), while one study reported

an increase in WM in the left middle temporal branch (arcuate fascicle (AF)) and the right parietal branch of the SLF (SLF II; Zhang et al., 2012). Interestingly, the SLF was only found to differ between patients with PTSD and trauma control subjects, suggesting changes due to traumatic experience. The SLF is one of the major fiber bundles connecting the parietal, occipital and temporal lobe with the frontal lobe. The SLF is subdivided into three major tracts and their major functions include higher aspects of motor behaviour (SLF I), the perception of visual (SLF II) and auditory space (AF) as well orofacial and hand actions (for a review see Makris et al., 2005). De Schotten et al. (2011) emphasized the key role of the SLF in a visuo-spatial network with an increased processing speed of visuospatial information along the right hemispheric SLF II. Alterations in the left SLF on the other hand are associated with decreased visual spatial processing in a variety of neurological and mental disorders including Williams Syndrome (Hoeft et al., 2007), spatial neglect (Shinoura et al., 2009), early-onset schizophrenia (Karlsgodt et al., 2008) and social anxiety disorder (Baur et al., 2011). Although a wide range of literature found that the SLF is a key player in spatial attentional processing across different modalities, it stays unclear how its malfunctioning is connected to alterations in other major WM fiber tracts such as the CC or the ACC and PCC. In patients with PTSD, the SLF might play an important role in a wider network of visual-spatial attention in information processing and autobiographical memory. Changes in the WM microstructure of the SLF might have an overarching effect on several brain circuits involved in PTSD such as the early detection and processing as well the emotional response to the cue, which further influences how well the cue is embedded in the environment (see Figure 2).

Fourthly, we want to briefly emphasize a growing evidence of changes in FA in white matter tracts in frontal regions including the superior- and middle frontal gyrus (SFG; MFG) in aa-PTSD in comparison to trauma control subjects (see also Appendix Table 1 and 3; Li et al., 2016; Schuff et al., 2011; Sun et al., 2013; Sun et al., 2015) and healthy control subjects (Zhang et al., 2011). In our sample, two studies found a decrease in FA in the SFG and MFG

(Sun et al., 2013; Sun et al., 2015) and two an increase specifically in the left SFG (Li et al., 2016; Zhang et al., 2011). Interestingly, the SFG was found to support cognitive functions like spatial cognition (Boisgueheneuc et al., 2006) or as being part of a lateralized parietal-frontal resting state network (van den Heuvel & Hulshoff Pol, 2010). Parts of the medial SFG, better known as mPFC are involved in top-down control of subcortical regions and executive functions and known to be impaired in patients with PTSD (Brewin et al., 2010; Flor & Wessa, 2010; Lang et al., 2009; Liberzon & Abelson, 2016). The mPFC was suggested to support association learning between contexts, events, locations and their emotional responses (Euston, Gruber, & Mcnaughton, 2013). A decreased functioning of the SFG as part of higher level working memory might play a role in how patients with PTSD can 'keep up' with environmental changes, which in turn might influence more long-term learning processes like extinction recall or fear renewal mentioned above. Symptoms like biased attention or heightened impulsivity might be the result. This is in line with current neurobiological models of the development and maintenance of PTSD, similarly associating the MFG to executive networks. Liberzon & Abelson (2016) argue that the dorsolateral PFC (part of the MFG) in combination with other prefrontal regions is activated during reappraisal. These assumption stay of course highly speculative until more research is carried out specifically locating the areas of the SFG impacted by changes in WM and their specific cognitive functions it might support (see Figure 2).

6.1 Critical evaluation and future directions

The recent development of GingerAle makes it possible to calculate brain-wide analyses of cluster changes across studies. Due to the heterogeneity of findings across studies and the small number of studies reported, we only included those studies using whole brain analysis.

In addition, research groups tend to use different protocols for the DTI parameters. Following our approach, we were able to subdivide the studies in groups reporting a significant increase or decrease in FA across the whole brain. Due to the global comparison, the construction of Ale maps leading to a meta-analysis is possible but at the same time the interpretations of the results is limited to a rather general level, like the direction of change. A next step would thus be the quantification of change using ROI analysis, which would quantify the FA change further by allowing researchers to calculate standardized effect sizes. Using effect sizes would also enable to include moderators, such as scanner type or symptom severity of PTSD. For this next step several prerequisites will be needed concerning study design and methodology of diffusion tensor imaging studies in patients with PTSD (for a summary see Appendix Table A2).

First, four key study design-specific considerations are proposed to enhance the explanatory power of future studies. The average sample size should be increased per group to ensure enough statistical power to be able to perform statistical tests including methods for bias corrections. A meta-analysis of all meta-analyses (n=46) published between 2006 and 2009 found a median statistical power of 8% across 461 individual neuroimaging studies (Button et al., 2013). The relative bias of research findings in the field of neuroscience was found to be negatively related to the statistical power of studies, indicating that higher power improves the validity of the results. Importantly, studies should aim to have at least two matched control groups, including healthy participants without any traumatic experiences and healthy participants with trauma experiences. As mentioned previously, a second control group is essential to draw conclusions about whether structural WM changes arise due to neuroplastic changes after traumatic experience or whether these WM changes are also associated with symptoms of PTSD or may even be a pre-existing vulnerability factor. An important goal of future studies should be to clearly define target groups including subgroups

within underage and adult patients with PTSD. We propose four target groups of patients suffering from PTSD, which are clearly understudied up to this point: b) children with traumatic experience in childhood, b) adolescents with traumatic experience in childhood; c) adolescents with traumatic experience in adolescence; d) adults with traumatic experience in childhood. In a recent survey of almost 6500 adolescent-parent pairs (aged 13-17 years), McLaughlin et al. (2013) found that 61.8% of the adolescents experienced a lifetime potential traumatic experience. The lifetime prevalence of developing PTSD in the group of adolescents according to the DSM-IV criteria was 4.7% with a significantly higher prevalence for females with 7.3% in comparison to males with 2.2%. In this context, it will become even more important to take into account moderators such as sex or comorbid disorders in underage but also adult populations suffering from PTSD. In the same line of argumentation, clearly stated inclusion and exclusion criteria are essential for increasing the validity with which group differences in FA values are associated with clinical symptoms of PTSD. Clearly stated criteria also make it possible to later compare more refined groups of studies in a meta-analysis.

Second, several methodological considerations are proposed to ensure high quality of data. Although the majority of studies reported basic demographic information including gender ratio, age or race, this information is crucial for replication and comparison between studies and should be clearly stated. Furthermore, the assessment of clinical disorders should include at least one common scale for the assessment of PTSD and at least one for common comorbid disorders such as depression, anxiety disorder and substance misuse. Breslau, Davis, Peterson, & Schultz (2000) found that the risk to develop depression was increased in adults with PTSD in comparison to trauma exposed adults without PTSD. The neural mechanisms of PTSD and depression might overlap and are important to take into account when investigating correlations between clinical assessments and changes in FA. In addition,

a variety of clinical disorders were found to have comorbid PTSD including disorders such as schizophrenia, bipolar disorder or borderline personality disorder (Mueser et al., 1998). In these cases, PTSD might not be the primary outcome of structural changes in WM but rather an additional factor in the equation. A clear assessment of comorbid disorders is needed to understand these relations between disorders. In addition, the chronicity of PTSD might influence structural long-term changes and should be assessed and included in the analysis as covariate. Finally, the type of traumatic event experienced varies dramatically related to age and sex (McLaughlin et al., 2013; Mueser et al., 1998) and may influence the characteristics and severity of PTSD symptoms. A list of the type and number of traumatic experiences to which participants were exposed to should be included.

Third, we raise some methodological considerations concerning the acquisition, the pre-processing, the analyses and the reporting of DTI data. Since DTI is a rather novel technique in the field of neuroscience, the past ten years have seen a development towards a more standardized manner of acquiring and handling diffusion data. The heterogeneity in the results presented in this review can partly be explained by the variance in DTI methods applied, in the protocols used for acquiring the data as well as scanner type and field strength. For data acquisition and data pre-processing we recommend to follow the guidelines suggested by Jones et al. (2013). In the case of data analysis, two approaches are most common in DTI: whole brain and region of interest analyses. As mentioned previously, studies using whole brain analysis in research on patients with PTSD have the advantage to be included in meta-analyses because the limited number of studies using ROIs, at least in adult-onset with PTSD, focus on different regions, which made a meaningful comparison across studies difficult at the point in time of this review. In children with PTSD, the picture is reversed with almost all studies using region of interest analysis on different segments of the corpus callosum. Finally, the interpretation and reporting of DTI in PTSD has to be done with great caution. Studies

should include the coordinates of foci of significant changes in FA as well as the cluster size and peak values. Several studies could not be included in the meta-analysis due to missing data. For the interpretation of DTI data and specifically FA, we again refer to the excellent list of 'do's' and 'don'ts' in the overview article by Jones et al. (2013). Up to date, many articles interpret changes in FA in the context of PTSD as changes in 'white matter integrity'. The FA value, however, varies across the brain and can be low in areas where, for example, fibers cross. In their review, Zatorre et al. (2012) mention at least three processes, which can lead to an increase in FA: fiber organization, myelin formation and myelin remodelling. Furthermore, changes in glial cells, myelin context or the permeability of membranes might also contribute to changes in FA (Sampaio-Baptista & Johansen-Berg, 2017). In addition, stochastic errors, model simplifications or given anatomical structures like crossing fibers or changes in packing density (Jones et al., 2013) can influence the results. Overall, fractional anisotropy has a high sensitivity and a low specificity for the above mentioned anatomical properties to which it is often associated. For future research, it would be necessary to compare changes in FA to changes in GM or functional connectivity (Zatorre et al., 2012) in PTSD patients and the appropriate controls. Furthermore, a wide range of DTI acquisition procedures is in use in combination with various software packages for DTI pre-processing and data analysis. The high heterogeneity in findings for FA differences between studies in individuals with PTSD in comparison to healthy control subjects or subjects with trauma experience might therefore be partly the result of the high number of existing procedures to measure, pre-process and analyse data based on DTI. Methodological variability based on type of scanner, magnetic field strength, measurement parameters or pre-processing steps like motion correction are potential moderators influencing the magnitude and direction of FA change. Also, there is no theoretical framework explaining or predicting white matter changes in PTSD in specific

areas or fiber tracts. Since PTSD is not explicitly impacting on WM, a theory why and where changes in WM should occur, is needed.

6.2 Limitations

Several limitations apply to our systematic review. First, despite the increased number of studies published in the past five years on WM alterations in adult-onset PTSD, only a limited number of studies could be included. The majority comprised a sample size of 15-20 individuals with PTSD in comparison to only one control group, either trauma-exposed or healthy controls. Only one study in adult-onset PTSD and one study in childhood-PTSD had a larger sample size of over 75 participants and only one study in each of these two subgroups compared PTSD patients to two control groups. Second, the heterogeneity of the WM tracts identified as well as the direction of change, with some studies reporting an increase and others a decrease in FA, allow only a preliminary interpretation of the results. Another explanatory factor to be taken into account in the future are methodological differences in software and scanner types used as well as diverse methodological approaches to assessment and analysis. A final note on GingerAle, which was originally designed for summarising results of changes in GM. By applying the same same technique to changes in white matter taken from DTI two problems arise: the analysis space and error distribution are different. In addition, studies using tract based spatial statistics (TBSS) with individual skeletons should be treated differently than DWI analysis, which they are currently not. To encounter these problems ne toolboxes and software packages are urgently needed with the growing number of studies focusing on structural changes in white matter.

7. Conclusions and future directions

This review provides novel conclusions on WM changes in individuals with underage-onset PTSD and traumatic experience in childhood, adult-onset PTSD with traumatic experience in

childhood and adult-onset PTSD with traumatic experience in adulthood. The studies reported revealed some patterns of changes in WM integrity including the CC, ACC, PCC, SLF and SFG/MFG. In the group of adult-patients with traumatic experience in adulthood, changes in FA were found in the cingulum, most prominently with decreases in the ACC and increases in the PCC, the SLF and frontal tracts associated with the SFG and MFG. These findings are in line with recent psychobiological models of PTSD focusing on brain networks such as a context learning and memory, salience processing, emotional control and executive functions. In the group of children with PTSD and adults with PTSD after traumatic experience in childhood, almost exclusively changes in the corpus callosum are reported, particularly in the anterior and posterior midbody, the isthmus and the splenium. Although most of the studies included found significant correlations between PTSD symptom scales and their reported WM alterations, future studies should focus on specific symptoms like intrusions or overgeneralization as well as effects of WM changes on functional connectivity. This would allow for easier identification of mechanisms behind clusters of symptoms, enhance a mechanism-oriented approach to psychopathology, and help to embed findings into a larger theoretical framework. We suggest that future studies on WM in underage and adult populations suffering from PTSD should focus on more specifically selected groups of participants, including adolescent populations and adults with PTSD and trauma experience in childhood. Furthermore, future studies will have to take into account covariates such as demographic data (e.g. age, gender), the assessment of clinical factors (e.g. comorbidity, type of trauma experience, PTSD chronicity) as well as methodological considerations (e.g. acquisition and pre-processing of DTI data). Finally, whereas the assessment of structural changes in WM due to the experience of traumatic events and the development of PTSD is highly valuable, a theoretical foundation is needed putting possible alterations in FA in association with symptom clusters of PTSD or functional network changes.

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9 Appendix

Table 1

PTSD vs. HC — **Adults with PTSD (trauma in adulthood)** — **PTSD vs. TC**

Region	WB	ROI	↑	↓
cingulum [1 (l. ant.); 9 (rostral ant., subgenual ant., dorsal ant.)]	x	x	x	x
frontal gyrus [15 (sup. and orbital); 18 (l. sup.)]	x	x	x	x
occipital gyrus [15 (r. inf.)]	x			x
temporal gyrus [15 (sup.)]	x			x

Region	WB	ROI	↑	↓
angular gyrus [14 (post.)]	x			x
cingulum [3 (r.); 4 (bil. post.); 6, 7 (dorsal, hippocampal); 8 (l. ant.); 14 (ant.); 15 (r. ant.); 17 (r. post.); 19 (l. and r. post.)]	x	x	x	x
forceps mayor [11 (l.)]	x		x	
forceps minor [6]	x			x
fornix [7]		x	x	
fronto-occipital fasciculus [6 (inf. and sup.)]	x	x		x
frontal gyrus [11 (l. sup. and middle); 14 (precentral & prefrontal); 15 (medial, gyrus rectus); 16 (commisural tract connecting sup. and middle)]	x		x	x
hippocampus [17 (body)]	x	x		x
internal capsule [14 (post.)]	x			x
longitudinal fasciculus [4 (l. sup.); 6 (sup.); 12 (inf)]	x			x
midbrain [15 (r.)]	x			x
middle temporal gyrus [15 (r.); 19 (l.)]	x		x	x
parietal sub-gyrus [19 (r.)]	x		x	
precuneus [19 (r.)]	x		x	
stria terminalis [7]		x	x	
thalamic radiation [6 (ant.)]	x			x

Table 2

PTSD vs. HC — **Adults with PTSD (trauma in childhood)** — **PTSD vs. TC**

Region	WB	ROI	↑	↓	→
Corpus callosum [20; 21 (genu, ant. mid-body, mid-body, isthmus)]		x		x	x

Table 3

PTSD vs. HC — **Children with PTSD (trauma in childhood)** — **PTSD vs. TC**

Region	WB	ROI	↑	↓	→
Corpus callosum – rostrum [30]		x		x	
Corpus callosum – genu [22]		x		x	
Corpus callosum – ant. midbody [22; 23; 24; 26; 30]		x		x	
Corpus callosum – post. midbody [22; 23; 24; 26; 30]		x		x	
Corpus callosum – isthmus [22; 23; 24; 30]		x		x	
Corpus callosum – splenium [22; 23; 24; 29 (l.); 30]	x	x		x	
Prefrontal cortex [28]		x			x

Region	WB	ROI	↑	↓	→
Corpus callosum – total [25]		x			x

A1. These tables summarize all the regions mentioned in the reviewed studies in which a significant change in FA was found between adult patients with PTSD after traumatic experience in adulthood and healthy control patients (HC; left table) or trauma control patients (TC; right table). The tables are subdivided in three groups: a) adults with PTSD and traumatic experience in adulthood, b) adults with PTSD and traumatic experience in childhood and c) children with PTSD and traumatic experience in childhood. The *first column* of each tables indicates the white matter tract or more global region in which a significant change in FA was reported. The *second* and *third column* show, if the change in this specific tract or region was found after using a whole brain analysis (WB) or setting a region of interest (ROI). The arrows indicate if a significant increase (upwards pointing) or decrease (downwards pointing) was found or if no significant change (rightwards pointing) was reported for the specific region. (ant. - anterior; bil. - bilateral; inf. - inferior; l. - left; post. - posterior; r. - right; sup. – superior)

Study Design

sample sizes:
increase of group sizes

control groups:
healthy and trauma controls

target groups:
a. children with traumatic experience in childhood
b. adolescents with traumatic experience in childhood
c. adolescents with traumatic experience in adolescence
d. adults with traumatic experience in childhood

inclusion/ exclusion criteria:
clearly stated

Methods

Supporting Information

Demographics:
gender, age and race (including distribution, mean, standard deviation and range)

Assessments:
a. PTSD assessment with at least two common scales
b. comorbidity (at least depression and anxiety disorders)
c. type of traumatic experience clearly stated
d. chronicity of PTSD

Methods

Data acquisition
follow steps described by Jones et al. (2012, p. 3-6)

Data preprocessing
follow steps described by Jones et al. (2012, p. 13-14)

Data analysis
information needed:
a. analysis used (whole brain/ ROI)
b. method of white matter assessment stated

Data reporting
information needed:
a. coordinates of foci
b. cluster size with peak value

Future Directions

larger sample sizes; whole brain and ROI approach; include covariates (e.g. symptom severity, comorbidity, stress levels, genetic variances, cognitive tests); more specific target groups (see above); types of trauma; sex differences;

A2. Considerations for future DTI studies with PTSD patients concerning study design and methodology.

2.2 Study 2:

Structural white and gray matter differences in a large sample of patients with Posttraumatic Stress Disorder and a healthy and a trauma-exposed control group: Diffusion Tensor Imaging and Region-Based Morphometry[2]

[2] Publication:

Siehl, S., Wicking, M., Pohlack, S., Winkelmann, T., Zidda, F., Steiger-White, F., King, J., Burgess, N., Flor, H., & Nees, F. (2020). Structural white and gray matter differences in a large sample of patients with Posttraumatic Stress Disorder and a healthy and trauma-exposed control group: Diffusion tensor imaging and region-based morphometry. *NeuroImage: Clinical*, *28*. doi: 10.1016/j.nicl.2020.102424

Title page

Title: Structural white and gray matter differences in a large sample of patients with Posttraumatic Stress Disorder and a healthy and trauma-exposed control group: Diffusion Tensor Imaging and Region-Based Morphometry

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Abstract

Differences in structural white and gray matter in survivors of traumatic experiences have been related to the development and maintenance of Posttraumatic Stress Disorder (PTSD). However, there are very few studies on diffusion tensor imaging and region based morphometry comparing patients with PTSD to two control groups, namely healthy individuals with or without trauma experience. It is also unknown if differences in white and gray matter are associated. In this cross-sectional study, we examined white- and gray matter differences between 44 patients with PTSD, 49 trauma control and 61 healthy control subjects. We compared the groups applying Tract-Based Spatial Statistics (TBSS) for a whole brain white matter analysis as well as ROI analyses for white and gray matter. First, trauma control subjects in comparison to patients with PTSD and healthy control subjects showed significantly a) higher fractional anisotropy (FA) in the left corticospinal tract and inferior fronto-occipital fasciculus than patients with PTSD, b) higher FA in the left inferior fronto-occipital-, right inferior – and right superior longitudinal fasciculi, c) higher FA in the forceps minor and d) higher volume of the left and right anterior insulae. Second, we show significant correlations between the FA in the forceps minor and the gray matter volume in the left and right anterior insulae. Third, the mean FA value in the forceps minor correlated negatively with symptom severity of PTSD and depression as well as trait anxiety, whereas the gray matter volume in the left anterior insula correlated negatively with symptom severity in PTSD. Our findings underline the importance of brain structures critically involved in emotion regulation and salience mapping. While previous studies associated these processes primarily to functional and task-based differences in brain activity, we argue that morphometrical white and gray matter differences could serve as targets in neuroscientifically-informed prevention and treatment interventions for PTSD.

Keywords: white and gray matter, PTSD, trauma, diffusion tensor imaging, neuroplasticity

1 Introduction

The experience of a traumatic event can lead to the development of Posttraumatic Stress Disorder (PTSD). The fifth edition of the Diagnostic and Statistical Manual (DSM-5; American Psychiatric Association, 2013) characterizes PTSD by four symptom clusters: a) the re-experience of the traumatic event in form of intrusions or flashbacks; b) avoidance behavior around thoughts, feelings or reminders of the event; c) negative alterations in cognitions and mood; d) heightened arousal and reactivity. In the past two decades, a large amount of neuroimaging studies investigated differences in brain morphology in patients with PTSD when compared to either healthy individuals with or without trauma experience (Bromis, Calem, Reinders, Williams, & Kempton, 2018; Daniels, Lamke, Gaebler, Walter, & Scheel, 2013; Kühn & Gallinat, 2013; Siehl, King, Burgess, Flor, & Nees, 2018). The volumetric change of regions in the brain is an important indicator for underlying disease mechanisms and potential target regions for interventions. However, only few studies include more than one comparison group, with studies either focusing on a sample of healthy control subjects (HC) or a sample of healthy individuals that have experienced at least one traumatic event, so called trauma control subjects (TC). Choosing one or the other as a comparison group leads to very different results and conclusions. We therefore include both control groups in our study comparing patients with PTSD to TC and HC subjects. Furthermore, white and gray matter differences are largely studied independently and possible associations between them are rarely discussed within a common theoretical framework. We would like to bridge the gap between imaging techniques by studying structural differences in white- and gray matter within a single sample. By studying multiple imaging modalities, we aim to draw conclusions on how these differences are interrelated and how novel prevention and intervention tools might benefit from multiple outcome variables.

An estimated half of the brain volume consists of white matter with short and long reaching fibers passing on information (Sampaio-Baptista & Johansen-Berg, 2017). An important mechanism of the human brain is the ability of white matter tracts to change during maturation of the human brain (Giedd & Rapoport, 2010; Lövdén et al., 2010) or when learning occurs (Scholz, Klein, Behrens, & Johansen-Berg, 2009; Wang & Young, 2014; Zatorre, Fields, & Johansen-Berg, 2012), a process called white matter plasticity (Sampaio-Baptista & Johansen-Berg, 2017). White matter plasticity also plays an important role in the development of anxiety disorders in general (Jenkins et al., 2016) and PTSD in particular (Daniels et al., 2013; Siehl et al., 2018). Recent meta-analyses comparing patients with PTSD and TCs and HCs showed mixed results with lower and higher fractional anisotropies (FA) in patients in the anterior and posterior part of the cingulum, the superior longitudinal fasciculus and frontal white matter tracts, such as the forceps minor and the uncinate fasciculus (Daniels et al., 2013; Siehl et al., 2018). As argued in more detail in Siehl, King, Burgess, Flor, & Nees (2018), alterations in the above mentioned white matter tracts in patients with PTSD might be associated with context learning, processing of emotionally salient cues and extinction of aversive memories. However, as mentioned before, most studies focused on the comparison between patients with PTSD and trauma control subjects, with only a single study comparing patients with PTSD to trauma and healthy control subjects (Sun et al., 2013). Information on structural white matter differences between patients with PTSD and HCs as well as TC and HC subjects are still scarce, and a more refined understanding is needed to further establish neural white matter tracts as markers following trauma exposure. This also includes a link to several clinical target measures, such as PTSD characteristics and comorbidity, which can co-determine these effects (Ginzburg, Ein-Dor, & Solomon, 2010).

Similar to white matter plasticity, there is gray matter plasticity due to axon sprouting, dendritic branching, neuro- or angiogenesis or changes in glia cells following for example

experience based learning (Kühn, Gleich, Lorenz, Lindenberger, & Gallinat, 2014; Zatorre et al., 2012). We can quantify volumetric gray matter differences by a technique called voxel-based morphometry (Ashburner & Friston, 2005), in which the volume of voxels in the whole brain is estimated and can be compared between groups. This approach can also be applied to particular regions of interest (ROIs) estimating regional volumes with a so called region-based morphometry (RBM; Gaser & Dahnke, 2016). Recent meta-analyses found a reduction in overall brain volume in patients with PTSD in comparison to trauma and healthy control subjects with the largest differences in the volume of the insulae, the hippocampi and the anterior cingulate cortices and the superior frontal gyri in ROI analyses and the medial prefrontal- and the anterior cingulate cortices in the whole brain voxel-based morphometry analysis (VBM; Kühn and Gallinat, 2013; Bromis *et al.*, 2018). In a large meta-analysis of 89 studies, Bromis et al. (2018) showed accumulated evidence of 38 studies reporting differences in the volume of the hippocampi, showing differences in the following three contrasts: patients with PTSD<HC subjects, patients with PTSD<TC subjects, TC<HC subjects. Furthermore, they reported a reduction of gray matter volume of the insulae between patients with PTSD<HC as well as between patients with PTSD<TC. This fits well to psychobiological models suggesting a downregulation of brain activity in areas associated to processing context information, such as the hippocampal formation, and emotion regulation in more frontal parts of the brain and an upregulation of brain activity in areas associated to salience processing and threat detection, in areas such as the insulae and amygdalae (Brewin, Gregory, Lipton, & Burgess, 2010; Liberzon & Abelson, 2016).

In the present study, we analyzed data from a large civilian sample including patients with PTSD, TCs, and HCs. We expected higher FA in frontal white matter, such as the forceps minor and uncinate fasciculus in TC and HC subjects in comparison to patients with

PTSD. Further, we expected higher gray matter volumes of the hippocampi in HC subjects in comparison to TCs and patients with PTSD, between TC subjects and patients with PTSD as well as HCs and TCs. We also expected higher gray matter volume of the anterior insulae in HC and TC subjects in comparison to patients with PTSD. We further explored gray matter differences in the following region of interests: amygdalae, posterior insulae, anterior and posterior cingulate cortices as well as the ventromedial prefrontal cortices (vmPFC). We expected a positive association between differences in white and gray matter. Finally, we expected significant negative correlations between symptom severity of PTSD and depression as well as trait anxiety and differences in white and gray matter volume.

2 Methods and Materials

2.1 Participants

The dataset in this study is pooled from three independent studies on key mechanisms of pavlovian learning in patients suffering from PTSD (Wicking et al., 2016; two studies are in preparation). The studies were performed between 2010 and 2018 and all imaging protocols used for white and gray matter assessment were identical. In total, 154 participants were included in this study with 44 patients with PTSD, 49 TC and 61 HC subjects (see Table 1). There were no significant between-group differences observed for sex and age.

Participants in all groups, including subjects in the HC group, were asked if they had experienced any traumatic event from a list of possible traumatic events, taken from the Posttraumatic Diagnostic Scale (Foa, 1995; Foa, Cashman, Jaycox, & Perry, 1997). Then, the Structured Clinical Interviews for DSM-IV-TR (American Psychiatric Association, 2000) I and II were carried out for each participant (SCID; Fydrich, Renneberg, Schmitz, & Wittchen, 1997; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) to assess PTSD, depression and

other possible comorbidities. Participants fulfilling the PTSD criteria in the SCID-I interview were assigned to the PTSD group. To verify the assignment in a second step patients with PTSD had to fulfill criteria B through F of the DSM-IV criteria in the German version of the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS; Blake et al., 1995; Schnyder & Moergeli, 2002). This second step was independent of the overall score in the CAPS.

The following exclusion criteria applied: any traumatic experience before the age of 18 years, comorbid current or lifetime psychotic symptoms, current alcohol/ drug dependence or abuse, borderline personality disorder, cardiovascular or neurological disorders, brain injury, acute pain, continuous pain or medication for attention deficit hyperactivity disorder, pregnancy and metal implants.

For patients with PTSD and individuals in the TC group, no significant differences were present in time since trauma. The groups differed significantly in the level of education and medication with patients suffering from PTSD taking more psychopharmacological medication than participants in the control groups. All participants in the TC and HC groups that reported the intake of psychopharmacological medication were prescribed this medication for other purposes than a diagnosed mental disorder (e.g. sleep disturbances). Patients with PTSD scored significantly higher on symptom severity of PTSD and depression as well as trait anxiety than both control groups.

All participants received a reimbursement for participation (10€/h) and travel expenses. Patients were offered treatment in the outpatient clinics of the Central Institute of Mental Health in Mannheim, if requested. The study was carried out conforming to the Code of Ethics of the World Medical Association (World Medical Association, Declaration of

Helsinki, seventh revision, 2013). The study was approved by the Ethical Review Board of the Medical Faculty Mannheim, Heidelberg University and all participants gave written informed consent including consent for data re-analysis.

2.2 Data acquisition

Whole-brain MRI images were acquired using a 3T Magnetom TRIO whole body magnetic resonance scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard 12-channel volume head coil. We obtained T1-weighted, magnetization-prepared, rapid-acquisition gradient echo (MPRAGE) images with the following parameters: TR = 2300 ms, TE = 2.98 ms, flip angle 9°, FOV: 256 × 256 mm^2, matrix size: 256 × 256, voxel size: 1.0 × 1.0 × 1.1 mm^3, 160 sagittal slices. For the diffusion images we applied a single shot echo-planar imaging sequence (TR = 14000 ms, TE = 86 ms, 64 axial slices, 2 mm slice thickness, FOV: 256 × 256 mm^2, matrix size: 128 × 128 mm^2), with one image without diffusion weighting and 40 diffusion-weighted images (b = 1000 s/mm^2) along forty non-collinear directions.

Table 1. Demographic and clinical characteristics of study sample.

Variable			Groups										Analysis			
			PTSD N=44				TC N=49				HC N=61					
			M	SD	n	(%)	M	SD	n	(%)	M	SD	n	(%)	X^2	*F*	*Df*	*p*
Sex (female)					22	50.0			26	53.1			27	44.3	0.88			.64
Age (in years)			42.8	11.2			41.1	13.6			43.0	13.9				0.02	1	.88
Education	<=12 years				23	52.3			14	28.6			19	31.1	6.82			.03
	>12 years				21	47.7			35	71.4			42	68.9				
Time since trauma (in years)			13.0	9.2			15.0	9.1			-	-				0.95	1	.33
CAPS			66.7	18.9			7.2	8.8			-	-				375.8	1	<.001 (PTSD>TC)
ADS			28.4	9.7			9.8	7.6			7.0	4.8				142.2	1	<.001 (PTSD>TC)
STAI-T			55.6	10.5			36.1	10.7			31.8	8.2				115.8	1	<.001 (PTSD>TC+HC)
Medication		**Total (yes)**			29	65.9			19	38.8			24	39.3				
		Psychopharmacological[1]			21				7				4		9.08			.01
		Non-Psychopharmacological[2]			8				12				20					
		Total (no)			15	34.1			30	61.2			37	60.7				
Type of traumatic event (index trauma)	Caused voluntarily	**Total (caused voluntarily)**			27	61.4			21	42.9			-		3.18			.08
		(1) Imprisonment			2				1				-					
		(2) Physical violence			8				4				-					
		(3) Sexual abuse			1				1				-					
		(4) Rape			3				1				-					
		(5) Wartime experience			10				4				-					
		(6) Witness of sudden death/ serious injury of so.			3				7				-					
		(8) Other experiences			0				3				-					
	Caused involuntarily	**Total (caused involuntarily)**			17	38.6			28	57.1			-					
		(1) Natural disaster			0				0				-					
		(2) Fire or explosion			4				2				-					
		(3) Accident			8				19				-					
		(5) Other experiences			3				5				-					

Table 1. Demographic and clinical characteristics of study sample.

[**Abbreviations:** ADS – Allgemeine Depressionsskala [Centre for Epidemiological Studies Depression Scale (CESD)]; CAPS – Clinician-Administered PTSD Scale; HC – Group of healthy control subjects, who have never experienced anything traumatic in their lives; M – mean; SD – Standard deviation; STAI-T – State-Trait Anxiety Inventory – Trait Anxiety; TC – Group of trauma control subjects, who have at least experienced one traumatic event but do not fulfill the criteria for PTSD; [1]Psychopharmacology: Aripiprazole, Pregabalin, Methylphenidate, Mirtazapine, Quetiapine, Sertraline, Trimipramine, Venlafaxine; [2]Non-Psychopharmacological: Etoricoxib, Bisoprolol, Beta-Blocker, Ibuprofen, Metamizole, Levothyroxine]

2.3 Preprocessing

2.3.1 White matter

First, the diffusion-weighted raw data were preprocessed using the Oxford Centre for Functional MRI of the Brain Software Library (FMRIB; FSL, version 6.0), UK; http://www.bmrib.ox.ac.uk/fsl; Behrens *et al.*, 2003). The preprocessing procedure included the following steps: a) correction for motion artefacts and eddy current distortions using the FMRIB Diffusion Toolbox (FDT); b) extraction of the skull from T1-images using the Brain Extraction Tool (BET); c) fitting diffusion tensors at each voxel independently to the data and calculation of FA maps using a DTI fit algorithm, with alignment to the MNI space. In a second step, we extracted the mean FA value for each of the twenty white matter tracts specified by the probabilistic JHU white-matter tractography atlas (Mori, Wakana, Van Zijl, & Nagae-Poetscher, 2005) for a ROI analysis. The probability threshold was set to 30%, meaning that each voxel contained the corresponding tract with a 30% probability. We assessed motion parameters and included participants up to a maximum translation of one mm in x-, y-, or z-direction and a maximum of 1° of any angular motion throughout the course of the scan. No participants were excluded due to motion during the scan of white matter.

2.3.2 Gray matter

Second, we preprocessed the T1 weighted images using the Computational Anatomy Toolbox (CAT12; http://www.neuro.uni-jena.de/cat). The CAT12 toolbox runs on Statistical Parametric Mapping (SPM12; Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB R2016a (The MathWorks Inc., Natick, MA, USA). The preprocessing included the following steps: a) spatial registration; b) segmentation into gray

and white matter and CSF; c) bias correction of intensity non-uniformities. The Neuromorphometric atlas (provided by Neuromorphometrics, Inc., MA, USA; http://www.neuromorphometrics.com) was chosen providing a total of 142 ROIs. In a second step, we extracted the mean gray matter volume for each subject for 14 predefined ROIs including both hippocampi, amygdalae, anterior and posterior insulae, anterior and posterior cingulate cortices as well as ventromedial prefrontal cortices. We assessed motion parameters and included participants up to a maximum translation of one mm in x-, y-, or z-direction and a maximum of 1° of any angular motion throughout the course of the scan. No participants were excluded due to motion during the scan of gray matter.

2.4 Analyses of structural brain data

2.4.1 White matter: whole brain analysis

First, Tract-based spatial statistics (TBSS) was applied for the analysis of voxelwise FA changes (Smith et al., 2006) using FSL software. TBSS projects the FA data of all subjects onto a mean FA tract skeleton, before applying voxelwise cross-subject statistics. For statistical testing we conducted a one-way, univariate analysis of covariance (ANCOVA) with permutation-based nonparametric inference on FA with age and sex as nuisance covariates. FSL's randomize was used with threshold-free cluster enhancement (TFCE; Smith & Nichols, 2009) and 5000 permutations per analysis to assess group differences between patients with PTSD, TC and HC subjects. For whole-brain multiple comparison correction, the statistical threshold was set at $\alpha<.05$ with family-wise error (FWE) correction at cluster level (cluster threshold $p<0.001$; Table 2).

2.4.2 White matter: ROI analysis

In a second step, we averaged the FA value across all voxels in each of the twenty white matter ROIs. The group difference of the mean FA of each tract between patients with PTSD, TC and HC subjects was assessed with 20 different ANCOVAs (one for each tract) with age and sex entered as nuisance variables. Bonferroni-corrections were applied across 20 tracts (significant at $\alpha<.0025$). In case the ANCOVA showed a significant group difference, Post-hoc t-tests were performed using Tukey's honestly significant difference (Tuckey's HSD) test as post-hoc single-step multiple comparison procedure.

2.4.3 Gray matter

We performed a RBM analysis on the gray matter data. RBM estimates a regional tissue volume for different regions in the brain based on a surface-based atlas. We took fourteen pre-defined ROIs (each bilateral: hippocampi, amygdalae, anterior and posterior insulae, anterior and posterior cingulate cortices, ventromedial prefrontal cortices) from results of two meta-analyses (Bromis et al., 2018; Simone Kühn & Gallinat, 2013). The group difference of the mean volume of each ROI between patients with PTSD, TC and HC subjects was assessed with fourteen different ANCOVAs (one for each tract) with age, sex and TIV entered as nuisance variables. Bonferroni-corrections were applied across 14 tracts (significant at $\alpha<.0036$). Identical to the analyses steps in white matter, in case of a significant group difference, post-hoc t-tests were performed using Tukey's honestly significant difference (Tuckey's HSD) test as post-hoc single-step multiple comparison procedure.

2.4.4 Correlation of white and gray matter differences

In a final step, we carried out a Pearson's product moment correlation to assess the association between the FA value in white matter tracts in which groups significantly differed and the volume of ROIs in which groups differed significantly. We applied Bonferroni corrections dividing the p-value by the number of correlations that were performed.

2.5 Clinical assessments

Posttraumatic Stress Disorder. The German version of the CAPS (Blake et al., 1995; Schnyder & Moergeli, 2002) was used to provide a categorical diagnosis of PTSD and to assess symptom severity, which is calculated by summing the frequency and intensity score, measured on two 5-point scales ranging from zero ("never"/ "none") to four ("most or all of the time"/ "extreme"). The CAPS score ranges from 0 to 100.

Depression. For the assessment of impairment due to depressive symptoms within the last week, we applied the German long version of the Center for Epidemiological Studies Depression Scale (ADS; Hautzinger & Bailer, 1993). The ADS is a self-report questionnaire with 20 items measured on a 4-point scale ranging from zero ("rarely or not at all (less than one day)") to three ("most often, all of the time (on five to seven days)"). The ADS score ranges from 0 to 60.

Trait anxiety. For the assessment of trait anxiety, we applied the German version of the trait-version of the State-Trait-Anxiety-Inventory (STAIT; Laux et al., 1981). The STAI-T is a self-report questionnaire including 20 questions, measured on a 4-point Likert scale ranging from one ("not at all") to four ("very much"). Higher scores are associated with higher levels of anxiety. The STAIT score ranges from 20 to 80.

2.6 Statistical analysis

All statistical analyses were performed in R-Statistics (Team, 2013). Data were assessed for outliers and normal distribution. All assumptions were met, if not mentioned otherwise below. Analyses of covariance (ANCOVA) were computed including age and sex (for DTI and RBM) as well as total intracranial volume (TIV; for RBM). In case of multiple comparisons (e.g. multiple FA comparisons of different white matter tracts) Bonferroni corrections were applied to counteract Type 1 errors. We applied Tukey's honestly significant difference (Tuckey's HSD) test as post-hoc single-step multiple comparison procedure. Missing data were excluded from the analyses. However, this applied only to the gray matter analyses, in which seven datasets were missing (n_{PTSD}=2; n_{TC}=2, n_{HC}=3) due to incomplete measurements or artefacts. Correlations were calculated based on Pearson's product moment correlation coefficient. This applied to correlations calculated between clinical assessments of PTSD, depression and trait anxiety and differences in white and gray matter volume as well as for correlations between differences in gray and white matter volume.

3 Results

3.1 White matter: whole brain analysis

Figure 1a illustrates significant between-group differences in FA ($\alpha \leq .05$ cluster-wise FWE-correction) based on a whole-brain TBSS, including age and sex as covariates. We found two significant clusters in the ANCOVA comparing all three groups. The first cluster was located in the left corticospinal tract (CST; cluster size k=46 voxels, *p*=.046, MNI: x=-27, y=-25, z=17) and the second cluster in the left inferior fronto-occipital fasciculus (IFOF; cluster size k=24 voxels, *p*=.045, MNI: x=-25, y=28, z=112).

Table 2. Results of TBSS analysis

Contrast	Cluster index	voxels	Significance	Peak voxel coordinate			Tracts
			p	*x*	*y*	*z*	
ANCOVA	2	46	.046	-27	-25	17	l CST
	1	24	.045	-25	28	12	l IFOF
Post-Hoc T-test (TC>HC)	7	28264	.009	-24	28	10	l IFOF
	6	1492	.034	45	-22	-1	r ILF
	5	233	.048	50	-46	0	r SLF
	4	34	.05	-19	-31	36	l ATR
	3	22	.05	36	-54	-8	r IFOF
	2	17	.05	35	-49	8	r IFOF
	1	1	.05	37	-51	-8	r IFOF
Post-Hoc T-test (TC>PTSD)	11	23058	.014	-27	-26	17	l CST
	10	305	.046	31	-33	14	r IFOF
	9	116	.049	35	-46	7	r IFOF
	8	109	.049	39	-44	-11	r ILF
	7	85	.049	47	-25	4	r ILF
	6	30	.049	32	-44	-15	n.c.
	5	22	.05	40	-39	-11	r ILF
	4	19	.05	57	-18	3	r ILF
	3	15	.05	37	-38	15	r SLF
	2	2	.05	40	-53	1	r ILF
	1	1	.05	27	-40	-18	n.c.

Table 2. Results of the whole brain cluster analysis of FA values (TBSS). ANCOVA includes comparison of all three experimental groups (patients with PTSD, TCs, HCs) and sex and age as covariates. Tracts were extracted according to the JHU white matter tractography atlas.

[**Abbreviations:** ATR – Anterior thalamic radiation; CST – Corticospinal tract; IFOF – Inferior fronto-occipital fasciculus; ILF – Inferior longitudinal fasciculus; L – Left; n.c. – not classified; R - Right; SLF – Superior longitudinal fasciculus]

Figure 1. Results of Diffusion Tensor Imaging

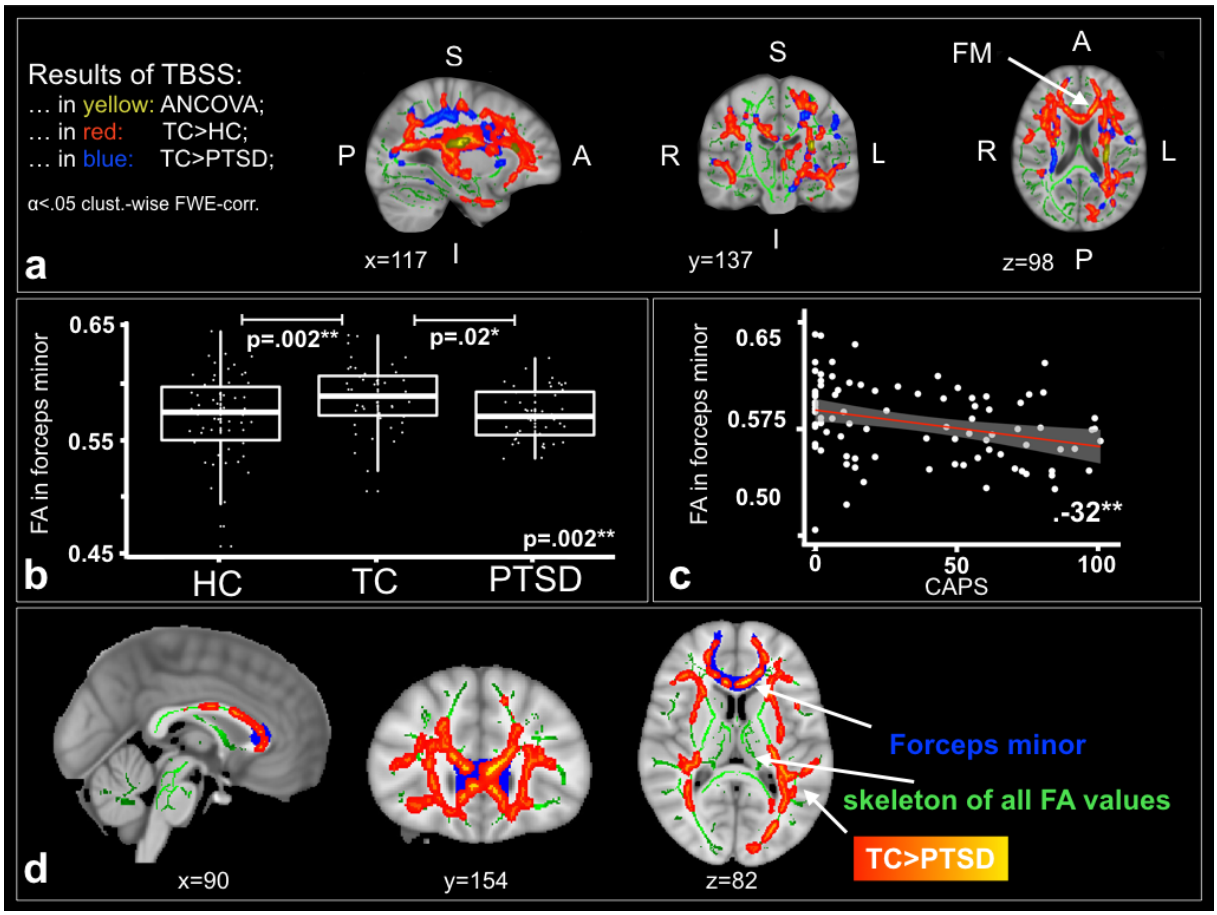

Figure 1. Diffusion Tensor Imaging. **a)** Results of TBSS analyses comparing the fractional anisotropy between patient with PTSD (n=44), TC (n=49) and HC (n=61) subjects in an ANCOVA (yellow), between TC>HC subjects in a post-hoc t-test (red) and between TC>PTSD in a post-hoc t-test (blue). Age and sex were included as covariates in the analyses. All results are FWE-corrected (α<.05). **b)** Boxplots with significant ($\alpha_{bonferroni\_cor}$=.05/20=.0025) differences in mean FA value of the forceps minor between patients with PTSD (n=44), TC (n=49) and HC (n=61) subjects (n=154). **c)** Significant correlation ($\alpha_{bonferroni\_cor}$=.05/4=.0125) between mean FA value in the forceps minor and the mean CAPS score for TC subjects (n=49) and patients with PTSD (n=44)**. d)** Anatomical images with mean FA skeleton used for the TBSS analysis (in green). The contrast between TC subjects and patients with PTSD is marked in yellow to red. The forceps minor is marked in blue as a region of interest for clarification.

[**Abbreviations:** ANCOVA - Analysis of Covariance; CAPS - Clinician-Administered PTSD Scale; FA - Fractional anisotropy; FM - Forceps minor; FWE - Family-wise error correction; HC - Healthy control subjects; I - Inferior; L - Left; P - Posterior; PTSD - Patients with posttraumatic stress disorder; R - Right; S - Superior; TBSS - Tract-based spatial statistics; TC - Trauma control subjects; * α<.05; ** α<.01; *** α<.001]

Table 3. Results of ROI analysis: white matter

Anatomical region	Hemisphere	Groups						Analyses						
		PTSD N=44		TC N=49		HC N=61		F_{group}	*df*	*p*	*contrast*	*Difference*	*CI [-95%; +95%]*	$P_{Tukey\ HSD}$	*Hedges' g*
		M	*SD*	*M*	*SD*	*M*	*SD*								
ATR	Left	.498	.020	.504	.022	.496	.024	1.89	2	.15					
	Right	.512	.023	.517	.025	.507	.024	2.35	2	.10					
Cingulum (cingulate gyrus)	Left	.633	.039	.655	.034	.642	.044	3.80	2	.02					
	Right	.612	.036	.621	.040	.602	.046	3.11	2	.04					
Cingulum (hippocampus)	Left	.583	.061	.606	.051	.579	.059	3.29	2	.04					
	Right	.627	.065	.645	.066	.615	.057	3.03	2	.05					
CST	Left	.631	.020	.639	.021	.631	.028	2.38	2	.10					
	Right	.653	.025	.660	.028	.655	.027	0.92	2	.40					
Forceps major		.750	.030	.755	.024	.751	.035	0.50	2	.61					
Forceps minor		**.571**	**.023**	**.587**	**.028**	**.569**	**.038**	**6.56**	**2**	**.002***	**TC-HC**	**0.02**	**0.005; 0.029**	**.002**	**0.53**
											PTSD-HC	0.002	-0.01; 0.01	.92	0.06
											TC-PTSD	**0.02**	**0.002; 0.028**	**.02**	**0.62**
IFOF	Left	.537	.026	.549	.028	.538	.038	2.39	2	.10					
	Right	.537	.028	.544	.029	.538	.034	0.68	2	.51					
ILF	Left	.511	.020	.521	.028	.506	.038	4.50	2	.01					
	Right	.541	.027	.553	.031	.539	.037	3.36	2	.04					
SLF (parietal)	Left	.493	.026	.509	.032	.501	.036	2.94	2	.06					
	Right	.540	.033	.553	.031	.542	.040	1.97	2	.14					
SLF (temporal)	Left	.537	.030	.552	.040	.543	.040	1.97	2	.14					
	Right	.557	.033	.557	.031	.557	.043	1.56	2	.21					
Uncinate	Left	.529	.040	.526	.034	.530	.037	0.18	2	.84					
	Right	.632	.045	.621	.045	.630	.046	0.77	2	.46					

Table 3. Tract by tract comparisons of FA values between all three experimental groups (patients with PTSD, TCs, HCs). An ANCOVA was performed for each individual tract including age and sex as covariates.

*$\alpha_{bonferroni\_cor}$=.05/20=.0025;

[**Abbreviations:** ATR – Anterior thalamic radiation; CST – Corticospinal tract; FA – Fractional anisotropy; HC – Healthy control subjects; IFOF – Inferior fronto-occipital fasciculus; ILF – Inferior longitudinal fasciculus; PTSD – Subjects suffering from posttraumatic stress disorder; SLF – Superior longitudinal fasciculus; TC – Trauma control subjects

The post-hoc contrast TC>HC resulted in seven clusters showing significantly different FA values with the three largest being the following (Figure 1; Table 2): a) left IFOF (cluster size k=28264 voxels, *p*=.009, MNI: x=-24, y=28, z=10), b) right inferior longitudinal fasciculus (ILF; cluster size k=1492 voxels, *p*=.034, MNI: x=45, y=-22, z=-1) and c) right superior longitudinal fasciculus (SLF; cluster size k=233 voxels, *p*=.048, MNI: x=50, y=-46, z=0). A second post-hoc contrast TC>PTSD resulted in eleven clusters showing significantly different FA values with the three largest being the following (Figure 1; Table 2): a) left CST (cluster size k=23058 voxels, *p*=.014, MNI: x=-27, y=-26, z=17), b) right IFOF (cluster size k=305 voxels, *p*=.046, MNI: x=31, y=-33, z=14) and c) right IFOF (IFOF; cluster size k=116 voxels, *p*=.049, MNI: x=35, y=-46, z=7). There was no significant difference between patients suffering from PTSD and HC subjects.

3.2 White matter: ROI analysis

When extracting 20 ROIs, one for each white matter tract, we found a significant difference in the mean FA of the forceps minor (F(2,149)=6.56, *p*=.002; $p_{bonf.cor.}$=.04). Post-hoc *t*-tests showed a significantly higher mean FA in the forceps minor for TC compared to HC ($M_{Difference}$=0.02; 95% CI 0.005 to 0.029; *p*=.002; Hedges' g= 0.53) and TC compared to patients with PTSD ($M_{Difference}$=0.02; 95% CI 0.002 to 0.028, *p*=.02; Hedges' g= 0.62). There was no significant difference between patients suffering from PTSD and HC (Figure 1; Table 3). The white matter dataset comprised 154 participants.

3.3 Gray matter

The RBM analysis revealed significant differences in GM volume (in cm^3) in the left (F(2,140)= 7.24, *p*=.001; $p_{bonf.cor.}$=.014) and right anterior insulae (F(2,140)= 6.06, *p*=.003; $p_{bonf.cor.}$=.042; Figure 2; Table 4). Post-hoc t-test comparisons showed that this difference in

Figure 2. Results of Region Based Morphometry

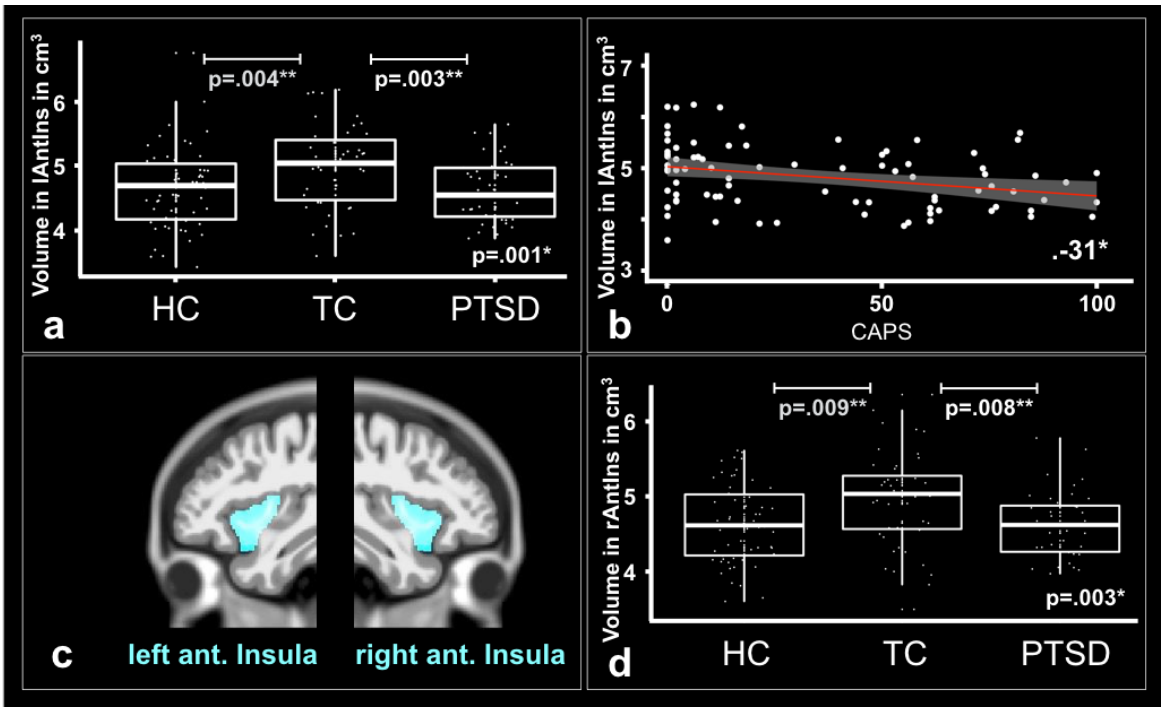

Figure 2. Region Based Morphometry. **a)** Boxplots with mean volume of left anterior insula (in cm^3) in all three groups. The results show a significant ($\alpha_{bonferroni\_cor}$=.05/14=.0036) difference in volume between patients with PTSD (n=42), TC (n=47) and HC (n=58) subjects. Post-hoc t-tests revealed significant differences in volume for the contrasts TC>HC subjects and TC>PTSD. **b)** Significant negative correlation ($\alpha_{bonferroni\_cor}$=.05/5=.0125) between mean volume of left anterior insula (in cm^3) and the mean CAPS score for TC subjects (n=47) and patients with PTSD (n=42). **c)** Outline of the left and right anterior insulae. **d)** Boxplots with mean volume of right anterior insula (in cm^3) in all three groups. The results show a significant ($\alpha_{bonferroni\_cor}$=.05/14=.0036) difference in volume between patients with PTSD (n=42), TC (n=47) and HC (n=58) subjects. Post-hoc t-tests revealed significant differences in volume for the contrasts TC>HC subjects and TC>PTSD.

[**Abbreviations:** CAPS - Clinician-Administered PTSD Scale; HC - Healthy control subjects; lAntIns - Left anterior insula; PTSD - Patients with posttraumatic stress disorder; rAntIns - Right anterior insula; TC - Trauma control subjects; * α<.05; ** α<.01; *** α<.001]

the left anterior insula was driven by the TC group, which showed a significantly higher mean GM volume than the HC subjects ($M_{Difference}$=0.35; 95% CI 0.09 to 0.60; *p*=.004; Hedges' g= 0.54) or than the group of patients suffering from PTSD ($M_{Difference}$=0.39; 95% CI 0.12 to 0.66; *p*=.003; Hedges' g= 0.67). The difference in the right anterior insula was also driven by

Table 4. Results of ROI analysis: gray matter

Anatomical region	Hemisphere	Groups						Analyses						
		PTSD N=41		TC N=47		HC N=58		F_{group}	df	p	contrast	Difference	CI [-95%; +95%]	$P_{Tukey\ HSD}$	Hedgesg
		M	*SD*	*M*	*SD*	*M*	*SD*								
Hippocampus	Left	3.18	0.29	3.32	0.35	3.18	0.33	3.37	2	.04					
	Right	3.52	0.33	3.61	0.39	3.50	0.38	1.50	2	.23					
Amygdala	Left	1.01	0.08	1.03	0.11	0.98	0.13	3.24	2	.04					
	Right	0.98	0.09	0.99	0.10	0.95	0.12	2.73	2	.07					
Anterior Insula	**Left**	**4.63**	**0.49**	**5.02**	**0.65**	**4.67**	**0.64**	**7.24**	**2**	**.001**	**TC-HC**	**0.35**	**0.09; 0.60**	**.004**	**0.54**
											HC-PTSD	0.05	-0.22; 0.31	.92	0.07
											TC-PTSD	**0.39**	**0.12; 0.66**	**.003**	**0.67**
	Right	**4.63**	**0.44**	**4.96**	**0.63**	**4.66**	**0.58**	**6.06**	**2**	**.003**	**TC-HC**	**0.30**	**0.06; 0.54**	**.009**	**0.50**
											HC-PTSD	0.03	-0.21; 0.28	.94	0.06
											TC-PTSD	**0.33**	**0.08; 0.59**	**.008**	**0.60**
Posterior Insula	Left	2.21	0.25	2.34	0.30	2.22	0.32	3.25	2	.04					
	Right	2.54	0.25	2.70	0.38	2.53	0.36	4.26	2	.02					
Anterior Cingulate Gyrus	Left	5.25	0.59	5.70	0.88	5.37	0.85	4.96	2	.01					
	Right	3.75	0.52	4.04	0.67	3.80	0.80	2.60	2	.08					
Posterior Cingulate Gyrus	Left	4.47	0.45	4.69	0.68	4.40	0.76	3.67	2	.03					
	Right	4.05	0.44	4.14	0.62	3.98	0.64	1.28	2	.28					
Ventromedial Prefrontal	Left	18.49	1.95	19.26	2.99	18.56	2.91	1.61	2	.20					
Cortex	Right	18.05	2.12	19.13	2.95	18.07	2.70	3.49	2	.03					

Table 4. ROI comparisons of mean gray matter volume between all three experimental groups (patients with PTSD, TCs, HCs) with an ANCOVA including sex, age and total intracranial volume (TIV) as covariates.

*$\alpha_{bonferroni\_cor}$=.05/14=.0036;

[**Abbreviations:** HC – Healthy control subjects; PTSD – Subjects suffering from posttraumatic stress disorder; TC – Trauma control subjects]

Figure 3. White and gray matter coupling

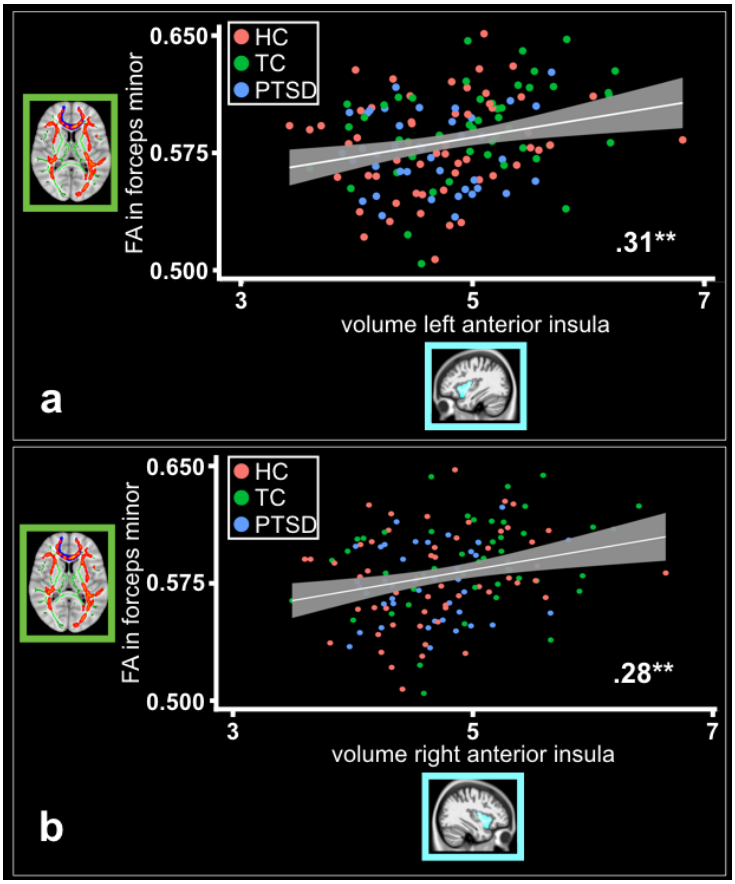

Figure 3. White and gray matter coupling. Significant positive correlation ($\alpha_{bonferroni\_cor}$=.05/4=.0125) between mean FA value in forceps minor and **a)** volume of the lAntIns (PTSD, n=42; TC, n=47; HC, n=58) and **b)** volume of the rAntIns (PTSD, n=42; TC, n=47; HC, n=58).

[**Abbreviations:** HC - Healthy control subjects; lAntIns - Left anterior insula; PTSD - Patients with posttraumatic stress disorder; rAntIns - Right anterior insula; TC - Trauma control subjects; * α<.05; ** α<.01; *** α<.001]

the TC group, which showed a significantly higher mean GM volume than the HC subjects ($M_{Difference}$=0.30; 95% CI 0.06 to 0.54; *p*=.009; Hedges' g= 0.50) or than the group of patients suffering from PTSD ($M_{Difference}$=0.33; 95% CI 0.08 to 0.59; *p*=.008; Hedges' g= 0.60). There was no significant difference between patients with PTSD and HC. The gray matter dataset comprised 147 participants, excluding seven participants due to artefacts or missing data.

3.4 Relationship between white and gray matter differences

As a measurement of white- and gray matter coupling, we correlated findings of structural (WM and GM) differences between TC subjects and patients with PTSD. We found a significant positive correlation between the mean FA in the forceps minor and the mean volume in the left anterior insula including subjects from all three groups (r(144)=.29, 95% CI 0.14 to 0.43, p=.00036; $p_{bonf.cor.}$=.001; Figure 3a). The correlation stayed significant, when we included only patients with PTSD and TC subjects (r(86)=.31, 95% CI 0.10 to 0.49, p=.0037; $p_{bonf.cor.}$=.015). Similarly, we found a significant positive correlation between the mean FA in the forceps minor and the mean volume in the right anterior insula (r(144)=.28, 95% CI 0.12 to 0.42, p=.0006; $p_{bonf.cor.}$=.0024). This association also stayed significant, when we included only patients with PTSD and TC subjects (r(86)=.29, 95% CI 0.09 to 0.47, p=.0059; $p_{bonf.cor.}$=.024; Figure 3b).

3.5 Relationship of brain changes and clinical measures

We found significant negative Pearson correlation coefficients for the contrast of TC>PTSD between the mean FA value in the forceps minor and the mean CAPS- (r(87)= -.32, 95% CI -0.12 to -0.49, p=.0026; $p_{bonf.cor.}$=.008; Figure 1c), STAIT- (r(84)=-.26, 95% CI -0.05 to -0.45, p=.014; $p_{bonf.cor.}$=.042) and ADS scores (r(83)=-.28, 95% CI 0.07 to 0.46, p=.011; $p_{bonf.cor.}$=.033). For the same contrast of TC>PTSD, we found a significant negative Pearson correlation coefficient between the mean GM volume in the left anterior insula and the mean CAPS score (r(82)=-.31, 95% CI -0.10 to -0.49, p=.005; $p_{bonf.cor.}$=.015). The correlations for the STAIT- (r(80)=-.25, 95% CI -0.04 to -0.44, p=.023; $p_{bonf.cor.}$=.069) and ADS score (r(78)=-.24, 95% CI -0.02 to -0.43, p=.035; $p_{bonf.cor.}$=.11) did not survive Bonferroni corrections. We did not find any significant correlations between our clinical measures and the GM volume difference in the right anterior insula.

4 Discussion

The present study used TBSS and ROI analysis for white matter and ROI analysis for gray matter regions to examine group differences in a large non-military sample of 154 patients with PTSD and trauma and healthy control subjects. We observed significant white- and gray matter differences in TC subjects compared to both patients with PTSD and HC subjects. In particular, TC subjects in comparison to patients with PTSD as well as HC subjects showed a significantly higher FA in the forceps minor and higher gray matter volume in the left and right anterior insulae. Interestingly, we did not find any differences in white or gray matter analyses between patients with PTSD and HC subjects. Our results suggest that TC subjects show higher interhemispheric frontal connections combined with larger volumes in brain areas associated with salience processing and threat detection than patients with PTSD and HC subjects. Furthermore, we found positive correlations between the FA value in the forceps minor and the volume of the left and right anterior insulae. These results suggest thathigher volumes in the FM and anterior insulae in TC subjects might be a result of resilience, as TC subjects are those individuals that experienced a traumatic event, but did not develop PTSD. Finally, our results demonstrate a link between morphometric white and gray matter differences and symptom severity of PTSD, depression and trait anxiety. We argue that the forceps minor and the left anterior insula could be used as target regions in neuroscientifically-informed treatment studies on PTSD.

Our TBSS analysis revealed significantly higher FA values in TCs than patients with PTSD in long reaching white matter fibers such as the left CST and left IFOF. The CST is one of the largest descending white matter tracts in humans and involved in voluntary movement of contralateral limbs (Natali & Bordoni, 2018). Although, previous studies mention differences in FA in the CST in anxiety related disorders (Jenkins et al., 2016), depression

(Sacchet et al., 2014) and neurogenerative disorders, such as Alzheimer's (Douaud et al., 2011), its role in PTSD is unclear. Douaud et al. (2011) also found that higher FA values in the CST were associated with higher values in the SLF. Future studies are needed to determine the function of the CST in affect- and anxiety related disorders. The IFOF on the other hand originates in the parietal and occipital lobes and connects them with regions in the lateral frontal cortex (Catani, Howard, Pajevic, & Jones, 2002). As a long reaching white matter tract, it is generally assumed to be involved in cognitive control, language processing (Almairac, Herbet, Moritz-Gasser, de Champfleur, & Duffau, 2015), and salience processing (Wang et al., 2016). Differences in the FA value of the IFOF have been previously linked to anxiety disorders in general (Jenkins et al., 2016) and PTSD in particular (Siehl et al., 2018). Furthermore, TC subjects showed a significantly higher FA value than HC subjects in the left IFOF, right ILF and right SLF. Similar to the IFOF, the SLF connects more posterior regions of the parietal, occipital and temporal lobe with the frontal lobe. The SLF is involved in a wide range of functions, such as the perception of visual and auditory space as well as aspects of motor behavior (de Schotten et al., 2011; Makris et al., 2005). In a previous systematic review, the authors did not find any differences in the SLF between TC and HC subjects (Siehl et al., 2018) and to the best of our knowledge, there is no study so far comparing the FA value in TC to HC subjects in a non-military sample. However, Our findings are in line with previous studies comparing patients with PTSD to TC subjects showing higher FA values in the SLF in TC subjects (Fani et al., 2012; Schuff et al., 2011). The ILF is a long reaching white matter tract connecting occipital and more posterior parts of the temporal lobe to more anterior parts of the temporal lobe. The ILF has been associated with visual cognition and socio-emotional processing of information (Herbet, Zemmoura, & Duffau, 2018) and previously been associated to show reduced FA values in patients with PTSD in comparison to TC subjects (Olson et al., 2017). Interestingly we don't find any differences in the ILF and SLF between TCs and patients with PTSD, but between TC and HC subjects. In a summary,

long reaching white matter fibers connecting more posterior regions of the brain to more anterior regions seem to play a role in the development of PTSD. We speculate that lower white matter connectivity is an understudied factor in PTSD leading to higher salience and lower contextual information processing.

Frontal white matter tracts such as the FM might play an important role in the development of PTSD, in particular altered emotion regulation. Our white matter ROI analyses demonstrated significantly higher FA values in the FM in TC subjects than patients with PTSD or HC subjects. The FA in the FM was found to be central for PTSD in earlier studies (Sripada et al., 2012a). The forceps minor originates from the genu of the corpus callosum and connects the medial and lateral surfaces of the prefrontal cortices of both hemispheres in a fork-like shape, supporting interhemispheric information exchange between medial and lateral surfaces of the frontal lobe. Presumably, the FM is part of a larger network of white matter tracts, including the uncinate fasciculus and the cingulum, involved in emotion regulation (Versace et al., 2015). A lower FA in the FM suggests a lower top-down control and a less well orchestrated functional connectivity between hemispheres in the PFC (Liberzon & Abelson, 2016). Interestingly, the FA value in the FM in TC subjects was also significantly higher than in HC subjects, while there was no difference between patients with PTSD and HC subjects. White matter plasticity in the FM might occur after trauma experience as an adaptive change to strengthen networks involved in emotion regulation. However, longitudinal studies are needed to test this hypothesis. We did not find any significant FA differences between the groups in the uncinate fasciculus.

Lower gray matter volume in the insulae might be associated to weaker salience mapping in patients with PTSD. The RBM analysis on gray matter differences revealed a higher volume in the left and right insulae in TC subjects in comparison to both, patients with

PTSD as well as HC subjects. The insula is a major hub within the salience network and associated with the detection and autonomic response to salient events as well the facilitation of communication between large scale networks (Menon, 2011; Menon & Uddin, 2010). A larger volumetric size of the insula can be associated with a stronger salience mapping. Stronger salience mapping after the experience of a traumatic event might lead to a better integration of cognitive, homeostatic and affective systems within the brain (Damasio & Carvalho, 2013; Pessoa, 2008). It also fits well to recent studies on neurofeedback, which found stronger functional connectivity between the PFC and the amygdala and insula after targeting areas in the salience network for up- or down regulation (Cohen Kadosh et al., 2016; Lubianiker et al., 2019; Paret et al., 2016). We did not find volumetric differences for the hippocampi, amygdalae, posterior insulae, anterior and posterior cingulate cortices or vmPFCs after Bonferroni corrections (see Table 4). We argue that this is partly due to low power and heterogeneity of the sample concerning the trauma type. Future studies should investigate volumetric gray matter differences with a larger sample focusing for example on one particular trauma type.

Structural differences in the FM and insulae are associated and point to the importance of the salience network in PTSD and its function in safety learning. We observed a positive association between the FA in the forceps minor and the volume of the left and right insulae (see Figure 3), which supports the association between structural white and gray matter differences in patients with PTSD in comparison to TC subjects. This is also in line with previous studies emphasizing the central role of the insulae and the right amygdala within the salience network in PTSD (Cisler et al., 2014; Peterson, Thome, Frewen, & Lanius, 2014; Rabinak et al., 2011; Sripada et al., 2012b; Zhang et al., 2015), with the insulae playing a particular role in discrimination learning of safety cues (Lissek et al., 2014). The inclusion of two healthy control groups is important for the interpretation of the results at this point. The

volumetric size of the left and right anterior insulae did not significantly differ between HCs and patients with PTSD. Due to our cross-sectional design, we can only speculate that this volumetric difference in the anterior insulae could emerge, post trauma, as an adaptive, functional neuroplastic change. The volumetric difference, alongside the difference in the FA of the FM, might lead to an increased functional connectivity in the salience network in TCs in comparison to patients with PTSD. This is in line with a recent study on healthy but highly trauma-exposed firefighters in comparison to non-firefighters, which found a higher functional connectivity in the salience network for the highly trauma exposed population of firefighters with the insula as a seed region (Jeong et al., 2018). Although it becomes more difficult to explain why there is no difference between patients with PTSD and HC subjects, it might also be possible that this difference existed before the traumatic event. Future studies on neurofeedback could investigate the effect of an up regulation of the anterior insulae in patients with PTSD in comparison to TC subjects and its effect on the functional connectivity within the salience network.

In our study, we included participants that experienced different types of traumatic events with the traumatic event either being caused voluntarily (e.g. physical violence, sexual abuse) or involuntarily (e.g. accidents, fire or explosion). Exposure to voluntarily caused events, in particular events involving interpersonal violence such as rape or sexual assault, show the strongest association with subsequent traumatic events (Benjet et al., 2016) and higher risk of developing PTSD (Kessler et al., 2017). Although our groups of patients with PTSD and TC subjects did not differ significantly in the type of trauma, patients with PTSD were more frequently exposed to voluntarily caused events, specifically physical violence and wartime experience. TC subjects on the other hand experienced more involuntarily caused events such as accidents. Whereas changes in white (Daniels, Lamke, Gaebler, Walter, &

Scheel, 2013b; Giedd & Rapoport, 2010; Siehl et al., 2018) and gray matter (Bromis et al., 2018; Kribakaran, Danese, Bromis, Kempton, & Gee, 2020) due to traumatic experiences were found to be age sensitive, it is not clear whether the different types of traumatic events impact white and gray matter trajectory differently. One would assume given the large differences in cognition, emotion and perception following either a voluntarily or involuntarily caused event. Future research is needed here to further assess differences in white and gray matter structures in adults with PTSD and trauma in adulthood with different types of trauma experiences.

These structural white and gray matter differences in areas related to salience processing and top-down control could inform behavioral prevention and treatment strategies. Psychotherapeutic interventions could benefit from neuroscientific findings by specifically selecting treatment techniques that focus on the flexibility (up- and down regulation) of salience processing and salience mapping, such as mindfulness-based interventions (Lanius, Frewen, Tursich, Jetly, & McKinnon, 2015), to increase the connectivity between the salience network and the frontal lobe in patients with PTSD. Higher emotional control, possibly mediated via the FM in combination with a threat-detection system that is well embedded might facilitate healthy recovery after the exposure to traumatic events.

4.1 Limitations

A limitation of this study is clearly its cross-sectional design, which only allows limited interpretation of the results. A longitudinal design would be needed to disentangle, if structural differences, especially between patients with PTSD and TC subjects, occur due to pre-existing vulnerabilities or if these differences have developed after trauma experience. Furthermore, our sample focused on adults with trauma experience in adulthood (after 18 years of age) only. White and gray matter are known to develop differently in underage

populations suffering from PTSD in comparison to adults with PTSD, so we can draw only limited conclusions for this population from our sample. Further, the patients showed higher intake of medication and less years spending in education than both control groups. The differences in education might partly be explained by the experience of the traumatic event which on average participants in the PTSD and TC group experienced in their early to late twenties. Arguably, patients suffering of PTSD couldn't continue their education due to the illness. Another possible argument could be the socio-economic background of participants which might have influenced the differences in years of education. This was however not assessed in our sample. While there was no difference between TC and HC control group in medication and education, we can't fully rule out that group differences between patients with PTSD and both control groups are confounded.

4.2 Conclusions

In this cross-sectional study, we found structural white and gray matter differences in brain regions related to emotional control and threat detection in healthy traumatized control subjects in comparison to patients suffering from PTSD and HC subjects. First, TCs in comparison to patients with PTSD and HCs showed a higher FA in the forceps minor and a larger volume in the left and right anterior insulae. We argue that these morphometric differences might be associated with stronger emotion regulation and salience mapping in TC subjects. Second, we found a positive correlation between FA in the FM and gray matter volume in the insulae, showing that white and gray matter differences are associated and important for understanding the development of PTSD. Finally, the mean FA value in the forceps minor correlated negatively with symptom severity of PTSD, depression as well as trait anxiety, while gray matter volume in the left anterior insula correlated negatively with symptom severity in PTSD. Our results add important information for individualized

prevention and neuroscientifically-informed treatment interventions such as neurofeedback, which could target the anterior insulae as a region to be up-regulated in patients with PTSD to strengthen functional connectivity within the salience network and between the salience network and regions in the frontal lobe. Finally, future studies could investigate long-term differences in the forceps minor before and after an intervention.

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Data availability statement: We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. Ethical restrictions to protect participant confidentiality prevent us from making anonymised study data, publicly available. This also refers to the analysis/experimental code, and any other digital materials, where participant-related anonymised information (like sex or psychopathological status) are also included. Readers seeking access to the study data and materials should contact the corresponding author based on a formal collaboration agreement. This formal collaboration agreement indicates that data will be shared with other researchers who agree to work with the authors, and for the sole purpose of verifying the claims in the paper. The data and materials will be released to requestors after approval of this formal collaboration agreement by the local Ethics Committee of the Medical Faculty Mannheim.

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2.3 Study 3:

Cued and contextual conditioning in patients with posttraumatic stress disorder and a healthy and trauma-exposed control group: A study using functional magnetic resonance imaging and virtual reality.[3]

[3] Publication:

Siehl, S., Wicking, M., Pohlack, S., Winkelmann, T., Zidda, F., Steiger-White, F., Nees, F, & Flor, H. (2020). *Cued and contextual conditioning in patients with posttraumatic stress disorder and a healthy and trauma-exposed control group: A functional magnetic resonance imaging study using virtual reality.* Manuscript in preparation.

Title: Cued and contextual conditioning in patients with posttraumatic stress disorder and a healthy and trauma-exposed control group: A functional magnetic resonance imaging study using virtual reality.

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Abstract

Objective: Psychobiological models of Posttraumatic stress disorder (PTSD) suggest that deficiencies in discriminating safe from dangerous contexts are a central for its development. In particular, configural learning, binding multiple elements into a coherent context representation, might be deficient in patients with PTSD if there is not a single cue predicting the danger.

Methods: A novel combined cue-context conditioning paradigm was applied using virtual reality. Contexts consisted of four different rooms with furniture, in which two rooms were conditioned with a painful electrical stimulus (dangerous), one uncued (unpredictable) and one cued (predictable), and two contexts without a painful stimulus (safe). The authors assessed 20 patients with PTSD, 21 healthy trauma-exposed and 22 non-trauma-exposed participants using self-report measures, skin conductance responses and functional magnetic resonance imaging (fMRI).

Results: Patients with PTSD in contrast to non-trauma-exposed but not trauma-exposed individuals showed lower brain activity in the ventromedial prefrontal cortex in the unpredictable and a higher brain activity in the hippocampi in the predictable context. During cued contextual conditioning, patients with PTSD also showed significantly lower skin conductance responses in comparison to both control groups. There were no differences in self-reports between the groups.

Conclusion: These results suggest that patients with PTSD indeed show a different neural response during cued and uncued contextual learning than non-trauma exposed but not trauma-exposed subjects. The ventromedial prefrontal cortex seem to be less engaged during uncued, and the hippocampi more engaged during cued contextual fear acquisition.

Treatments of PTSD could specifically enhance configural learning strategies to potentially benefit exposure effects.

Keywords: context conditioning, PTSD, trauma, virtual reality, neuroplasticity, functional connectivity

1 Introduction

Studies of fear learning, using pavlovian conditioning (1), have greatly advanced our understanding of the psychobiological mechanisms of posttraumatic stress disorder (PTSD), which is characterized by symptoms like re-experiencing, avoidance, hyperarousal and alterations in mood and cognition (2). In pavlovian fear conditioning, an originally neutral stimulus is paired with a biologically relevant stimulus (unconditioned stimulus (US)), such as pain, to become a conditioned stimulus (CS). This CS can then elicit a conditioned response such as increased heart rate that is usually but not always similar to the response to the original unconditioned response (UR), without the US being present. In differential conditioning, two CSs are differentiated of which one is predictive of the US (CS+; danger signal) and the second is not (CS-; safety signal). This association between the US and the CS is learned during fear acquisition and can be overwritten during fear extinction. The CS can be a single object (cue) or an entire internal or external environment (context). Psychobiological models of PTSD (3,4) have focused on contextual fear learning as a central mechanism underlying psychopathology. The term 'context' has been defined very broadly as " ... the set of circumstances around an event" (2, p. 418) and conditioning research has developed a variety of study protocols to investigate contexts in humans, most often environmental or spatial contexts. Spatial context conditioning paradigms have used distinct or transitioning colored backgrounds, static background images, videos of environments or virtual reality (5). Context conditioning can further be enhanced by increasing the temporal unpredictability of the US (6). The larger the time frame, in which a US can occur, the larger the unpredictability and the higher the levels of anxiety (7). In general, patients with PTSD show a reduced capacity to use context information to regulate fear responses (8) during fear extinction (9), memory of the extinction (extinction recall; 8) and when the already

extinguished fear is renewed (fear renewal; 9). Previous work has shown that patients with PTSD are deficient in acquiring context conditioning, but improve when cues are added to predict danger or safe context (12).

Neurobiological findings point towards distinct neural circuits involved in cue and context conditioning (3). The most prominent brain regions involved in contextual conditioning are the hippocampus and ventromedial prefrontal cortex (vmPFC), with the amygdala being the most prominent mediator of cue conditioning. The hippocampus has long been proposed as an epicenter for processing environmental context (13,14), in particularly for learning conjunctive associations (15) as a form of context conditioning. Conjunctive associations are a form of association learning in which many individual elements or cues in a particular context are encoded as a whole, also referred to as configural learning. Patients with PTSD show difficulties in conjunctive based learning of contexts, eventually leading to an element based association, meaning that each cue in the environment is individually associated to the dangerous stimulus (16). Each individual cue is then potentially able to elicit a fear response across contexts, with the amygdala being more active (17), independent of the context being originally safe or dangerous. When fear is elicited in an original safe context, corrective responses could for example involve emotional downregulation of the fear response or redirecting ones attention towards safety related stimuli. Patients with PTSD however show difficulties in emotion and attention related processes which are associated to functional activity in the vmPFC (3,16). Most studies on contextual conditioning have used configural learning paradigms (18). The aim of our study was to create contexts based on configural learning with several conditions, in which either a cue or the whole context is predictive of the US.

In this study, we investigated context processing in patients with PTSD in comparison to HC and TC subjects in a combined cue-context conditioning paradigm using virtual reality

and functional magnetic resonance imaging (fMRI). Participants were presented with four different contexts, two during the context conditioning (unpredictable, safe) and two during the cue conditioning (predictable, safe). We predicted that patients with PTSD would have difficulties in discriminating safe and dangerous contexts from each other, if there is no additional cue predicting the US in the environment (unpredictable). However, if there is an additional cue predicting, if the context is dangerous or safe (predictable), patients with PTSD should be equally could in differentiating the two environments. In the unpredictable in comparison to a safe context, we therefore hypothesized that patients with PTSD in comparison to HC and TC subjects would a) report higher arousal, valence and contingency ratings, b) show an elevated skin conductance response, c) show smaller BOLD activities in the hippocampi, vmPFC and amygdalae. During cued context conditioning, we expected that all three groups report a) higher arousal, valence and contingency ratings as well as b) elevated skin conductance responses for the CS+ in comparison to the CS- in the predictable context but not in the safe context. In addition, we expected higher BOLD activity in the amygdalae in the predictable context in patients with PTSD in comparison to TC and HC subjects.

2 Methods

2.1 Participants

Twenty patients suffering from PTSD, 21 age- and sex matched trauma control (TC) and 22 never traumatized healthy control subjects participated in this study (*Table 1*; details on recruitment and inclusion and exclusion criteria can be found in *Suppl. methods*). All trauma-exposed subjects fulfilled the trauma criteria of the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; 18) assessed with the German version of the Structured Clinical Interview (SCID-I; 19). Based on the SCID-I and the results of the Clinician-Administered PTSD Scale (CAPS; 20,21), participants were assigned to the respective groups. Healthy control subjects had never experienced any traumatic event in their lives and had never met any criterion for a DSM-IV-TR disorder. All participants received a reimbursement for participation (10€/h), travel and potential costs for accommodation. Patients suffering from PTSD were offered treatment in one of the outpatient clinics of the CIMH. The study was carried out in accordance with the Code of Ethics of the World Medical Association (23). The study was approved by the Ethical Review Board of the Medical Faculty Mannheim, Heidelberg University and all participants gave written informed consent.

2.2 Procedure and study design

The study consisted of two sessions on two consecutive days, each lasting for approximately five to seven hours. On the first day, participants completed questionnaires and clinical assessments on PTSD (described in more detail below) as well as the SCID-I. During the first experimental phase participants completed a training- and habituation phase outside the Magnetic Resonance Imaging (MRI) scanner, while sitting in front of a computer screen with a head mounted display (HMD). Participants then determined the intensity of the painful

stimulus (see *Suppl. methods*) before completing the context and cue acquisition phases inside the MRI scanner. On the second day, participants took part in the context and cue extinction phases inside the MRI scanner. This was followed by a final testing phase including cognitive and neuropsychological assessments. Finally, the SCID-II (24) personality assessment was conducted with participants who reached the cut-off values in the accompanying screening assessment.

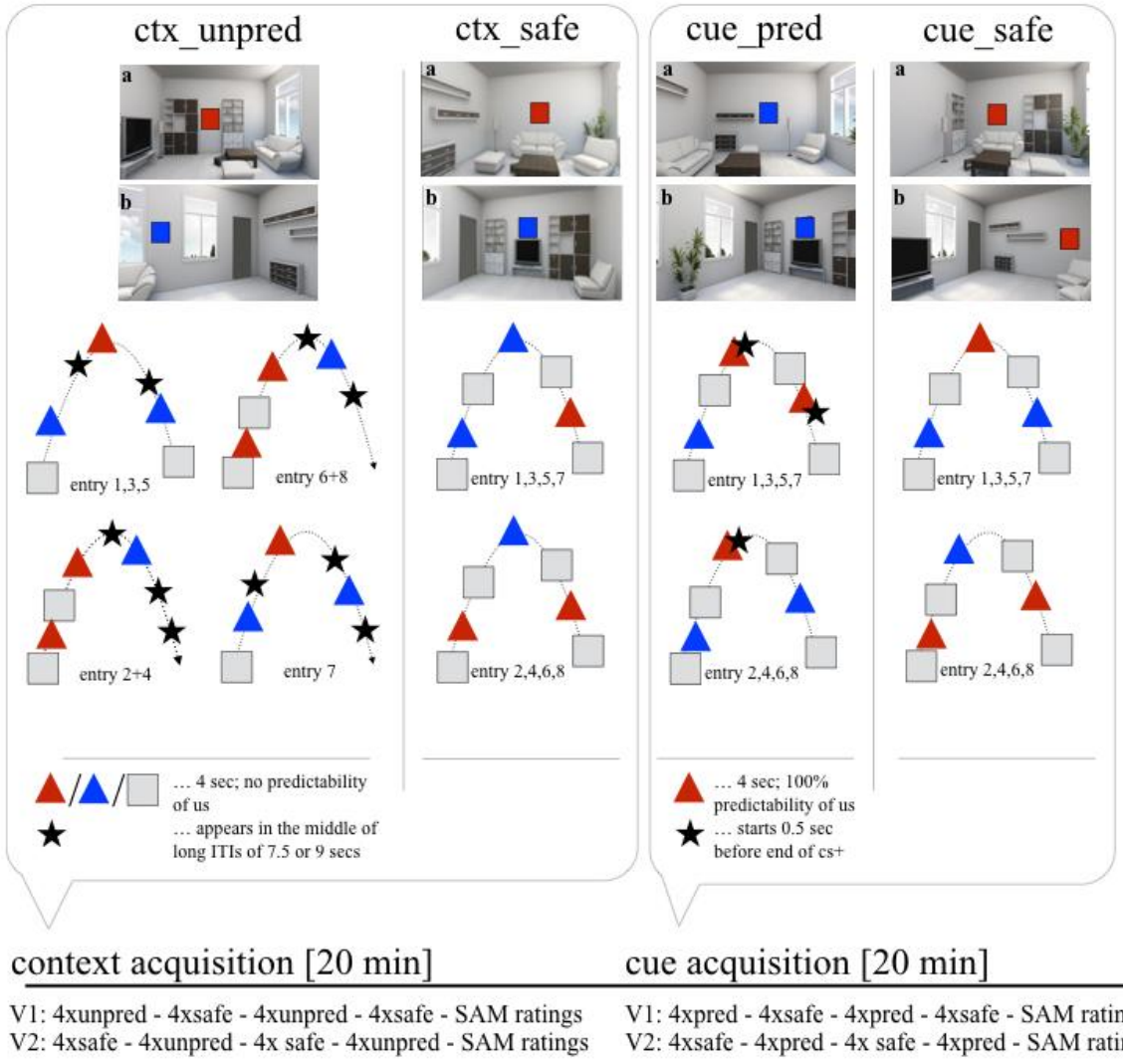
2.3 Stimuli and experimental procedure

During the experimental phase of this combined cue and context conditioning paradigm, participants were passively navigated through virtual contexts (living rooms) on a parabola shaped trajectory with a constant slow-paced walking speed of 0.45 km/h and an egocentric viewpoint (see *Figure 1*). The perspective rotated slightly from right to left and right again, so that each of the four walls was entirely visible at least once. The virtual contexts consisted of several objects (bookshelves, chest of drawers, floor lamp, potted plant, racks, seating corner, television, see *Figure 1*) and were built using an online software toolbox Open-Source Graphics Rendering Engine (OGRE; www.ogre3d.org) and the support of a software company (Glodeck Software GmbH) using Visual Studio Professional (2010, Redmond, WA, USA). The arrangement of the objects differed for each context. Two colored squares, serving as CS+ and CS-, were presented on the walls of each context in a counterbalanced fashion and were built in Microsoft Office Power Point (2007, Redmond, WA, USA). The virtual contexts were presented on a Dell laptop (Dell Precision M4600; Round Rock, Texas, USA) with a HMD (Trivisio Scout, Kaiserslautern, Rheinland-Pfalz, Germany) outside the scanner and MRI suitable goggles (VisuaStimDigital, Northridge, California, USA) inside the scanner using the same laptop in both cases with a resolution of 800x600 pixels. Ratings were

performed on the laptop keyboard during habituation and on a four button optical response pad (Current Designs, Philadelphia, Pennsylvania, USA) during acquisition and extinction.

A total of four different contexts (context unpredictable [ctx_unpred], context safe [ctx_safectx], cue predictable [cue_pred], cue safe [cue_safe]) and two different cues (CS+, CS-) were presented during habituation, acquisition and extinction. Each of the four main experimental conditions (context and cue acquisition, context and cue extinction) consisted of 8 room entries per condition following a block design (e.g. context acquisition: 4 x ctx_unpred – 4 x ctx_safe - 4 x cue_pred – 4 x cue_safe). The order of appearance of rooms within each block and of the CSs were counterbalanced using an original (context acquisition: 2 x ctx_unpred-ctx_safe; cue acquisition: 2 x cue_pred-cue_safe) and parallel (context acquisition: 2 x ctx_safe- ctx_unpred; cue acquisition: 2 x cue_safe-cue_pred) version of the experiment. During a pilot study participants had difficulties acquiring the context conditioning with a preceding cue conditioning. We therefore decided to keep the order in which the conditions appeared on each day steady with context acquisition/ extinction appearing before cue acquisition/ extinction (see *Figure 1*).

Habituation. During habituation (HAB) participants were passively walked through all four rooms twice and were instructed to pay attention to the interior design of each context. At the end participants were asked “How many different architects designed the rooms?” to guarantee that participants payed attention and could differentiate between the contexts. Furthermore, participants saw each CS separately for 4s with an inter-trial-interval (ITI) of 2s in front of a grey background and included within each context. Participants then rated the arousal, valence and contingency of each context, CS and context with CS on a seven point scale using self-assessment manikins (SAM; 24). In addition, participants’ pain thresholds and the intensity of the painful stimulation were determined (see *Suppl. Methods*), followed by a habituation of the US.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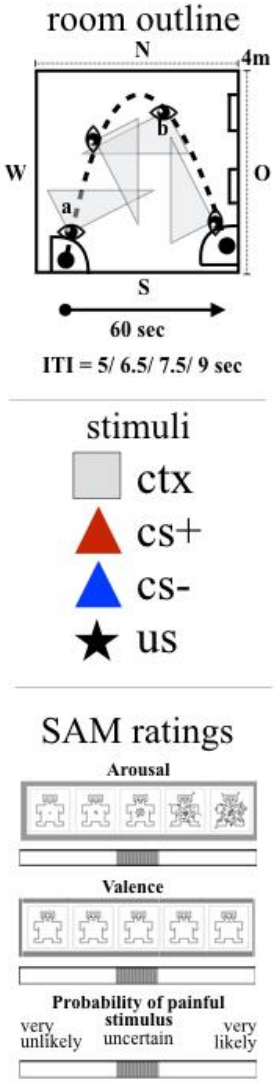
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uncertain
very likely

Figure 1. Paradigm across each of the four conditions (CTX_unpred, CTX_safe, CUE_pred, CUE_safe) exemplary for both acquisition phases.

[Abbreviations: CS – conditioned stimulus; CTX – Context; pred – Predictable; ITI – Inter-Trial-Interval; SAM – self-assessment manikin; unpred – Unpredictable; US – unconditioned stimulus]

Acquisition (see *Figure 1*). During context acquisition, participants were walked through two different contexts, one so called unpredictable (ctx_unpred) and one safe (ctx_safe) context. In the *ctx_unpred* condition, a US was presented at different points in time appearing in the middle of long ITIs between the CTX/CS+/CS- stimuli of 7.5-9 seconds. The CS+ and CS- were presented one to two times per room for four seconds each with additional CTX triggers in each condition. None of the stimuli predicted the appearance of the US in the *ctx_unpred* condition. The *ctx_safe* condition was identical to the *ctx_unpred* except that there was no US presented. At the end of both acquisition phases, participants rated each stimulus (CTX/CS+/CS-) and a combination of them (e.g. CS+ in *ctx_safe*) on the SAM (25) for arousal and valence and the probability of a painful stimulus on a visual analogue scale. During cue acquisition, participants were presented with another two contexts, the so-called predictable (*cue_pred*) and safe (*cue_safe*) context. In the *cue_pred* condition, the 4s presentation of one of the two colored squares (blue/red) was followed by the presentation of the US, which started 0.5 seconds before the end of the CS+. During the *cue_safe* condition, participants received no painful stimulus.

Extinction. The extinction phase consisted of the same four conditions, as the acquisition phase (*ctx_unpred_ext*; *ctx_safe_ext*; *cue_pred_ext*; *cue_safe_ext*) except that participants received no painful stimulus in either condition.

2.4 Skin Conductance

Skin Conductance Response (SCR) was continuously recorded separately for each condition on the medial, inner side of the left foot using two silver/ silver chloride electrodes. SCRs were recorded with a galvanic skin response magnetic resonance module and Brain Amp Amplifier and Brain Vision Recorder 1.05 (Brainproducts, Munich, Germany). The sampling rate was 5000 Hz, filters were DC and 250 Hz, which we downsampled to 10 Hz using Brain

Vision Analyzer 2.0 (Brainproducts, Munich, Germany). After manual artefact correction using Ledalab V3.4.9 (www.ledalab.de) in Matlab R2016a (The MathWorks Inc., Natick, MA, USA), smoothing with a Gaussian window width of 40 samples, a 6-fold optimization was applied to perform a continuous decomposition analysis (26). A response window of 1-7.5s after stimulus onset was chosen (27) with a minimum threshold criterion of 0.01 µS. The data was normalized using a logarithmic ($y = \log(x + 1)$) transformation.

2.5 Clinical and neuropsychological assessments and self-reports

A more detailed description of all assessments and self-reports described in this section can be found in *Suppl. Methods*.

2.5.1 Clinical assessments

All participants were assessed for their handedness using the Edinburgh Handedness Inventory (EHI; (28)) and for color blindness using the Ishihara color-blindness test (29). Trauma severity and characteristics of PTSD symptomatology were assessed with the CAPS (21). In addition we assessed potential maltreatment during childhood with the Childhood Trauma Questionnaire (CTQ; (30)). The German long version of the Center for Epidemiological Studies Depression Scale (ADS; (31)) was used to assess depression. Trait anxiety was assessed using the trait-version of the State-Trait-Anxiety-Inventory (STAI-T; (32)). The Neuroticism-Extraversion-Openness to experience Five-Factor Inventory (NEO-FFI; (33)) was employed to assess personality traits. In addition, any kind of medication, psychopharmacological or non-psychopharmacological, was recorded.

2.5.2 Neuropsychological assessments and Debriefing

On day two, we assessed general intelligence (IQ) with the "Kurztest für allgemeine Basisgrößen der Informationsverarbeitung" [Short Test for General Factors of Information Processing] (KAI; (34)) and the Culture Fair Intelligence Test (CFT; (35); see *Table 1*). Four subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB®

[Cognitive assessment software]. Cambridge Cognition (2019). www.cantab.com) were applied including the test on Pattern Recognition Memory (PRM), Spatial Span (SSP), Paired Associates Learning (PAL) and the Spatial Recognition Memory (SRM; *Suppl. Methods, Suppl. Table 1*). After acquisition, participants completed a debriefing questionnaire (see *Suppl. Methods* for details).

2.6 MRI Data Acquisitions

Blood-oxygenation-level-dependent (BOLD) contrasts of whole-brain functional images were acquired using a T2*-weighted Gradient-Echo-Planar Imaging (EPI) sequence (protocol parameters: TR = 2700 ms; TE = 27 ms; matrix size = 96 x 96; field of view = 220 x 220 mm^2; flip angle = 90°; GRAPPA PAT 2; sequence length: 19:02min). Each of the 420 volumes per condition consisted of 40 axial slices (slice thickness = 2.3 mm; gap = 0.7 mm; voxel size = 2.3 mm^3) measured in interleaved, descending slice order and positioned along a tilted line to the anterior-posterior commissure (AC-PC orientation). An automated high-order shimming technique was used to maximize magnetic field homogeneity. The fMRI data was analyzed using Statistical Parametric Mapping (SPM12; Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB R2016a (The MathWorks Inc., Natick, MA, USA).

2.7 Statistical analysis

The fMRI data were analyzed using Statistical Parametric Mapping (SPM12; Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB R2016a (The MathWorks Inc., Natick, MA, USA). Before preprocessing, the first five volumes of each scanning session were discarded to allow for T_1 equilibration effects. Participants were excluded in case their motion parameter estimates exceeded 2.3 mm in x-, y-, or z-direction and a maximum of 1° of any angular motion throughout the course of the

scan. Preprocessing included realignment, normalization to the standard space of the Montreal Neurological Institute (MNI; SPM12 template), slice time correction to reference slice one, coregistration of structural and functional volumes and smoothing of each functional volume with a 8.0 x 8.0 x 8.0 mm^3 Gaussian kernel. On the first level, we set up four different general linear models (GLM), one for each phase (context acquisition, cue acquisition, context extinction, cue extinction) including the following six experimental predictors in each model: 1) conditioned fear context [CTX+], 2) conditioned safety context [CTX-], 3) conditioned fear cue in fear context [CS+ in CTX+], 4) conditioned fear cue in safety context [CS+ in CTX-], 5) conditioned safety cue in fear context [CS- in CTX+], 6) conditioned safety cue in safety context [CS- in CTX-]. As an example, for the context conditioning phase this resulted in the following six predictors: ctx_unpred, ctx_safe, cs+ (in ctx_unpred), cs+ (in ctx_safe), cs- (in ctx_unpred), cs- (in ctx_safe). In addition, each model contained six parameters describing the rigid body transformation to account for head motion (in mm: x-, y-, z-direction; in degrees: pitch-, roll-, yaw-direction).

All statistical analyses were performed in R-Statistics (36). Data were assessed for outliers, normal distribution, homoscedasticity, multicollinearity. All assumptions were met, if not mentioned otherwise below. Descriptive data were analyzed with analyses of variance (ANOVAs; e.g. age) or independent t-tests in case of two sample comparisons (e.g. trauma diagnostics). Chi-squared tests were performed to assess statistical differences in frequency distributions (e.g. sex). For the analyses of the self-report ratings (arousal, valence, contingency) and the SCR we performed two separate analyses each. In case of the self-report ratings, we performed a 3 (Groups) x 3 (Phase: HAB, ACQ, EXT) repeated measures ANOVA (rmANOVA) for each of the four contexts. For the difference scores (CS+-CS-) of the ratings, we performed two separate 3 (Groups) x 2 (condition: context or cue) rmANOVAs, one for the acquisition and one for the extinction phase. In case of the SCRs, we

performed four different 3 (Groups) x 2 (contexts: e.g. ctx_unpred and ctx_safe) rmANOVAs, one for each phase (ACQ or EXT) and condition (context or cue). The difference scores (CS+-CS-) of the SCRs were calculated in a similar fashion with four separate 3 (Groups) x 2 (contexts: e.g. ctx_unpred and ctx_safe) rmANOVAs. Finally, for the ROI analyses we assessed group differences with independent t-tests between PTSD and HCs or PTSD and TCs, separately for the contexts of interest (*ctx_unpred*, *cue_pred*) and the three ROIs (Hippocampi, vmPFC, Amgdalae). We applied Bonferroni corrections to counteract Type 1 errors due to multiple comparisons. We further applied Tukey's honestly significant difference (Tukey's HSD) test as post-hoc single-step comparison procedure. We report the sample size for each type of analysis. There were few cases of missing data, motion artefacts or outliers for each analysis. These are reported in the results section.

			Groups												Analysis				
			PTSD [N=20]				TC [N=21]				HC [N=22]								
			M	*SD*	*n*	*(%)*	*M*	*SD*	*n*	*(%)*	*M*	*SD*	*n*	*(%)*	X^2	*F*	*T*	*Df*	*p*
Demographics																			
Sex (female)					10	50.0			9	42.9			11	50.0	0.29			2	.87
Age (in years)			45.4	11.3	20		40.9	12.4	21		40.6	11.2	22			1.09		2	.34
Education	<=12 years				12	60.0			6	28.6			4	18.2	9.67			2	.008**
	>12 years				7	35.0			15	71.4			18	81.8					Post-hoc: .015; PTSD≠TC+HC
Handedness		Right/Left/Both			13/5/2				15/3/3				16/4/2		1.03			4	.91
Intelligence quotients		KAI	102.6	12.1	17		114.1	14.8	21		110.0	16.3	21			2.92		2	.062
		CFT	114.7	20.1	18		120.9	10.3	21		118.5	10.9	21			0.94		2	.40
Trauma severity																			
Time since trauma (in years)			9.2	7.3	15		14.6	9.3	14								1.75	24.7	.09
Type of traumatic event (index trauma)	Caused voluntarily	**Total (caused voluntarily)**			11	55.0			9	42.9					0.61			1	.44
		(1) Imprisonment			0				0										
		(2) Physical violence			3				1										
		(3) Sexual abuse			3				2										
		(4) Rape			0				3										
		(5) Wartime experience			3				0										
		(6) Witness of sudden death/ serious injury of so.			2				1										
		(7) Other experiences			0				2										
	Caused involuntarily	**Total (caused involuntarily)**			9	45.0			12	57.1									
		(1) Natural disaster			0				1										
		(2) Fire or explosion			0				0										
		(3) Accident			9				7										
		(4) Sudden death of so.			0				4										
		(5) Other experiences			0				0										

		Groups												Analyses								
		PTSD [N=20]				TC [N=21]				HC [N=22]												
		M	*SD*	*n*	*(%)*	*M*	*SD*	*n*	*(%)*	*M*	*SD*	*n*	*(%)*	X^2	*F*	*T*	*Df*	*p*	*Cont.*	*Diff,*	*CI [-95%; +95%]*	$p_{Tukey\ HSD}$	*Hedges' g*
Trauma diagnostics																							
CAPS Combined		61.3	19.0	20		12.0	15.7	21								9.02	36.9	<.001					
CAPS Severity		30.2	10.3	20		7.4	9.9	21								7.20	37.9	<.001					
CAPS Frequency		31.1	9.9	20		5.0	7.3	21								9.56	35.1	<.001					
CTQ		47.5	17.3	19		41.0	12.9	21		36.3	11.7	22			3.27		2	.045	T-H	4.7	-5.6; 15.0	.52	0.38
																			P-H	11.2	0.7; 21.8	.035	0.77
																			P-T	6.5	-4.1; 17.2	.31	0.43
Comorbidities																							
Other Axis I disorders	Yes/No			13/7				6/15				0/22		21.05			2	<.001					
Other Axis II disorders	Yes/No			6/14				0/22				0/22		14.26			2	<.001					
ADS		25.5	10.6	19		13.7	11.3	21		5.77	4.34	22			23.58		2	<.001	T-H	7.9	1.2; 14.6	.018	0.94
																			P-H	19.7	12.8; 26.6	<.001	2.51
																			P-T	11.8	4.8; 18.8	<.001	1.08
STAI-T		52.5	11.5	19		40.4	12.3	21		31.3	7.7	22			20.28		2	<.001	T-H	9.1	1.3; 16.9	.019	0.89
																			P-H	21.2	13.2; 29.2	<.001	2.17
																			P-T	12.1	4.0; 20.2	.002	0.99
Medication	**Total (yes)**			3	15.0			4	19.0			1	4.6	2.18			2	.34					
	Psychopharmacological[1]			1				2				0											
	Non-Psychopharmacological[2]			2				2				1											
	Total (no)			17	85.0			17	71.4			21	95.4										

Table 1. Demographic and clinical Characteristics of study sample.

[**Abbreviations:** ADS – Allgemeine Depressionsskala [Centre for Epidemiological Studies Depression Scale (CESD)]; CAPS – Clinician-Administered PTSD Scale; CFT – Culture Fair Intelligence Test; CTQ – Childhood Trauma Questionnaire; HC – Group of healthy control subjects, who have never experienced anything traumatic in their lives; KAI – Kurztest für allgemeine Basisgrößen der Informationsverarbeitung [Short Test for General Factors of Information Processing]; STAI-T – State-Trait Anxiety Inventory – Trait Anxiety; TC – Group of trauma control subjects, who have at least experienced one traumatic event but do not fullfill the criteria for PTSD; [1]Psychopharmacological: Pregabalin; Quetiapine; Tetrahydrocannabinol; [2]Non-Psychopharmacological: Contraceptive pill; Levothyroxine; Mesalazine; Prednisolone]

3 Results

3.1 Sample characteristics

The experimental groups did not significantly differ in any of the demographic variables except for education ($X^2(2, 62) = 9.67$, $p = .008$). A post-hoc chi-square test of independence revealed that the level of education was unequal between patients with PTSD and the TC and HC group, respectively ($p = .015$; see *Table 1* for details), as previously shown. All detailed information on demographics, trauma severity, PTSD assessment and comorbidities can be found in *Table 1* and the *Suppl. Results*. In addition, we describe more detailed results on personality traits and neuropsychological assessment in *Suppl. Table 1* and in the *Suppl. Results*. There was no significant difference between the experimental groups on any of the seven evaluation and debriefing questions (see *Suppl. Methods*) concerning the difficulty of the study (*Suppl. Table 2* and *Suppl. Results*).

3.2 Self-reports

Ratings across contexts. We found significant main effects of phase (HAB, ACQ, EXT) across all four contexts for the arousal and contingency ratings with the highest scores during acquisition and the lowest scores during extinction. For the valence ratings, we found a significant main effect of phase for *ctx_unpred* and a significant group x phase interaction (see *Suppl. Figure 2a, Suppl. Table 3b-d*). We could not confirm our first hypothesis that patients with PTSD in comparison to HC and TC subjects report higher arousal, valence and contingency ratings during the unpredictable context. There was also no difference in the ratings between the groups for the predictable context.

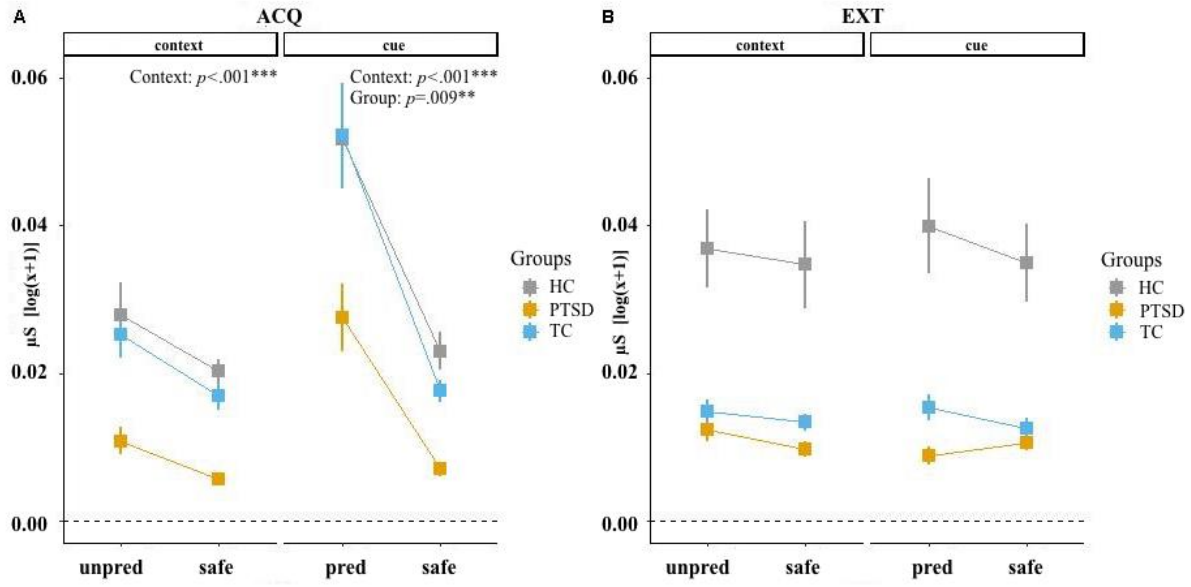

Figure 2. SCRs across each of the four conditions (CTX_unpred, CTX_safe, CUE_pred, CUE_safe), two phases (ACQ, EXT) and each group (HC, PTSD, TC). A) ACQ phase. B) EXT phase.

[**Abbreviations**: ACQ – Acquisition; CTX – Context; EXT – Extinction; HC – Healthy control subjects without trauma experience; pred – Predictable; PTSD – patients with PTSD; SCR – Skin conductance response; TC – healthy control subjects with trauma experience; unpred – Unpredictable]

Differences in ratings between CS+ - CS-. There were significant main effects of phase during acquisition for ratings of arousal ($F_{phase}(1, 56) = 39.13$, $p < .001$), valence ($F_{phase}(1, 56) = 21.54$, $p < .001$) and contingency ($F_{phase}(1, 56) = 42.89$, $p < .001$). There were neither other significant main effects of phase or group, nor any significant interaction of group x phase (see *Suppl. Figure 2b*, *Suppl. Table 3e*).

3.3 Skin Conductance

SCR across contexts. During acquisition, there was a significant main effect for context during context ($F_{context}(1, 36) = 14.55$, $p < .001$) and cue acquisition ($F_{context}(1, 34) = 66.07$, $p < .001$), as well as a main effect of group during cue acquisition ($F_{group}(2, 34) = 5.45$, $p < .009$). We did not find a significant main effect of group during the context condition, neither any interaction of group x context (see *Figure 2* and *Suppl. Table 4a* for details). We could

not confirm our second hypothesis that patients with PTSD in comparison to HC and TC subjects show an elevated SCR during context conditioning of the context unpredictable. However, we found a significantly lower SCR during cue conditioning for patients with PTSD in comparison to the two healthy control groups during the context predictable.

Differences in SCRs between CS+ - CS-. During acquisition, we found a significant main effect of group for the mean difference of CS+-CS- during context acquisition ($F_{group}(2, 36) = 3.93$, $p = .029$) and a main effect of context during cue acquisition ($F_{context}(1, 34) = 62.59$, $p < .001$). Patients with PTSD and TC subjects showed a significantly lower difference score than HC subjects during context acquisition. During cue acquisition, groups did not significantly differ in their difference scores but showed higher scores in the unpredictable context than in the *cue_safe* context, as predicted. There was no other significant main effect or interaction of group x context. During context extinction, we found a significant main effect of context for the mean difference of CS+-CS- ($F_{context}(1, 35) = 5.47$, $p = .025$). There was no other significant main effect of interaction of group x context (see *Suppl Figure 3* and *Suppl. Table 4b*).

3.4 Functional magnetic resonance imaging

Context unpredictable. We compared the beta values in the hippocampi during acquisition in the *ctx_unpred* condition and found no significant difference between patients with PTSD and HC ($T(30) = -1.87$, $p = .07$) or TC subjects ($T(33) = -1.11$, $p = .28$). Comparing the beta values in the vmPFC during *ctx_unpred*, we found significantly lower beta values for patients with PTSD in comparison to HC ($T(30) = -2.15$, $p = .040$, $p_{bonf.cor.} = .08$), which, however, did not survive Bonferroni correction. Here, we also observed marginally significantly lower beta values in the vmPFC between patients with PTSD and TC subjects ($T(33) = -2.02$, $p = .051$, $p_{bonf.cor.} = .10$). Finally, we compared the beta values within the amygdalae during acquisition in the *ctx_unpred* condition and found no significant difference between patients with PTSD

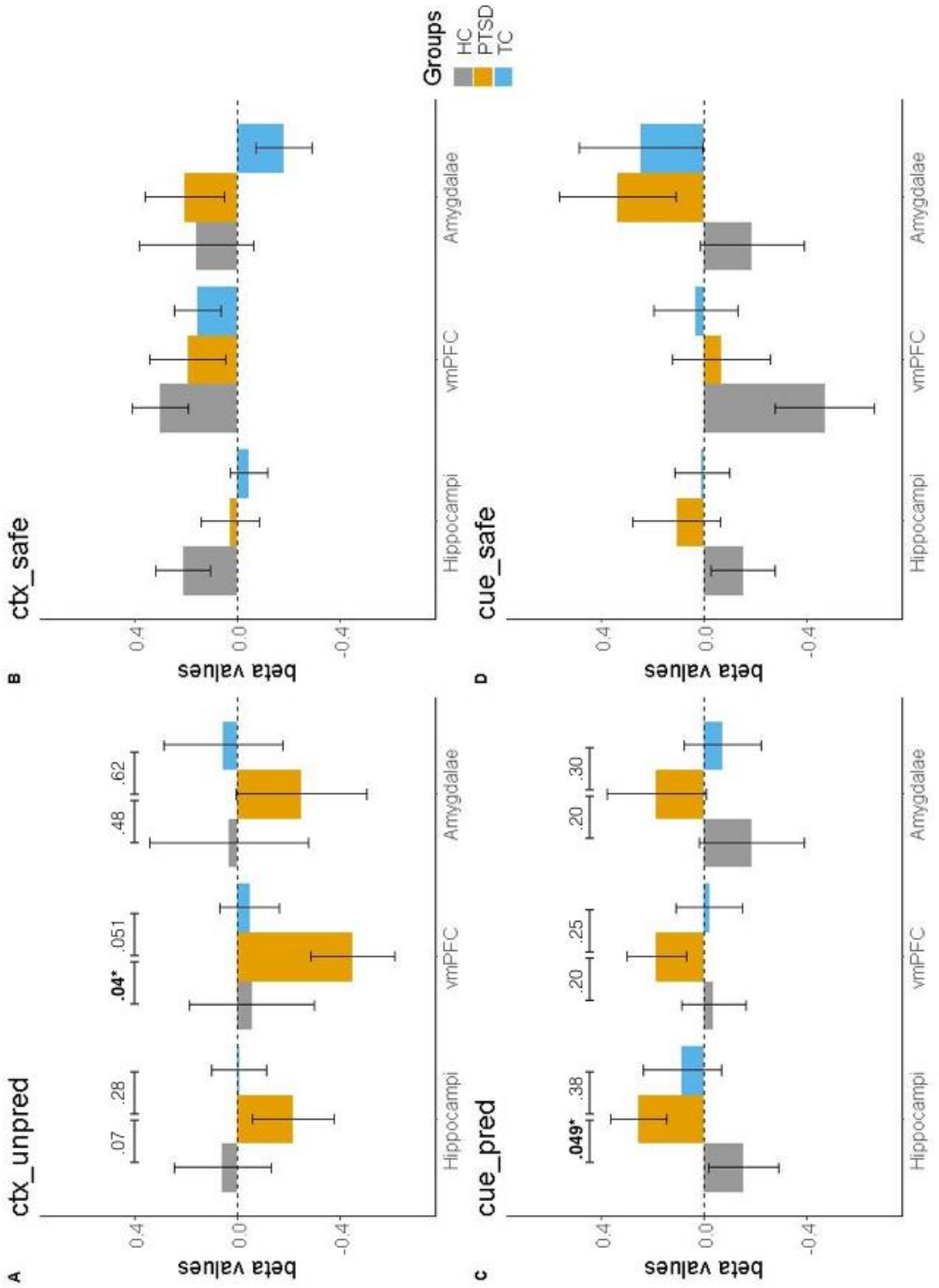
A
ctx_unpred
B
ctx_safe
C
cue_pred
D
cue_safe
beta values
0.4
0.0
-0.4
Hippocampi
vmPFC
Amygdalae
.07
.28
.04*
.051
.48
.62
.049*
.38
.20
.25
.20
.30
Groups
HC
PTSD
TC

Figure 3. Extracted beta values for Region-of-Interest (ROI) analyses on the hippocampi, amygdalae and vmPFC during acquisition and for each group (HC, PTSD, TC). A) During context unpredictable (ctx_unpred). B) During context safe (ctx_safe). C) During cue predictable (cue_pred). D) During cue safe (cue_safe).

$\alpha_{bonferroni\_cor} = .05/2 = .025$

[**Abbreviations:** CTX – Context; HC – Healthy control subjects without trauma experience; pred – Predictable; PTSD – patients with PTSD; TC – healthy control subjects with trauma experience; unpred – Unpredictable]

and HC ($T(31) = -0.71$, $p = .48$) or TC subjects ($T(33) = -0.51$, $p = .62$; see *Figure 3a* and *Suppl. Table 5a* for details). There were no significant differences in betas values during the context safe condition (see *Suppl. Table 5b*).

Cue predictable. In addition, we compared the beta values in the hippocampi during acquisition in the *cue_pred* condition and found significantly lower beta values for patients with PTSD in comparison to HC ($T(30) = 2.05$, $p = .049$, $p_{bonf.cor.} = .10$), which, however, did not survive Bonferroni correction. There was no significant difference between patients with PTSD and TC subjects ($T(33) = 0.90$, $p = .38$). Within the vmPFC, we did not find any significant differences in the beta values during acquisition in the *cue_pred* condition between patients with PTSD and HC ($T(31) = 1.31$, $p = .20$) or TC subjects ($T(33) = 1.18$, $p = .25$). Lastly, we also did not find a significant difference in beta values of the amygdalae during acquisition in the *cue_pred* condition between patients with PTSD and HC ($T(31) = 1.32$, $p = .20$) or TC subjects ($T(33) = 1.06$, $p = .30$; see *Figure 3b* and *Suppl. Table 5a* for details). There were no significant differences in betas values during the cue safe condition (see *Suppl. Table 5b*).

4 Discussion

The present study investigated behavioral and physiological differences in cued- and uncued-contextual fear acquisition in patients with PTSD in comparison to healthy trauma or non-trauma exposed control subjects. During uncued-context conditioning (unpredictable), patients with PTSD showed a marginally significantly lower ROI activity in the vmPFC, but showed similar arousal, valence, contingency ratings and SCRs in comparison to the two control groups. The difference in the vmPFC did not survive Bonferroni correction. During cued context conditioning (predictable), patients with PTSD showed a marginally significantly higher ROI activity in the hippocampi, and lower SCR across both contexts than TC and HC subjects. There were no significant differences between the groups in the behavioral ratings for the contexts or the differential cue learning. Our results point towards two distinct systems in play, namely an elemental and configural learning, with the first being intact in patients with PTSD and the latter being impaired.

Using a novel combined cue-context conditioning paradigm, which contrasted cued- and uncued context conditioning, we could partly confirm our hypothesis that patients with PTSD show difficulties in discriminating uncued safe and dangerous contexts from each other during fear acquisition. Lower BOLD activity in the vmPFC in patients with PTSD in the unpredictable but not the safe context are in line with previous studies finding similar results with healthy individuals who score high on trait anxiety (7). Animal and human studies on context conditioning (3), found a downregulation of the vmPFC in combination with a downregulation of the hippocampus, primarily to be associated with context extinction or retrieval (9,10). Our findings point in the direction that the vmPFC might already play a role in fear acquisition (37). If this is the case, one would assume that less recruitment of the vmPFC in the unpredictable context might lead to an increased fear response measured behaviorally or via SCR (7). However, we did not observe an elevated SCR or higher arousal or valence ratings during context conditioning in patients with PTSD in comparison to TC and

HC subjects. This is in contrast to previous studies that found differences in behavioral ratings and functional brain activity in patients with PTSD in comparison to TC and HC subjects (12). Here, patients with PTSD showed an increased fear to the safe and dangerous context in both cued and uncued conditions. However, this study mainly focused on extinction and extinction recall.

While we did not find any significant differences in the brain activity of the hippocampi and amygdalae between the groups during uncued-contextual fear acquisition, we did so for the hippocampi during cued-contextual fear acquisition. We found a marginally significantly higher activity of the hippocampi in patients with PTSD in comparison to HC but not TC in the predictable context. This suggests a higher recruitment of memory related-context processing of the environment in which the cue is predictive of the US within a dangerous context (3). The characteristics of a combined cue-context conditioning protocol suggest that participants would have to keep in mind the contexts learned during context conditioning, while processing the cues in the second phase. In our particular case, the uncued-context conditioning phase always preceded the cued-context conditioning phase. Interestingly, patients with PTSD in comparison to HC already show a marginally significantly lower BOLD activity in the hippocampi in the unpredictable context during context conditioning. Lower activity in both regions of interest, the hippocampus and the vmPFC, which are essential for encoding a configural memory representation, could lead to an insufficient context encoding. This could further lead to an insufficant extinction of fear on the second day, which most studies on contextual fear conditioning investigating patients with PTSD report (3). In a next step, we will assess extinction learning of cued and uncued contextual learning. A follow-up analysis should be applied to a) investigate within group differences between cued and uncued contextual conditioning and b) to assess differences in

between group connectivity in the hippocampal-vmPFC connectivity during each condition and its association with SCR and behavioral ratings.

4.1 Limitations

Two main limitations apply to our study comprising aspects of the study design and concerning non responders. Whereas the complexity of the design allows for the simultaneous examination of context and cue related triggers and their interaction, the design limits the choice of where to select the context triggers from in a given environment. To minimize overlapping, or additive, effects in SCR or BOLD activity, the triggers had to be far enough apart from each other (see Figure 1). This, however, extended each trial to 50 secs, which in turn limited our total number of trials per given condition to eight. With this rather low number of trials, each missing data point became a potential dropout. This issue was further exacerbated by the interdependence of the triggers in the unpredictable context. Here, almost each trial represented a unique composition of positions for the CSs, US and context triggers. A fear response in a given context is most likely not limited to a single predictive cue or multiple contextual features but might also generalize to objects being non-predictive to the occurrence of the painful stimulus. This is, however, a known issue in the community and not limited to our study (27) and the presented results have to be interpreted within the boundaries of the study design. A second limitation concerns a rather high number of potential non-responders in the SCR. The SCR was measured on the foot instead of the hand of participants, because participants received the painful stimulus on the left hand and responded with the response pad on the right hand. The signal on the foot might not have been strong enough. A potential solution could be to measure SCR on the shoulder instead (38). This would have to be tested in a follow-up study.

4.2 Conclusions

In this cross-sectional study, we show that patients with PTSD in comparison to TC but not HC subjects show lower functional brain activity in the vmPFC during an unpredictable contextual and higher functional brain activity in the hippocampi during a predictable contextual fear acquisition. Our results support the model that patients with PTSD show deficiencies in configural learning. Future studies are needed to investigate if the alterations in configural learning are a predisposing factor of PTSD or establish after trauma exposure. Finally, trauma focused exposure-based treatments that focus on conjunctive integration of features within traumatic memories during exposure might benefit from an enhanced activation of the vmPFC during exposure.

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Supplemental Information

Supplemental methods

Participants

We recruited participants through the outpatient clinic of the Institute of Cognitive and Clinical Neuroscience and advertisement on the recruitment website of the Central Institute of Mental Health in Mannheim. In addition, we recruited patients from local psychotherapy and psychiatry practices as well as local clinics and outpatient units. Prior to testing, a telephone screening was conducted with all participants. The following exclusion criteria were applied: any traumatic experience before the age of 18 years, borderline personality disorder, comorbid current or lifetime psychotic symptoms, current substance dependence or abuse, cardiovascular or neurological disorders, acute pain, continuous pain or medication for attention deficit hyperactivity disorder, pregnancy and metal implants.

Procedure and study design

The electric stimulus was delivered through a cupric (copper) electrode attached to the participants' right hand by an electrical stimulus generator (Digitimer, DS7A, Welwyn Garden City, UK). Increasingly painful stimuli (50 ms bursts, 12 Hz) were administered to participants to obtain the pain threshold and tolerance. The pain intensity and unpleasantness was rated by participants on a Likert scale ranging from 0 (not at all painful/ not at all unpleasant) to 10 (extremely painful/ extremely unpleasant). Participants were asked to rate when a) they felt the electrical stimulus at all, b) when the pain intensity reached seven out of ten points for them and c) when the pain intensity reached an unbearable level (nine out of ten). This procedure was repeated three times in order to obtain a value of 80% of the pain

tolerance. To achieve this, the values of the last two runs were entered into the following formula:

$$[(Mean_{pain\_tolerance} - Mean_{pain\_threshold}) * 0.8] + pain\_threshold$$

In case, participants did not rate the pain as aversive after the habituation phase, we increased the intensity by 0.4 mA.

Clinical and neuropsychological assessments and self-reports

Handedness. The Edinburg Handedness Inventory (EHI; Oldfield, 1971) is a self-report questionnaire in which participant report with which hand they perform a series of sixteen tasks (e.g. writing, holding a spoon). Participants are requested to put a "+" in the column (left hand or right hand) with which they perform the task. If both hands are used for the completion of the task, participants mark this with a "+" in both columns and if exclusively one hand is used, participants mark this with "++" in one of the columns. The "+" are counted and a sum score is built to highlight the dominant hand.

Color-blindness. Participants completed the Ishihara color-blindness test (Ishihara, 1987) which consists of 19 colored dotted items, each depicting a letter, a number or a combination of both. The test separately assesses red-green (15 items) and blue-yellow (three items) color blindness.

Intelligence Testing. The Intelligence score was estimated with a subtest of the Cattell Culture Fair Intelligence Test (CFT, Weiß, 1998) and the „Kurztest für allgemeine Basisgrößen der Informationsverarbeitung" [Short Test for General Factors of Information Processing] (KAI; Lehrl, Gallwitz, Blaha, Ebersberg, & 1991). In the CFT, participants completed four tests with increasing difficulty. Each test consisted of eight to fourteen questions, in which participants were asked to recognize a pattern/rule within a sequence of figures and apply this rule to either complete the row or figure out "the odd one in the row".

The number of correct responses of all four tests is summed up and the IQ is taken from a table based on a validation sample. In the KAI, participants had to remember a sequence of numbers and digits, starting from three up to the maximum of nine in a row. The test ended when participants could not recall the sequence correctly after the second time.

Posttraumatic Stress Disorder. To assess symptom severity, we used the German version of the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS; Blake et al., 1995; Schnyder & Moergeli, 2002). The CAPS combined score is calculated by summing the frequency and severity (or intensity) score, measured on two 5-point scales ranging from zero ("never"/ "none) to four ("most or all of the time"/ "extreme"). The CAPS combined score can range from 0 to 100, with either subscore ranging from 0 to 50.

Childhood Trauma Experience. The Childhood Trauma Questionnaire (CTQ; Bernstein, Fink, Handelsman, & Foote, 1994) is a 40 item self-report instrument assessing the severity of traumatic childhood experiences, such as emotional abuse and neglect, physical abuse and neglect as well as sexual abuse. The first 34 items ask how often each event occurred during the participant's upbringing and each item is rated on a 5-point Likert scale ranging from 1 ("never at all") to 5 ("very often"). For the purpose of this study, we only report the overall sum score, which is calculated by the sum of the five subscales. The overall score can range from 25 to 125. In the last six items, participants are asked to select the age or period in which the neglect or abuse occurred ranging from one to twenty years of age.

Time since trauma and the type of the index event were assessed with the interview on the severity of the trauma [Interview zur Traumaschwere]. The type of traumatic events are hereby subdivided into seven voluntarily (e.g. imprisonment, rape) or five involuntarily (e.g. natural disaster, accident) caused events.

Comorbidities. The German long version of the Center for Epidemiological Studies Depression Scale (ADS; Hautzinger & Bailer, 2003) was applied to assess possible comorbid impairment due to depressive symptoms within the last week. The ADS is a self-report questionnaire with 20 items measured on a 4-point scale ranging from zero ("rarely or not at all [less than one day]") to three ("most often, all of the time [on five to seven days]") with a sum score ranging from 0 to 60. Trait anxiety was assessed with the German version of the trait-version of the State-Trait-Anxiety-Inventory (STAI-T; Laux, 1981). The self-report questionnaire comprises of 20 questions, measured on a 4-point Likert scale ranging from one ("not at all") to four ("very much") with higher scores being associated with higher levels of trait anxiety and sum scores ranging from 20 to 80.

Personality Traits. The 60 item version of the Neuroticism-Extraversion-Openness to experience Five-Factor Inventory (NEO-FFI; Ostendorf & Angleitner, 2004; Costa & McCrae, 2008) was used to assess personality traits. Participants can rate each item on a 5-point Likert scale ranging from "strong rejection" to "strong approval". Five trait-dimensions of personality are depicted, namely neuroticism, extraversion, openness to experience, agreeableness and conscientiousness. A sum score is built for each of the five dimensions from twelve items each.

Neuropsychological assessments. Spatial learning and memory were tested with the Cambridge Neuropsychological Test Automated Battery (CANTAB® [Cognitive assessment software]. Cambridge Cognition (2019). All rights reserved. www.cantab.com). First, the Pattern Recognition Test (PRM) is a 2-choice forced discrimination paradigm assessing visual pattern recognition memory. In an initial learning phase, participants are presented with a series of complex visual patterns, one at a time. In a recognition phase, either directly after the testing phase or after a few minutes (delayed), participants have to choose between a novel pattern and a pattern which they have already seen. The outcome variables are the reaction

time of a participant's response (mean correct latency) and the accuracy of the responses (percent correct). Second, the Spatial Span (SSP) was assessed with a visuospatial working memory capacity paradigm. Here, participants have to first learn a sequence of two to nine squares that are arranged on the screen and are highlighted in color. They then have to select the squares in the correct order by clicking on the respective squares. When the sequence is correct, participants are presented with an additional square in the next sequence. The outcome variables are the longest sequence successfully recalled (span length), the number of errors (total errors) and the reaction time to the first and last response (speed of response). Third, the Spatial Recognition Memory (SRM) is also a 2-choice forced discrimination paradigm assessing visual-spatial recognition memory. In a learning phase, participants are presented with a sequence of white squares appearing at five different locations on the screen. In the recognition phase, participants are presented with pairs of white squares with one square being in a novel location and one square in a previously shown location. The outcome measures include, similarly to the PRM, the reaction time and accuracy of the responses. Finally, the Paired Associates Learning (PAL) assesses visual memory by showing one to six patterns in a range of white boxes on the screen. Participants have to remember the patterns and location where it appeared. As outcome measures, a memory score is calculated, the mean number of trials to success as well as the total number of trials and errors are measured.

Manipulation Check

Emotional state. Positive and negative affect were measured before and after the acquisition phase on day one and before and after the extinction phase on day two with the Positive And Negative Affective Schedule (PANAS; Watson, Clark, & Tellegen, 1988) and a six item Visual Analogue Scale (VAS). The PANAS has 20 items with ten items each concerning positive and negative affect. Responses are given on a 5-point forced choice scale ranging from 1 ("not at all") to 5 ("extremely"). The sum scores for each subscale can vary

between 10-50 points, with higher scores indicating higher positive/negative affect. The responses on the VAS ranged from 0 (“applies not at all”) to 10 (“applies completely”) with six items describing the current mood: 1) “high mood”, 2) “irritated”, 3) “balanced”, 4) “gloomy mood”, 5) “sluggish”, 6) “activated”.

Debriefing. A set of seven questions were asked at the end of habituation and acquisition on day one of the experiment. The questions were the following: 1) “How many different architects designed the rooms?”, 2) “How quickly did you manage to distinguish the rooms from each other?” with possible responses being “during context acquisition/ during cue acquisition/ not at all”, 3) “Did you find the instructions understandable?” with responses ranging from 1 (“difficult”) to 10 (“easy”), 4) “Did you find the ratings understandable?” with responses ranging from 1 (“difficult”) to 10 (“easy”), 5) “How well did you get along with the keyboard?” with responses ranging from 1 (“very badly”) to 10 (“very good”), 6) “How exhausting did you find the experiment?” from 1 (“very exhausting”) to 10 (“not exhausting at all”), 7) “How attentive were you during the experiment?” from 1 (“not at all”) to 10 (“very”).

Statistical Analysis

fMRI. A response window of 1-7s after stimulus onset for all parameters (ctx, cs+, cs-) was chosen for BOLD responses. We then extracted beta values from the first level from a priori defined ROIs, namely the hippocampi, the amygdalae and the vmPFC. The masks were taken from the Wake Forest University Pick Atlas 3.0.5b (Maldjian, Laurienti, Kraft, & Burdette, 2003) choosing bilaterally the hippocampi and amydalae from the Automated Anatomical Labeling Atlas (AAL; (Tzourio-Mazoyer et al., 2002)). For the vmPFC, we chose Brodmann areas (BA) 11, 12 and 25 (Wicking et al., 2016). Beta values were extracted directly from SPM12 with customized MATLAB scripts.

Supplemental results

Sample characteristics

Demographic Information. All detailed information can be found in *Table 1*. The sample did not significantly differ in the distribution of gender ($X^2(2, 63) = 0.29$, $p = .87$) with approximately 50% females in each group, nor in age ($F(2, 60) = 1.09$, $p = .34$) with participants' age ranging from 20 to 62 years across groups. The groups did significantly differ in the level of education ($X^2(2, 62) = 9.67$, $p = .008$) whereby the distribution of the level of education of patients with PTSD ($N_{\leq 12}$=12/ $N_{>12}$=7) was significantly lower from the two control groups ($p_{bonf.cor.} = .015$) as assessed by a chi-square post-hoc test. Finally, there were no significant differences between the groups in the distribution of handedness ($X^2(4, 62) = 1.03$, $p = .91$), or the intelligence quotients as assessed with the KAI ($F(2, 56) = 2.92$, $p = .06$; range 82 to 142) and the CFT ($F(2, 57) = 0.94$, $p = .40$; range 69 to 140; see *Table 1* for details).

Trauma severity. All detailed information can be found in *Table 1*. Time since trauma did not significantly differ between patients with PTSD and TC subjects ($T(24.7) = 1.75$, $p = .09$; 95% CI -.96 to 11.85), ranging from 1 to 30 years. The groups did also not significantly differ across the two types of traumatic events ($X^2(1, 41) = 0.61$, $p = .44$; see *Table 1* for details).

Trauma diagnostics. All detailed information can be found in *Table 1*. Patients with PTSD showed a significantly higher overall CAPS score than TC subjects ($T(36.9) = 9.02$, $p < .001$; 95% CI -60.38 to 38.22) as well as significantly higher CAPS severity ($T(37.9) = 7.20$, $p < .001$; 95% CI -29.34 to -16.46) and CAPS frequency ($T(35.1) = 9.56$, $p < .001$; 95% CI -31.58 to -20.52) scores. There was a significant difference in the CAPS score between the experimental groups ($F(2, 59) = 3.27$, $p = .045$), with patients with PTSD showing

significantly higher scores than TC subjects ($M_{Difference}$ = 11.2; 95% CI 0.7 to 21.8, p = .035; *Hedges'g* = 0.77; see *Table 1* for details).

Comorbidities. All detailed information can be found in *Table 1.* Patients with PTSD showed significantly higher numbers of comorbidities than both control groups, both on axis I (X^2(2, 63) = 21.05, p < .001) and on axis II disorders (X^2(2, 63) = 14.26, p < .001). Comorbidities on Axis I disorders were comprised of current major depressive disorder (MDD; N_{PTSD} = 10), previous MDD (N_{PTSD} = 8; N_{TC} = 2), general anxiety disorder (GAD; N_{PTSD} = 2), panic disorder (N_{PTSD} = 4; N_{TC} = 2) substance dependence (N_{PTSD} = 2; N_{TC} = 1) and alcohol abuse (N_{PTSD} = 1; N_{TC} = 2), previous manic episode (N_{PTSD} = 2), current dysthymia (N_{PTSD} = 1) and bulimia (N_{PTSD} = 1). Comorbidities on Axis II disorders for patients with PTSD comprised of avoidant personality disorder (N_{PTSD} = 4), obsessive-compulsive personality disorder (N_{PTSD} = 1) and depressive personality disorder (N_{PTSD} = 1; see *Table 1* for details). The groups differed significantly in their depression score (F(2, 59) = 23.58, p < .001; range 0 to 42) with post-hoc tests revealing significantly higher depression in patients with PTSD compared to TC ($M_{Difference}$ = 11.8; 95% CI 4.8 to 18.8, $p_{Tukey\ HSD}$ < .001; *Hedges'g* = 1.08), between patients with PTSD and HC ($M_{Difference}$ = 19.7; 95% CI 12.8 to 26.6, $p_{Tukey\ HSD}$ < .001; *Hedges'g* = 2.51) as well as between TC and HC ($M_{Difference}$ = 7.9; 95% CI 1.2 to 14.6, $p_{Tukey\ HSD}$ = .018; *Hedges'g* = 0.94; see *Table 1* for details). The groups also differed significantly in their STAI-T score (F(2, 59) = 20.28, p < .001; range 23 to 70) with post-hoc tests revealing a significantly higher STAI-T score between patients with PTSD and TC($M_{Difference}$ = 12.1; 95% CI 4.0 to 20.2, $p_{Tukey\ HSD}$ = .002; *Hedges'g* = 0.99), between patients with PTSD and HC ($M_{Difference}$ = 21.2; 95% CI 13.2 to 29.2, $p_{Tukey\ HSD}$ < .001; *Hedges'g* = 2.17) and between TC and HC ($M_{Difference}$ = 9.1; 95% CI 1.3 to 16.9, $p_{Tukey\ HSD}$ = .019; *Hedges'g* = 0.89; see *Table 1* for details). Finally, the experimental groups did not significantly differ in the distribution of intake of any prescribed medication (X^2(2, 63) = 2.18,

p = .34), with three subjects reporting the intake of low doses of psychopharmacological medication (N_{PTSD} = 1; N_{TC} = 2; longterm usage of Tetrahydrocannabinol, Pregabalin, Quetiapin), five subjects reporting the intake of non-psychopharmacological medication (N_{PTSD} = 2; N_{TC} = 2; N_{HC} = 1; contraceptive pill, L-Thyroxine, Mesalazine, Prednisolone) and 55 subjects reporting no intake of any medication; see *Table 1* for details).

Personality traits. All detailed information can be found in *Suppl. Table 1.* The experimental groups did not significantly differ on extraversion (F(2, 55) = 3.03, p = .056; range 6 to 43), openness to experience (F(2, 57) = 0.77, p = .47; range 10 to 45) and conscientiousness (F(2, 58) = 2.23, p = .12; range 17 to 45). They did, however, significantly differ on neuroticism (F(2, 56) = 12.87, p < .001; range 2 to 37), with post-hoc tests revealing a significantly higher neuroticism score for patients with PTSD versus TC ($M_{Difference}$ = 7.6; 95% CI 1.1 to 14.1, $p_{Tukey\ HSD}$ = .019; *Hedges'g* = 0.89), for patients with PTSD compared to HC ($M_{Difference}$ = 13.9; 95% CI 7.3 to 20.4, $p_{Tukey\ HSD}$ < .001; *Hedges'g* = 1.77) and a marginally significantly higher score for TC versus HC ($M_{Difference}$ = 6.3; 95% CI 0.0 to 12.6, $p_{Tukey\ HSD}$ = .051; *Hedges'g* = 0.77). The groups did also significantly differ on agreeableness (F(2, 56) = 4.98, p = .010; range 16 to 46), with post-hoc tests revealing significantly lower agreeableness scores for patients with PTSD versus HC ($M_{Difference}$ = -6.1; 95% CI -11.2 to -1.0, $p_{Tukey\ HSD}$ = .014; *Hedges'g* = 0.92) and for TCs versus HCs ($M_{Difference}$ = -5.0; 95% CI -9.8 to -0.1, $p_{Tukey\ HSD}$ < .045; *Hedges'g* = 0.79), with no significant difference between patients with PTSD and TC ($M_{Difference}$ = -1.2; 95% CI -6.4 to 4.1, $p_{Tukey\ HSD}$ = .86; *Hedges'g* = 0.16; see *Suppl. Table 1* for details).

Neuropsychological Assessment. There was no significant difference between patients with PTSD, TC and HC subjects in any of the scores of the PRM, PRM delayed, SSP, SRM or PAL (see *Suppl. Table 1* for details).

Debriefing. All detailed information can be found in *Suppl. Table 2*. The groups did not significantly differ on any of the debriefing questions. After habituation, the groups reported a similar number of architects designing the rooms ($F(2, 49) = 2.62$, $p = .08$; range 2 to 9). After acquisition, the groups did not significantly differ on when they could distinguish the contexts ($X^2(4, 61) = 6.07$, $p = .19$) with the majority of participants (67%) being able to distinguish the rooms from each other during context acquisition. In addition, participants across all groups found the instructions ($F(2, 59) = 0.53$, $p = .39$; range 5 to 10) and ratings ($F(2, 60) = 2.65$, $p = .11$; range 3 to 10) understandable, could handle the keyboard ($F(2, 60) = 1.58$, $p = .21$; range 1 to 10) and were similarly exhausted after ($F(2, 58) = 2.26$, $p = .14$; range 1 to 10) and attentive during ($F(2, 59) = 0.07$, $p = .80$; range 1 to 10) the experiment (see *Suppl. Table 2* for details).

Self-reports

Ratings of the unconditioned stimulus. All detailed information can be found in *Suppl. Table 3a*).The experimental groups did not significantly differ in the ratings of the intensity of the US ($F(2, 58) = 0.54$, $p = .59$) at the end of habituation. For the pain intensity rating, there was a significant main effect of phase ($F_{phase}(2, 108) = 31.27$, $p < .001$) and a significant interaction of phase x group ($F_{group\ x\ phase}(4, 108) = 3.05$, $p = .02$). The pain intensity ratings of the US were higher during habituation than during context and cue conditioning across all three groups. However, the pain intensity ratings for the US were higher for TC subjects than patients with PTSD and HC subjects during context and cue conditioning. For the valence ratings of the US, we found a significant main effect of phase ($F_{phase}(2, 108) = 18.46$, $p_{GG} < .001$) and a significant interaction of group x phase ($F_{group\ x\ phase}(4, 108) = 3.06$, $p_{GG} = .031$). Similar to the pain intensity ratings, the valence ratings of the US were higher for the habituation than for cue and context conditioning across all three groups. However, the

valence ratings of the US stayed higher for TC subjects than patients with PTSD and HC subjects during cue and context conditioning (*Suppl. Table 3a*).

Ratings across contexts. All detailed information can be found in *Suppl. Figure 2a, Suppl. Table 3b-d*. We found a significant main effect of phase for arousal ratings in the *ctx_unpred* ($F_{phase}(2, 82) = 4.33$, $p = .022$), ctx_safe ($F_{phase}(1, 46) = 6.45$, $p = .015$), *cue_pred* ($F_{phase}(2, 82) = 6.03$, $p = .004$) and *cue_safe* ($F_{phase}(1, 46) = 9.55$, $p = .003$) condition. The arousal ratings were highest after acquisition across all the groups. There was no significant main effect of group and no significant interaction of group x phase in the arousal ratings (*Suppl. Table 3b*). In the valence rating for each context, we only found a significant main effect of phase for the *ctx_unpred* ($F_{phase}(2, 82) = 8.90$, $p < .001$) and a significant interaction of group x phase in *ctx_safe* ($F_{group\ x\ phase}(2, 46) = 3.69$, $p = .033$; *Suppl. Table 3c*). The valence ratings were highest after acquisition across all the groups for *ctx_unpred*. For ctx_safe, the valence ratings were higher during acquisition than extinction, while for TC subjects it was the opposite, hence the significant interaction. For the contingency ratings, we observed significant main effects of phase across all four contexts, namely *ctx_unpred* ($F_{phase}(2, 82) = 10.56$, $p < .001$), *ctx_safe* ($F_{phase}(1, 46) = 13.36$, $p < .001$), *cue_pred* ($F_{phase}(2, 82) = 5.37$, $p = .007$) and *cue_safe* ($F_{phase}(1, 46) = 16.57$, $p < .001$). The contingency ratings were highest after acquisition across all the groups and contexts.

Differences in ratings between CS+ - CS-. All detailed information for the difference scores of CS+ - CS- can be found in *Suppl. Figure 2b* and *Suppl. Table 3e*. A significant main effect of phase was found for the difference ratings during acquisition for arousal ($F_{phase}(1, 56) = 39.13$, $p < .001$), valence ($F_{phase}(1, 56) = 21.54$, $p < .001$) and contingency ($F_{phase}(1, 56) = 42.89$, $p < .001$). All three groups seemed to be able to recognize the CS+ as danger signal during cue conditioning in the predictable context.

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		Groups												Analyses								
		PTSD [N=20]				TC [N=21]				HC [N=22]												
		M	*SD*	*n*	*(%)*	*M*	*SD*	*n*	*(%)*	*M*	*SD*	*n*	*(%)*	X^2	*F*	*T*	*Df*	*p*	*Cont.*	*Diff,*	*CI [-95%; +95%]*	$p_{Tukey\ HSD}$	*Hedges' g*
NEO-FFI - Neuroticism		26.6	9.2	18		19.0	9.4	21		12.8	6.2	20			12.87		2	<.001					
																			T-H	6.3	-0.0; 12.6	.051	0.77
																			P-H	13.9	7.3; 20.4	<.001	1.77
																			P-T	7.6	1.1; 14.1	.019	0.89
NEO-FFI - Extraversion		22.9	8.2	16		26.7	7.2	21		29.1	7.4	21			3.03		2	.056					
NEO-FFI - Openness to experience		27.9	9.3	17		31.2	7.5	21		29.5	7.9	22			0.77		2	.47					
NEO-FFI - Agreeableness		31.4	7.1	17		32.5	6.4	20		37.5	6.3	22			4.98		2	.010					
																			T-H	-5.0	-9.8; -0.1	.045	0.79
																			P-H	-6.1	-11.2;-1.0	.014	0.92
																			P-T	-1.2	-6.4; 4.1	.86	0.16
NEO-FFI - Conscientiousness		30.6	8.0	18		32.6	5.3	21		34.8	5.8	22			2.23		2	.12					
Neuropsychological Assessments																							
PRM	Mean correct latency	2.45	0.74	18		2.11	0.59	21		2.19	0.53	21			1.60		2	.21					
	Percent correct	90.3	10.4	18		94.8	4.15	21		94.0	9.18	21		12.64			8	.13					
PRM delayed	Mean correct latency	2.13	0.49	18		2.02	0.55	21		2.24	1.27	21			0.36		2	.70					
	Percent correct	75.5	16.0	18		85.2	13.1	21		82.9	14.8	21		13.66			16	.62					
SSP	Span length	5.61	1.85	18		6.57	1.21	21		6.63	1.34	19			2.79		2	.07					
	Total errors	12.8	5.87	18		15.1	7.11	21		13.8	5.64	19			0.67		2	.52					
	Mean time to first response	2.42	0.66	18		2.73	0.40	21		2.90	0.69	19			3.07		2	.055					
	Mean time to last response	3.14	1.03	18		3.50	0.63	21		3.58	0.73	19			1.57		2	.22					
	Total usage errors	2.72	2.11	18		2.24	1.34	21		2.53	1.95	19			0.36		2	0.70					
SRM	Mean correct latency	2.00	0.44	18		2.09	0.58	21		2.06	0.51	21			0.17		2	.84					
	Percent correct	78.3	10.6	18		79.3	8.70	21		76.7	9.79	21		17.09			18	.52					
PAL	First trial memory score	19.0	2.68	18		20.6	3.75	21		20.6	5.31	21			0.95		2	.39					
	Mean trials to success	1.62	0.44	18		1.46	0.32	21		1.48	0.62	21			0.62		2	.54					
	Total error (adjusted)	15.6	12.6	18		9.76	8.50	21		12.0	16.3	21			1.01		2	.37					
	Total trials	12.8	3.26	18		11.7	2.59	21		11.6	4.25	21			0.68		2	.51					

Suppl. Table 1. Assessment of personality traits and Neuropsychological assessments.

[**Abbreviations:** Cont. – Contrast; H – Healthy control subjects; NEO-FFI – Neuroticism-Extraversion-Openness to experience Five-Factor Inventory; PAL – Paired Associates Learning; PRM – Pattern Recognition Memory; P – patients with PTSD; SRM – Spatial Recognition Memory; SSP – Spatial Span; T – Trauma control subjects]

Debriefing		PTSD				TC				HC				Analysis			
		M	*SD*	*n*	*%*	*M*	*SD*	*n*	*%*	*M*	*SD*	*n*	*%*	X^2	*F*	*Df*	*p*
1. How many different architects designed the rooms?		6.04	2.37	14		6.69	1.76	18		5.25	1.77	20			2.62	2	.08
2. How quickly did you manage to distinguish the rooms from each other?	During Context ACQ			10	52.6			14	70.0			17	77.3	6.07		4	.19
	During Cue ACQ			7	36.9			6	30.0			5	22.7				
	Not at all			2	10.5			0	0.0			0	0.0				
3. Did you find the instructions understandable? [1 “difficult”; 10 “easy”]		9.00	1.34	20		9.7	0.80	20		9.24	1.22	21			0.53	1	.39
4. Did you find the ratings understandable? [1 “difficult”; 10 “easy”]		8.15	1.87	20		8.7	1.72	20		8.95	1.17	22			2.65	1	.11
5. How well did you get along with the keyboard? [1 “very badly”; 10 “very good”]		8.80	1.61	20		8.35	2.32	20		9.45	1.06	22			1.58	1	.21
6. How exhausting did you find the experiment? [1 “very exhausting”; 10 “not exhausting at all”]		5.00	2.81	19		6.40	2.04	20		6.14	2.10	21			2.26	1	.14
7. How attentive were you during the experiment? [1 “not at all”; 10 “very”]		7.21	2.15	19		7.65	1.53	20		7.36	1.33	22			0.07	1	.80

Supplementary Table 2. Results of debriefing questionnaire asked at the end of the habituation (Question 1) and at the end of acquisition (Question 2-7).

[**Abbreviations:** HC – Healthy control subjects without trauma experience; PTSD – patients with PTSD; TC – healthy control subjects with trauma experience]

US

Groups	n	HAB M (SD)	ACQ Con M (SD)	ACQ Cue M (SD)	Analyses
Intensity (in mA)					
PTSD	[n=19]	4.68 (3.39)	-	-	F(2, 58)= 0.54, p=.59
TC	[n=20]	4.80 (2.41)	-	-	
HC	[n=22]	3.96 (2.72)	-	-	
Pain					
PTSD	[n=17]	7.29 (0.77)	5.47 (1.94)	5.94 (1.71)	Group: F(2, 54)= 2.29, p=.11
TC	[n=20]	7.10 (0.45)	6.55 (0.76)	6.55 (0.76)	**Phase: F(2, 108)= 31.27, p<.001*** HAB > ACQ_{Con} + ACQ_{Cue}
HC	[n=20]	7.25 (0.44)	5.40 (2.06)	5.50 (1.82)	**GroupxPhase: F(4, 108)= 3.05, p=.02*** TC_{ACQ_con} > $PTSD_{ACQ\_con}$ + HC_{ACQ_con} TC_{ACQ_cue} > $PTSD_{ACQ\_cue}$ + HC_{ACQ_cue}
Valence					
PTSD	[n=17]	7.29 (0.69)	5.76 (1.92)	6.18 (1.88)	Group: F(2, 54)= 3.02, p=.057
TC	[n=20]	7.10 (0.45)	6.75 (1.02)	6.85 (1.18)	**Phase: F(2, 108)= 18.46, p_{GG}<.001*** HAB > ACQ_{Con} + ACQ_{Cue}
HC	[n=20]	7.10 (0.55)	5.60 (1.90)	5.35 (2.21)	**GroupxPhase: F(4, 108)= 3.06, p_{GG}=.031*** TC_{ACQ_con} > $PTSD_{ACQ\_con}$ + HC_{ACQ_con} TC_{ACQ_cue} > HC_{ACQ_cue}

Suppl. Table 3a. Intensity (in Milliampere), pain intensity ratings and valence ratings of the US during HAB and ACQ.

[**Abbreviations:** ACQ – Acquisition; Con – Context; EXT – Extinction; HAB – Habituation; HC – Healthy control subjects without trauma experience; mA – Milliampere; PTSD – patients with PTSD; TC – healthy control subjects with trauma experience; US – Unconditioned Stimulus]

Arousal

Groups	n	HAB M (SD)	ACQ M (SD)	EXT M (SD)	Analyses
CTX_unpred					
PTSD	[n=14]	2.21 (1.73)	2.46 (1.68)	1.54 (0.91)	Group: F(2, 41)= 1.40, p=.26
TC	[n=17]	2.41 (1.24)	3.47 (2.22)	2.24 (1.44)	**Phase: F(2, 82)= 4.33, p_{GG}=.022*** ACQ > HAB + EXT
HC	[n=13]	2.15 (1.25)	2.27 (0.90)	2.23 (1.13)	GroupxPhase: F(4, 82)= 1.38, p=.25
CTX_safe					
PTSD	[n=16]	-	2.31 (1.52)	1.69 (1.40)	Group: F(2, 46)= 0.80, p=.46
TC	[n=18]	-	2.72 (1.22)	2.42 (2.10)	**Phase: F(1, 46)= 6.45, p=.015*** ACQ > EXT
HC	[n=15]	-	2.60 (1.45)	1.90 (1.14)	GroupxPhase: F(2, 46)= 0.33, p=.72
CUE_pred					
PTSD	[n=14]	2.46 (1.83)	2.83 (1.83)	2.00 (1.40)	Group: F(2, 42)= 1.30, p=.28
TC	[n=17]	2.50 (1.35)	3.62 (2.33)	2.79 (2.27)	**Phase: F(2, 82)= 6.03, p=.004**** ACQ > HAB + EXT
HC	[n=13]	1.85 (0.90)	2.62 (1.34)	2.04 (1.25)	GroupxPhase: F(4, 82)= 0.56, p=.69
CUE_safe					
PTSD	[n=16]	-	2.28 (1.48)	1.78 (1.03)	Group: F(2, 46)= 0.34, p=.72
TC	[n=18]	-	2.56 (1.12)	2.08 (1.41)	**Phase: F_P(1, 46)= 9.55, p=.003**** ACQ > EXT
HC	[n=15]	-	2.63 (1.25)	1.97 (1.34)	GroupxPhase: F(2, 46)= 0.12, p=.89

Supplementary Table 3b. Mixed repeated measures ANOVAs (rmANOVA) across arousal ratings for each of the four conditions (ctx_unpred, ctx_safe, cue_pred, cue_safe) and each of the three phases (HAB, ACQ, EXT).

[**Abbreviations:** ACQ – Acquisition; CTX – Context; EXT – Extinction; HAB – Habituation; HC – Healthy control subjects without trauma experience; p_{GG} – Greenhouse-Geisser correction; pred – Predictable; PTSD – patients with PTSD; SCR – Skin conductance response; TC – healthy control subjects with trauma experience; unpred – Unpredictable]

Valence

Groups	n	HAB M (SD)	ACQ M (SD)	EXT M (SD)	Analyses
CTX_unpred					
PTSD	[n=14]	3.54 (1.67)	3.71 (1.99)	3.36 (1.79)	Group: F(2, 41)= 0.30, p=.74
TC	[n=17]	3.26 (1.38)	4.18 (2.08)	3.18 (1.49)	**Phase: F(2, 82)= 8.90, p_{GG}<.001*** ACQ > HAB + EXT
HC	[n=13]	2.81 (1.49)	3.85 (1.63)	2.81 (1.63)	GroupxPhase: F(4, 82)= 0.92, p=.45
CTX_safe					
PTSD	[n=16]	-	3.53 (1.79)	3.22 (1.81)	Group: F(2, 46)= 0.86, p=.43
TC	[n=18]	-	3.33 (1.37)	3.72 (2.12)	Phase: F(1, 46)= 2.26, p=.14
HC	[n=15]	-	3.40 (1.66)	2.33 (0.96)	**GroupxPhase: F(2, 46)= 3.69, p=.033*** HC_{EXT} > $PTSD_{EXT}$ + TC_{EXT}
CUE_pred					
PTSD	[n=14]	3.89 (1.91)	3.63 (1.91)	4.00 (2.12)	Group: F(2, 42)= 0.19, p=.83
TC	[n=17]	3.65 (1.43)	3.65 (1.94)	3.88 (2.18)	Phase: F(2, 82)= 0.19, p=.83
HC	[n=13]	3.37 (1.91)	3.81 (1.68)	2.96 (1.89)	GroupxPhase: F(4, 82)= 1.08, p=.37
CUE_safe					
PTSD	[n=16]	-	3.69 (1.71)	3.84 (1.94)	Group: F(2, 46)= 1.83, p=.17
TC	[n=18]	-	3.25 (1.31)	3.61 (1.92)	Phase: F_P(1, 46)= 0.01, p=.94
HC	[n=15]	-	3.00 (1.21)	2.53 (1.70)	GroupxPhase: F(2, 46)= 1.29, p=.29

Supplementary Table 3c. Mixed repeated measures ANOVAs (rmANOVA) across valence ratings for each of the four conditions (ctx_unpred, ctx_safe, cue_pred, cue_safe) and each of the three phases (HAB, ACQ, EXT).

[**Abbreviations:** ACQ – Acquisition; CTX – Context; EXT – Extinction; HAB – Habituation; HC – Healthy control subjects without trauma experience; p_{GG} – Greenhouse-Geisser correction; pred – Predictable; PTSD – patients with PTSD; SCR – Skin conductance response; TC – healthy control subjects with trauma experience; unpred – Unpredictable]

Contingency

Groups	n	HAB M (SD)	ACQ M (SD)	EXT M (SD)	Analyses
CTX_unpred					
PTSD	[n=14]	2.64 (1.70)	3.68 (1.87)	2.11 (2.26)	Group: F(2, 41)= 1.12, p=.34
TC	[n=17]	3.12 (1.60)	4.29 (1.98)	2.38 (1.75)	**Phase: F(2, 82)= 10.56, p_{GG}<.001*** ** EXT < HAB + ACQ
HC	[n=13]	3.08 (1.80)	3.12 (2.58)	1.58 (1.10)	GroupxPhase: F(4, 82)= 0.55, p=.70
CTX_safe					
PTSD	[n=16]	-	3.22 (1.91)	2.06 (2.15)	Group: F(2, 46)= 0.92, p=.41
TC	[n=18]	-	3.64 (1.75)	2.64 (2.17)	**Phase: F(1, 46)= 13.36, p<.001*** ACQ > EXT
HC	[n=15]	-	3.33 (2.53)	1.57 (0.89)	GroupxPhase: F(2, 46)= 0.42, p=.66
CUE_pred					
PTSD	[n=14]	2.89 (1.96)	2.75 (2.03)	1.89 (1.71)	Group: F(2, 42)= 2.65, p=.83
TC	[n=17]	3.41 (1.65)	4.24 (2.22)	2.79 (2.28)	**Phase: F(2, 82)= 5.27, p=.007** EXT < HAB + ACQ
HC	[n=13]	2.81 (1.74)	2.62 (1.96)	1.85 (1.39)	GroupxPhase: F(4, 82)= 0.53, p=.72
CUE_safe					
PTSD	[n=16]	-	2.78 (1.83)	1.56 (1.14)	Group: F(2, 46)= 0.99, p=.38
TC	[n=18]	-	2.94 (1.70)	2.17 (1.56)	**Phase: F_P(1, 46)= 16.57, p<.001*** ACQ > EXT
HC	[n=15]	-	2.57 (1.46)	1.43 (0.82)	GroupxPhase: F(2, 46)= 0.29, p=.75

Supplementary Table 3d. Mixed repeated measures ANOVAs (rmANOVA) across contingency ratings for each of the four conditions (ctx_unpred, ctx_safe, cue_pred, cue_safe) and each of the three phases (HAB, ACQ, EXT).

[**Abbreviations:** ACQ – Acquisition; CTX – Context; EXT – Extinction; HAB – Habituation; HC – Healthy control subjects without trauma experience; p_{GG} – Greenhouse-Geisser correction; pred – Predictable; PTSD – patients with PTSD; SCR – Skin conductance response; TC – healthy control subjects with trauma experience; unpred – Unpredictable]

Ratings [Diff CS+-CS-]

Arousal		**PTSD**	**TC**	**HC**	**Analyses**
		[n=19]	[n=17]	[n=19]	
HAB		1.06 (1.53)	0.95 (1.41)	0.76 (1.51)	F(2, 52)= 0.18, p=.83
ACQ	Con	0.21 (1.87)	0.20 (1.62)	-0.45 (1.40)	Group: F(2, 56)= 0.64, p=.53 **Phase: F(1, 56)= 39.13, p<.001***
	Cue	1.97 (1.97)	1.75 (2.51)	1.48 (2.42)	$ACQ_{cue} > ACQ_{con}$ GroupxPhase: F(2, 56)= 0.15, p=.86
EXT	Con	0.82 (1.67)	0.15 (1.15)	0.69 (1.62)	Group: F(2, 55)= 1.27, p=.29 Phase: F(1, 55)= 0.15, p=.70
	Cue	0.88 (1.47)	0.30 (1.41)	0.67 (0.94)	GroupxPhase: F(2, 55)= 0.11, p=.90
Valence		**PTSD**	**TC**	**HC**	**Analyses**
		[n=19]	[n=17]	[n=19]	
HAB		0.85 (1.28)	0.63 (1.63)	0.26 (1.26)	F(2, 52)= 0.81, p=.45
ACQ	Con	-0.13 (1.94)	0.48 (1.60)	0.48 (1.59)	Group: F(2, 56)= 1.11, p=.34 **Phase: F(1, 56)= 21.54, p<.001***
	Cue	1.71 (2.19)	1.92 (2.12)	1.25 (3.33)	$ACQ_{cue} > ACQ_{con}$ GroupxPhase: F(2, 56)= 0.10, p=.90
EXT	Con	0.35 (1.52)	0.60 (1.26)	0.79 (1.52)	Group: F(2, 55)= 0.23, p=.80 Phase: F(1, 55)= 0.26, p=.61
	Cue	0.65 (1.61)	0.95 (1.56)	0.41 (1.06)	GroupxPhase: F(2, 55)= 1.98, p=.15
Contingency		**PTSD**	**TC**	**HC**	**Analyses**
		[n=20]	[n=19]	[n=20]	
HAB		1.18 (2.21)	1.08 (1.73)	0.82 (2.43)	F(2, 52)= 0.14, p=.87
ACQ	Con	-0.45 (2.19)	0.00 (2.73)	-0.42 (1.42	Group: F(2, 56)= 0.37, p=.69 **Phase: F(1, 56)= 42.89, p<.001***
	Cue	2.89 (3.55)	3.25 (3.38)	2.50 (3.39)	$ACQ_{cue} > ACQ_{con}$ GroupxPhase: F(2, 56)= 0.07, p=.93
EXT	Con	0.68 (1.46)	0.13 (1.44)	0.57 (2.07)	Group: F(2, 55)= 0.70, p=.50 Phase: F(1, 55)= 0.37, p=.55
	Cue	1.00 (2.24)	0.53 (1.37)	0.26 (0.96)	GroupxPhase: F(2, 55)= 1.04, p=.36

Suppl. Table 3e. Difference of ratings between CS+ - CS- for the ratings of arousal**,** valence and contingency during all three phases (HAB, ACQ, EXT) and for all three groups (PTSD, TC, HC).

[**Abbreviations:** ACQ – Acquisition; Con – Context; CS – conditioned stimulus; EXT – Extinction; HAB – Habituation; HC – Healthy control subjects without trauma experience; PTSD – patients with PTSD; TC – healthy control subjects with trauma experience]

SCR (in µS)

Groups	n	ctx unpred M (SD)	ctx safe M (SD)	Analyses	Cue pred M (SD)	Cue pred M (SD)	Analyses
ACQ							
PTSD	[n=14]	0.011 (0.014)	0.006 (0.010)	Group: F(2, 36)= 3.24, p=.051 **Context: F(1, 36)= 14.55, p<.001*** ctx_unpred > ctx_safe Group x Context: F(2, 36)= 0.34, p=.71	0.028 (0.026)	0.007 (0.009)	**Group: F(2, 34)= 5.45, p=.009** PTSD < HC + TC **Context: F(1, 34)= 66.07, p<.001*** cue_pred > cue_safe Group x Context: F(2, 34)= 1.75, p=.19
TC	[n=16]	0.025 (0.022)	0.017 (0.020)		0.052 (0.028)	0.018 (0.015)	
HC	[n=9]	0.028 (0.019)	0.020 (0.014)		0.052 (0.009)	0.023 (0.015)	
EXT							
PTSD	[n=12]	0.012 (0.017)	0.010 (0.014)	Group: F(2, 35)= 1.78, p=.18 Context: F(1, 35)= 1.23, p=.28 Group x Context: F(2, 35)= 0.04, p=.96	0.009 (0.013)	0.011 (0.014)	Group: F(2, 34)= 1.81, p=.18 Context: F(1, 34)= 2.31, p=.14 Group x Context: F(2, 34)= 2.25, p=.12
TC	[n=16]	0.015 (0.023)	0.013 (0.024)		0.015 (0.017)	0.013 (0.018)	
HC	[n=10]	0.037 (0.058)	0.035 (0.056)		0.040 (0.070)	0.035 (0.065)	

Supplementary Table 4a. Mixed repeated measures ANOVAs (rmANOVA) across SCRs for each of the two phases (context, cue) and each of the two phases (ACQ, EXT).

[**Abbreviations:** ACQ – Acquisition; CTX – Context; EXT – Extinction; HC – Healthy control subjects without trauma experience; pred – Predictable; PTSD – patients with PTSD; SCR – Skin conductance response; TC – healthy control subjects with trauma experience; unpred – Unpredictable; **µS** - Microsiemens]

SCR (in µS)

Diff. CS+-CS-

Groups	n	ctx unpred M (SD)	ctx safe M (SD)	Analyses	Cue pred M (SD)	Cue pred M (SD)	Analyses
ACQ							
PTSD	[n=14]	0.003 (0.010)	0.000 (0.006)	**Group: F(2, 36)= 3.93, p=.029*** HC > PTSD + TC	0.059 (0.062)	0.003 (0.007)	Group: F(2, 34)= 1.77, p=.19 **Context: F(1, 34)= 62.59, p<.001***** cue_pred > cue_safe
TC	[n=16]	0.004 (0.013)	-0.002 (0.009)	Context: F(1, 36)= 0.83, p=.37 Group x Context: F(2, 36)= 0.36, p=.70	0.098 (0.046)	0.004 (0.026)	Group x Context: F(2, 34)= 3.08, p=.059
HC	[n=9]	0.008 (0.015)	0.009 (0.019)		0.066 (0.029)	0.015 (0.023)	
EXT							
PTSD	[n=12]	-0.017 (0.047)	0.006 (0.016)	Group: F(2, 35)= 0.73, p=.49 **Context: F(1, 35)= 5.47, p=.025** ctx_unpred_ext > ctx_safe_ext	-0.001 (0.006)	0.000 (0.011)	Group: F(2, 34)= 0.87, p=.43 Context: F(1, 34)= 1.57, p=.22
TC	[n=16]	0.001 (0.001)	0.002 (0.012)	Group x Context: F(2, 35)= 2.48, p=.098	0.002 (0.009)	0.001 (0.015)	Group x Context: F(2, 34)= 1.31, p=.28
HC	[n=10]	-0.017 (0.047)	0.006 (0.016)		-0.022 (0.076)	0.005 (0.014)	

Supplementary Table 4b. Mixed repeated measures ANOVAs (rmANOVA) across SCRs for each of the two phases (context, cue) and each of the two phases (ACQ, EXT).

[**Abbreviations:** ACQ – Acquisition; CTX – Context; EXT – Extinction; HC – Healthy control subjects without trauma experience; pred – Predictable; PTSD – patients with PTSD; SCR – Skin conductance response; TC – healthy control subjects with trauma experience; unpred – Unpredictable; **µS** - Microsiemens]

ROI		PTSD			TC			HC			Analysis	
		M	SD	N	M	SD	N	M	SD	N	PTSD vs. HC	PTSD vs. TC
ctx_unpred	Hippocampi	-0.217	(0.66)	17	-0.007	(0.45)	18	0.190	(0.56)	15	T(30)=-1.87, p=.072	T(33)=-1.11, p=.28
	vmPFC	-0.451	(0.68)	17	-0.049	(0.49)	18	0.098	(0.77)	15	**T(30)=-2.15, p=.040**	T(33)=-2.02, p=.051
	Amygdalae	-0250	(1.04)	17	-0.090	(0.78)	17	0.034	(1.24)	16	T(31)=-0.71, p=.48	T(32)=-0.51, p=.62
cue_pred	Hippocampi	0.254	(0.45)	17	0.086	(0.64)	18	-0.056	(0.41)	15	**T(30)=2.05, p=.049**	T(33)=0.90, p=.38
	vmPFC	0.186	(0.48)	17	-0.020	(0.55)	18	-0.037	(0.50)	16	T(31)=1.31, p=.20	T(33)=1.18, p=.25
	Amygdalae	0.185	(0.80)	17	-0.072	(0.63)	18	-0.185	(0.81)	16	T(31)=1.32, p=.20	T(33)=1.06, p=.30

Suppl. Table 5a. Extracted beta values for Region-of-Interest (ROI) analyses on the Hippocampi, Amygdalae and vmPFC for context unpredictable (ctx_unpred) and context predictable (cue_pred) during acquisition and for each group (HC, PTSD, TC).

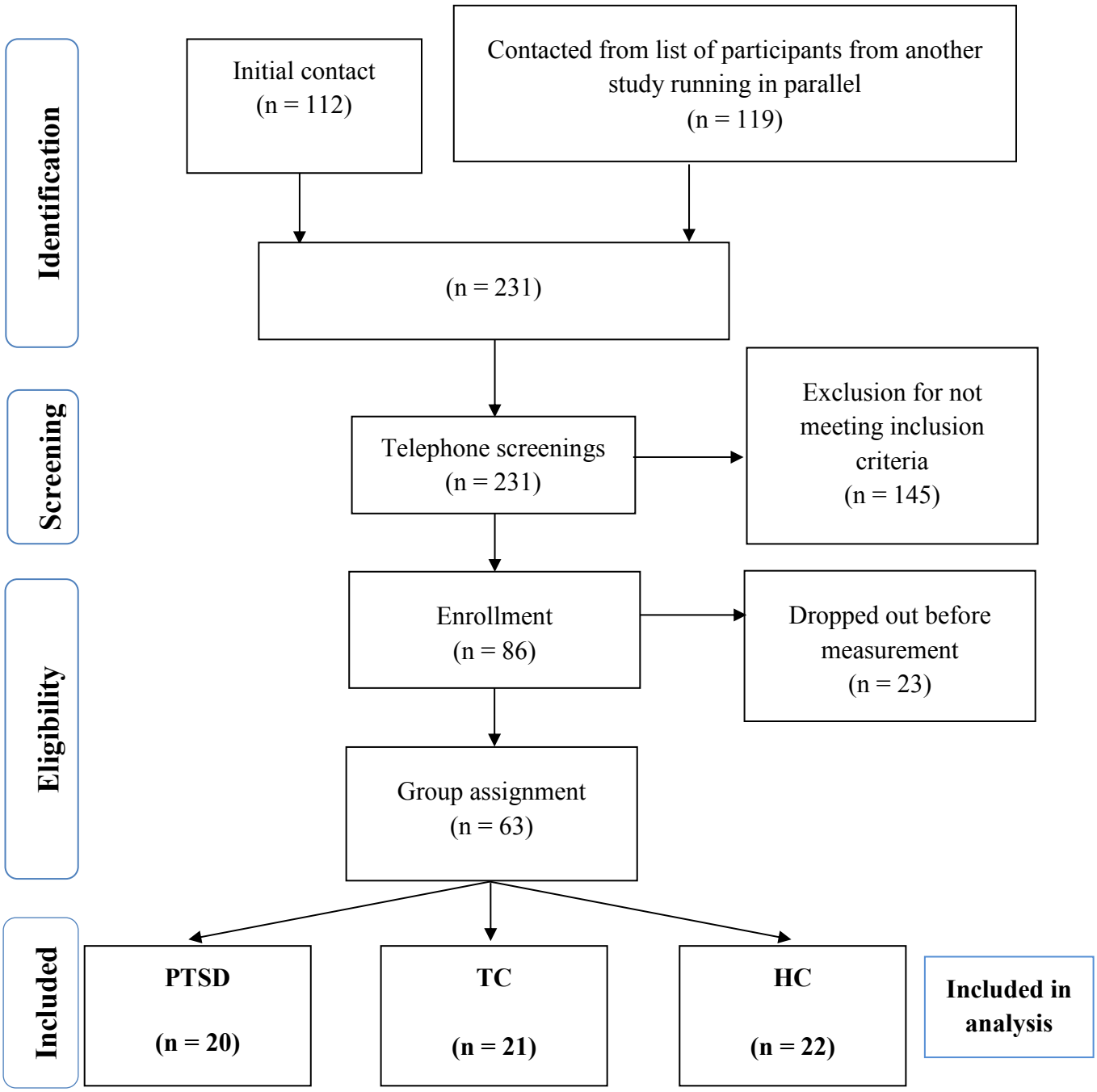
$\alpha_{bonferroni\_cor} = .05/2 = .025$

[**Abbreviations:** ctx – Context; HC – Healthy control subjects without trauma experience; pred – Predictable; PTSD – patients with PTSD; TC – healthy control subjects with trauma experience; unpred – Unpredictable]

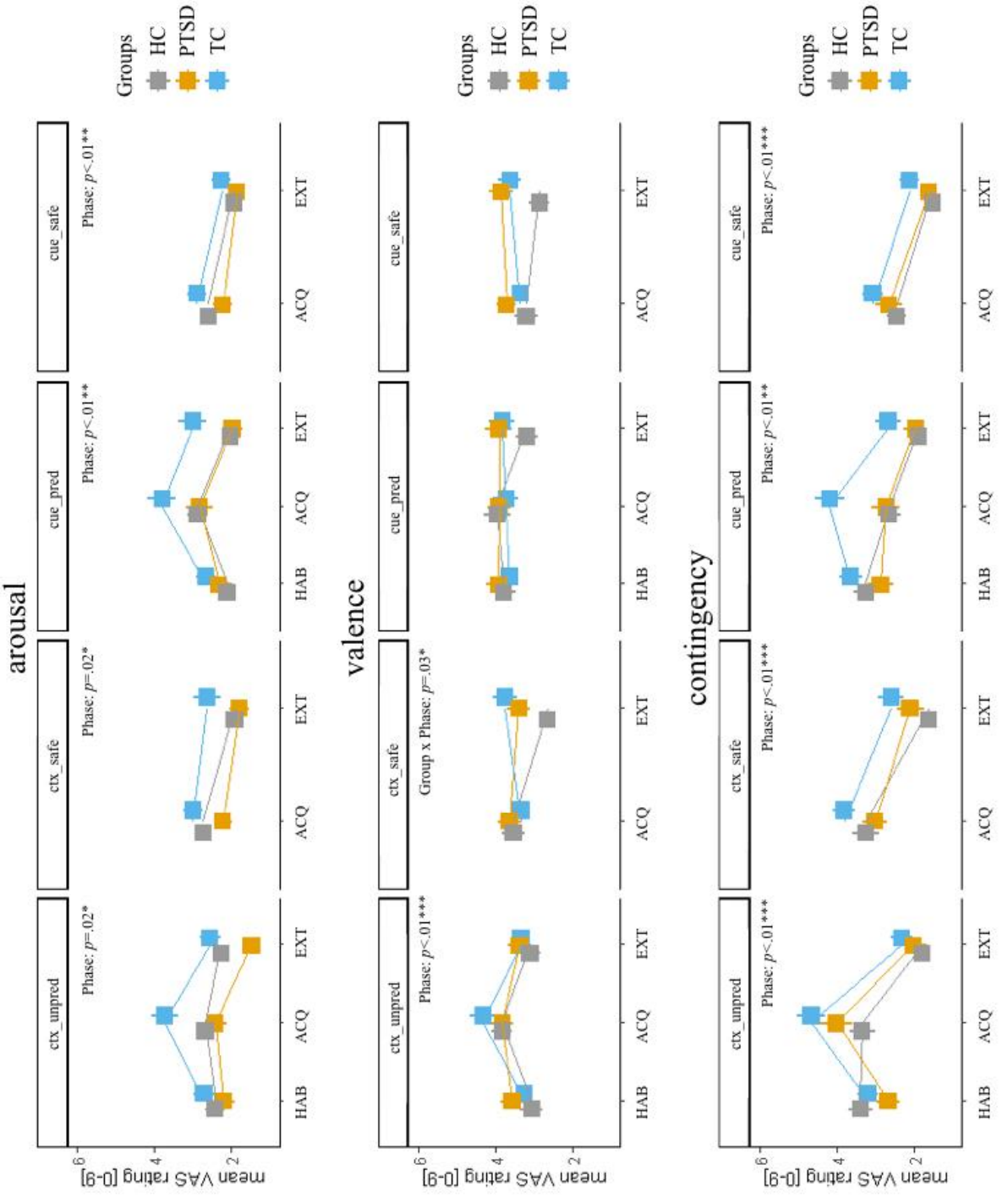
ROI			Hippocampi			vmPFC			Amygdalae	
	Groups	N	M (SD)	Analysis	N	M (SD)	Analysis	N	M (SD)	Analysis
ctx_safe	PTSD	17	0.029 (0.47)	F(2,48)=1.76, p=.18	16	0.068 (0.32)	F(2,48)=1.50, p=.23	17	0.204 (0.63)	F(2,48)=1.69, p=.20
	TC	18	-0.046 (0.31)		18	0.155 (0.38)		18	-0.182 (0.46)	
	HC	16	0.212 (0.44)		16	0.301 (0.44)		16	0.159 (0.90)	
cue_safe	PTSD	17	0.107 (0.70)	F(2,48)=0.98, p=.41	17	-0.067 (0.79)	F(2,48)=2.09, p=.14	17	0.337 (0.94)	F(2,48)=1.49, p=.24
	TC	18	0.009 (0.45)		18	0.034 (0.69)		18	0.247 (1.02)	
	HC	16	-0.153 (0.50)		16	-0.471 (0.78)		16	-0.187 (0.81)	

Suppl. Table 5b. Extracted beta values for Region-of-Interest (ROI) analyses on the Hippocampi, Amygdalae and vmPFC for context safe (ctx_safe) and cue safe (cue_safe) during acquisition and for each group (HC, PTSD, TC).

[**Abbreviations:** ctx – Context; HC – Healthy control subjects without trauma experience; pred – Predictable; PTSD – patients with PTSD; TC – healthy control subjects with trauma experience; unpred – Unpredictable]

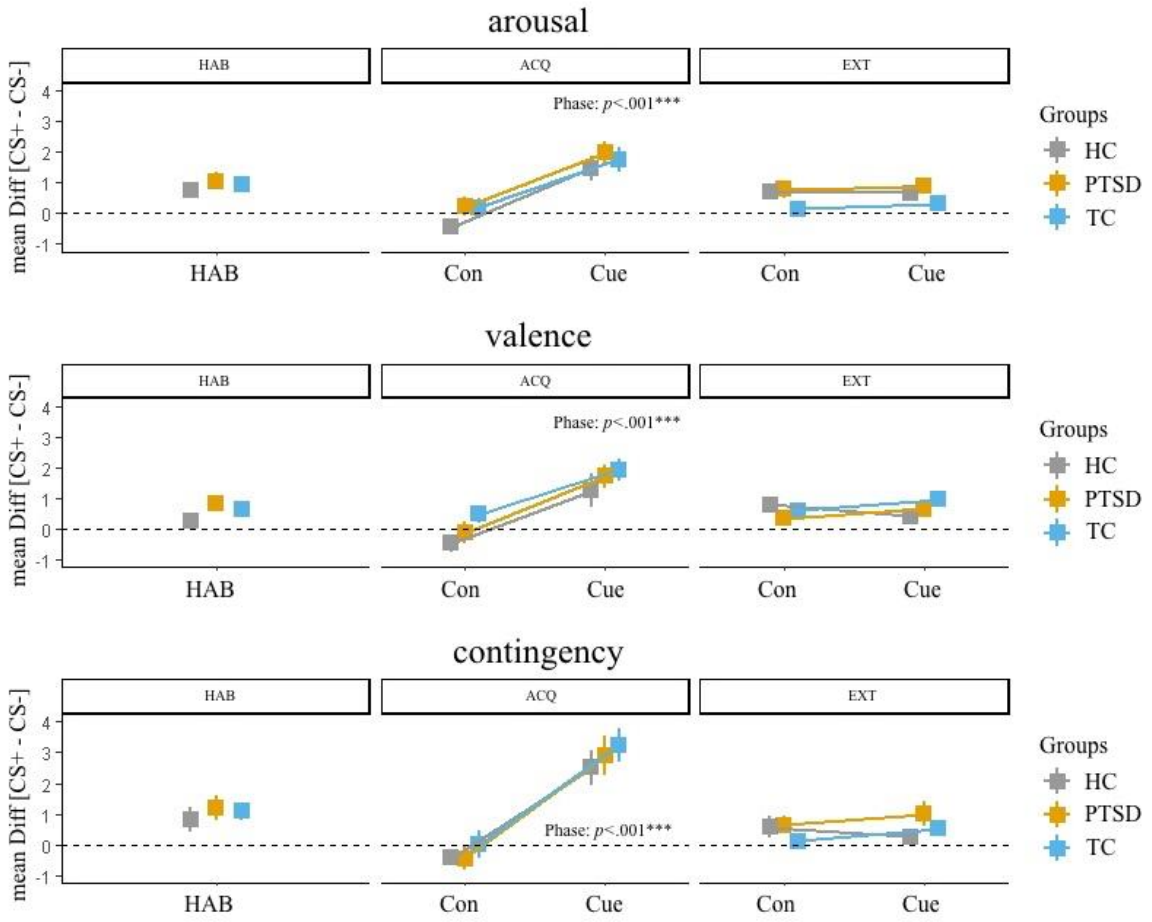


Suppl. Figure 1. Flowchart depicting identification, screening, eligibility and inclusion of subjects.


arousal
valence
contingency
ctx_unpred
ctx_safe
cue_pred
cue_safe
Phase: p=.02*
Phase: p<.01**
Phase: p<.01***
Group x Phase: p=.03*
Groups
HC
PTSD
TC
mean VAS rating [0-9]
HAB
ACQ
EXT

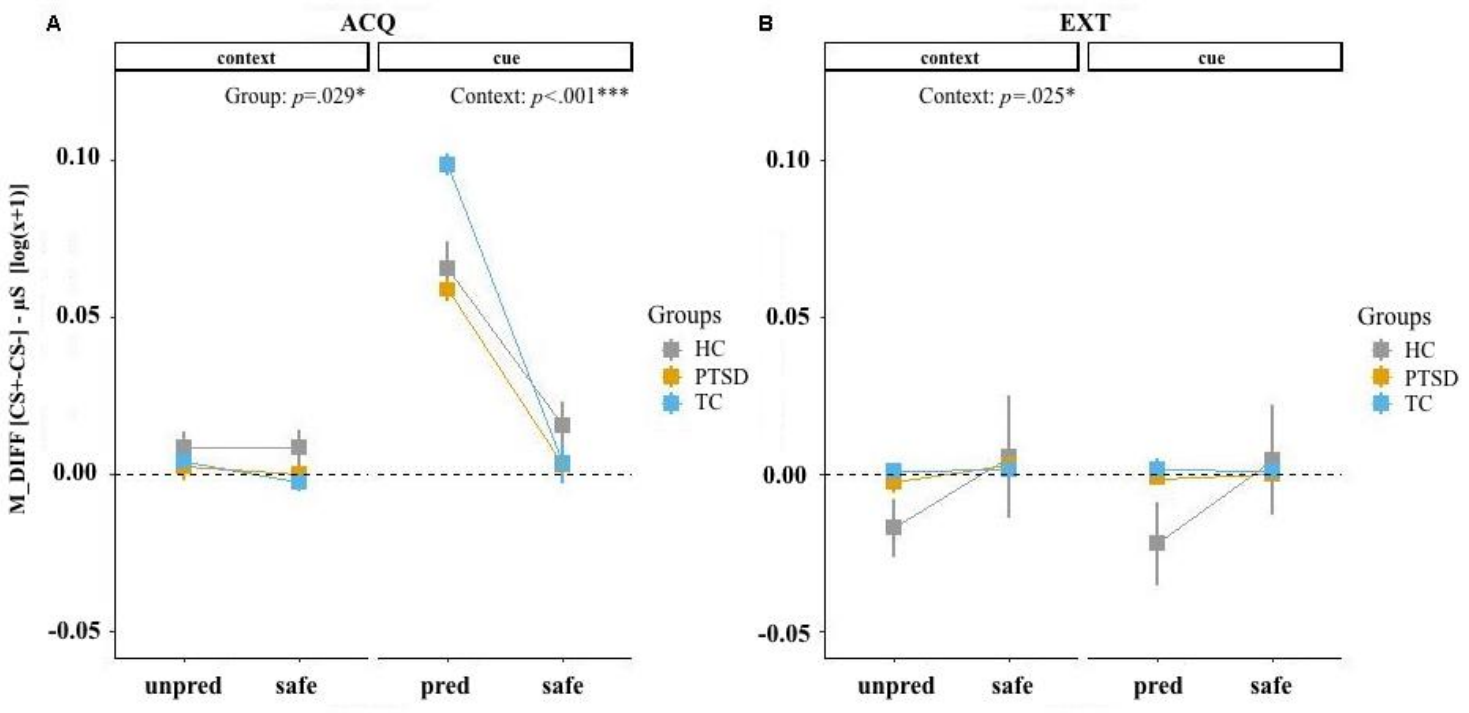
Suppl. Figure 2a. Arousal, valence and contingency ratings across each of the four conditions (ctx_unpred, ctx_safe, cue_pred, cue_safe), each of the three phases (HAB, ACQ, EXT) and each group (HC, PTSD, TC).

[**Abbreviations:** ACQ – Acquisition; CTX – Context; EXT – Extinction; HAB – Habituation; HC – Healthy control subjects without trauma experience; p_{GG} – Greenhouse-Geisser correction; pred – Predictable; PTSD – patients with PTSD; SCR – Skin conductance response; TC – healthy control subjects with trauma experience; unpred – Unpredictable; VAS – Visual Analogue Scale]



Suppl. Figure 2b. Difference scores (CS+ - CS-) for arousal, valence and contingency ratings across each of the three phases (HAB, ACQ, EXT) and each group (HC, PTSD, TC).

[**Abbreviations:** ACQ – Acquisition; Con – Context; EXT – Extinction; HAB – Habituation; HC – Healthy control subjects without trauma experience; PTSD – patients with PTSD; TC – healthy control subjects with trauma experience]



Suppl. Figure 3. Difference scores of CS+-CS- of the SCRs across each of the four conditions (CTX_unpred, CTX_safe, CUE_pred, CUE_safe), two phases (ACQ, EXT) and each group (HC, PTSD, TC). A) ACQ phase. B) EXT phase.

[**Abbreviations:** ACQ – Acquisition; CTX – Context; EXT – Extinction; HC – Healthy control subjects without trauma experience; M_DIFF – Mean difference of CS+ - CS- SCR; pred – Predictable; PTSD – patients with PTSD; SCR – Skin conductance response; TC – healthy control subjects with trauma experience; unpred – Unpredictable]

3 General Discussion

"You can't stop the waves, but you can learn to surf."

Jon Kabat-Zinn (1994), "Wherever you go, there you are"

The aim of this work was to study mechanisms of fear learning and context processing and associated structural and functional differences in patients with PTSD within a shared psychobiological model. In the systematic review and meta-analysis we show lower FA values of major white matter tracts in patients with PTSD in comparison to healthy control subjects with (TC) or without traumatic experiences (HC) including over 1700 participants. This reduction in the cingulum, superior longitudinal fasciculus, forceps minor and other prefrontal white matter tracts can be associated to spatial learning, a key process for contextual processing and emotional downregulation, both important in fear learning and emotional processing, as well as attention-guiding, a key process in threat detection. This is in line with results from the second study, in which we found lower FA values in the forceps minor, superior longitudinal fasciculus and several other long-reaching fiber tracts in patients with PTSD in comparison to TC but not HC subjects. Furthermore, lower volumetric gray matter was shown in the left and right anterior insulae, again between TC subjects and both patients with PTSD and HC subjects. Volumetric differences in the forceps minor and insulae were positively associated and correlated both negatively with symptom severity in PTSD. In the third study, we examined behavioral and physiological differences in fear learning in PTSD in a combined cue-context fear learning paradigm using virtual reality and fMRI. Comparing patients with PTSD to TC and HC subjects during the acquisition of the uncued and therefore unpredictable context, we found a marginally significantly lower ROI activity of the vmPFC but no differences in SCR or behavioral arousal, valence and contingency ratings. In the cued and therefore predictable context, we found a marginally significantly higher ROI activity in the hippocampus in patients with PTSD in comparison to HC but not TC subjects and significantly lower SCR in the predictable and safe context in comparison to both control groups. The results of our three studies suggest that neurobiological differences in patients with PTSD in prefrontal and long-reaching white matter tracts can be associated to context processing and threat detection. Lower BOLD activity in the vmPFC of patients with PTSD in

comparison to TC and HC subjects during uncued contextual fear acquisition complement these findings. Interestingly, there was no difference between the groups in the hippocampal activity in the uncued condition but in the cued (predictable) condition. Patients with PTSD showed higher hippocampal activity in the predictable context than HC subjects. In following sections, we will integrate our findings into the current literature, discuss limitations and provide some possible future directions.

3.1 Integration of findings into current literature

3.1.1 Connecting the dots: Neurobiological findings and their integration into a psychobiological model of PTSD

The first two studies of this dissertation summarize and empirically test structural white matter differences in patients with PTSD in comparison to HC and TC subjects. Our systematic review and meta-analysis showed that studies on underage populations with PTSD and adults with traumatic childhood experiences reported mostly lower FA values in the corpus callosum. In adults the results are more heterogeneous with some studies reporting lower and other higher FA values in tracts like the cingulum, frontal gyri or the ILF and SLF. Our second study partly supports these findings with lower FA values in tracts like the ILF and SLF in patients with PTSD in comparison to TC subjects. Both tracts have been associated with visual spatial attention (D'Andrea et al., 2019) and decision processes (Herbet, Zemmoura, & Duffau, 2018) as well as contextual processing of memory (Hodgetts et al., 2017). Only very few studies exist so far associating white matter differences to mechanisms related to fear learning and context processing. Fani et al. (2015) found a negative association between the FA value of the cingulum and the fear-potentiated startle response during early and late extinction in TC subjects. Similarly, Nees et al. (2019) found that a higher FA value in the cingulum (hippocampal branch) significantly correlated with higher SCRs during extinction of contextual conditioned responses in healthy individuals. In a subclinical sample of veterans with symptoms of PTSD, a positive correlation was found between the FA value in the uncinate fasciculus and startle responses during extinction (Costanzo et al., 2016). Overall, these studies suggest an association between physiological responses during extinction and the FA value of frontal white matter tracts, such as the cingulum or the uncinate fasciculus. Clearly, more studies are needed to confirm this association, especially in clinical populations suffering from PTSD.

Our findings of lower FA values in the forceps minor in patients with PTSD in comparison to TC subjects in the second study support the importance of frontal white matter tracts in PTSD. The forceps minor is a fork-like structure, connecting medial and lateral parts of the PFCs inter-hemispherically and is potentially involved in emotion processing within a larger network of frontal white matter tracts (Versace et al., 2015). Only one other study on human subjects has found a decreased value in the FA of the forceps minor in adolescent subjects with childhood maltreatment (Huang et al., 2012). There are no studies on human subjects associating the forceps minor to any mechanisms of fear learning. But studies on rodents suggest an involvement of prefrontal pathways in learning of expectancies of aversive events, including the forceps minor (Cho, Deisseroth, & Bolshakov, 2013; Furlong, Cole, Hamlin, & McNally, 2010). Frontal white matter tracts, such as the forceps minor, uncinate fasciculus and anterior parts of the cingulum and corpus callosum might be part of a large white matter network underlying psychological processes such as expectancy learning in fear-related contexts. Interestingly, we found that the FA value of the forceps minor and the volume of the left and right anterior insulae were positively associated, meaning that a higher streamline count in the forceps minor was associated with higher gray matter volumes in the anterior insulae. This is in line with previous research showing that the insula in combination with the PFC is involved in the anticipation of aversive stimuli (Simmons, Matthews, Stein, & Paulus, 2004). A recent study on healthy non-trauma exposed subjects, found that the insula in combination with the vmPFC encodes modality-specific features (e.g. unpleasantness) of an expected aversive event (Sharvit, Corradi-Dell'Acqua, & Vuilleumier, 2018). The authors suggest that the insula is a hub for gathering bottom-up sensory information to form a prior about what to expect from a potentially threatening stimulus. The vmPFC has arguably two functions, namely to keep information up to date about current events and in a top down manner to control these expectations formed in, for example, the anterior insula. This fits to findings that the insula plays a larger role in PTSD within the salience network (Liberzon & Abelson, 2016). Further research is needed to investigate the association of expectancy and higher volume in the anterior insula in combination with higher streamline count in white matter tracts within the PFC in healthy trauma-exposed subjects in comparison to patients with PTSD but not healthy non-trauma-exposed subjects.

The first two studies highlight the heterogeneity in the field of DTI-based research in patients with PTSD and emphasize the importance of concept-based categorizations of groups

according to key moderators like age of trauma experience and type of trauma. Research on structural brain development has shown vulnerable periods of brain maturation in adolescence and their association to psychiatric disorders in this period (Giedd et al., 1999; Giedd & Rapoport, 2010; Paus, Keshavan, & Giedd, 2008). Teicher, Samson, Anderson, & Ohashi (2016) have shown that the time point matters in regard of structural brain differences, with the vulnerability for changes in the FA of the inferior longitudinal fasciculus, for example, peaking around the age of eight and again around the age of thirteen. Similarly, the vulnerability for volumetric gray matter change in die hippocampal volume is largest in early childhood, around four years of age, and then peaks again during adolescence, between 12-15 years of age (Teicher et al., 2016). Meta-analyses on gray matter differences have subdivided patient samples according to, for instance, the age of the sample or the time point of the index trauma (Bromis et al., 2018; Kribakaran, Danese, Bromis, Kempton, & Gee, 2020), whereas meta-analyses focusing on white matter do not seem to consider this distinction yet when comparing results (Daniels, Lamke, Gaebler, Walter, & Scheel, 2013; Ju et al., 2020). In a recent multi-site study presenting TBSS results of over 3.000 individuals (Dennis et al., 2019), half of them with PTSD and the other half either trauma-exposed (TCs; 92%) or not (HCs), Dennis et al. (2019) found lower FA values in the tapetum, a part of the corpus callosum connecting both hippocampi inter-hemispherically in patients with PTSD in comparison to HC subjects. This result stayed significant when controlled for a variety of covariates including comorbidity (e.g. depression, alcohol used disorder) or medication. However, when controlling for childhood trauma, Dennis et al. (2019) did not find any significant difference between patients with PTSD and TC, emphasizing the importance of concept-based categorization of groups. Together with the Institute for Psychiatric and Psychosomatic Psychotherapy at the Central Institute of Mental Health, we are investigating gray matter differences using two existing datasets on female, adult patients with PTSD, one with trauma experience in adulthood (>18 years of age) and the other with trauma experience in childhood (<18 years of age). Each dataset consists of a TC and HC group. With this more specific categorization of treatment groups, we further hope to shed light on the contribution of timing of trauma on gray matter differences in patients with PTSD.

3.1.2 How predictable is unpredictable? Placing fear in its context.

Context matters in PTSD, in particular in contextual fear learning (Acheson et al., 2012; Flor & Wessa, 2010; Liberzon & Abelson, 2016). Even more so does the predictability of a potential danger within a context matter. Although various studies have studied context

conditioning and extinction in humans (Baas et al., 2008; Grillon et al., 2006; Lonsdorf, Haaker, & Kalisch, 2014; Stout et al., 2018; Suarez-Jimenez et al., 2018), only very few studies have investigated context conditioning in PTSD (Wicking et al., 2016), and even fewer studied uncued versus cued context conditioning in patients with PTSD (Steiger et al., 2015; for a review see Glenn et al., 2017). In our third study, we investigated fear acquisition using a combined cue-context paradigm in a virtual environment. Participants could either predict the painful stimulus by the appearance of a cue in a given context, a so-called predictable context, or only by the configuration of several stimuli within a context, in which no single cue was predictive of the painful stimulus, a so-called uncued or unpredictable context (Indovina et al., 2011; Schmitz & Grillon, 2012). We found that patients with PTSD were in principle able to distinguish an uncued dangerous from an uncued safe context and showed similar behavioral ratings of arousal, valence and contingency as well as SCR than TC and HC subjects. What differed was the functional brain activity of the vmPFC in the unpredictable context, with patients with PTSD showing lower activity than HC subjects. Although our hypotheses pointed in the right direction, there were no differences in the functional activity of the hippocampus or amygdala between the groups. Patients with PTSD were also able to distinguish a dangerous cued context from a safe cued context with no difference in behavioral ratings of arousal, valence and contingency between the groups. Patients with PTSD did, however, show differences in the physiological responses with lower SCR than HC and TC subjects across the predictable and safe context as well as marginally significantly higher hippocampal activity in the predictable context than HC subjects.

The vmPFC is a key region involved in downregulating fear in cued contextual fear learning (Indovina et al., 2011) with lower activity suggesting less fear regulation. A follow-up analysis would have to be performed to see whether lower activity of the vmPFC is associated with higher SCR or higher ratings of arousal and valence. Lower activity in the vmPFC is consistent with the results of our first two studies, suggesting that not only structural white matter differences but also functional processing in the PFC might underlie deficient fear learning and context processing. Our results should nevertheless be interpreted with caution, since these are somehow preliminary results with none of the differences in functional activity surviving Bonferroni correction.

While the involvement of the vmPFC in encoding of the unpredictable context is in line with previous findings (Indovina et al., 2011), it is somehow surprising that there were no

significant differences in the hippocampus between patients with PTSD and the healthy control groups. As argued in more detail above, the hippocampus has consistently been described as main hub for context processing (Phillips & Ledoux, 1992; Rudy, 2009; Smith & Mizumori, 2006), consistently been found in context conditioning paradigms (Kroes, Dunsmoor, Mackey, McClay, & Phelps, 2017), both in healthy participants as well as patients with PTSD (Maren et al., 2013). There are two possible explanations for why the hippocampus does not show the expected activation patterns. The first one relates to design and analysis, in that the time windows used for the context triggers in each room are not sufficient. While each participant's BOLD curves were checked individually for outliers and non-responders, the time frame of the context triggers has not been changed. One idea would be to subdivide each room into early, middle and late phases. This would be in line with previous studies, showing time-related differences in contextual fear acquisition (Baeuchl et al., 2015; Lonsdorf et al., 2017; Steiger et al., 2015). It would also fit well with our second explanation, that we would expect different activation patterns depending on the hemisphere and subregion of the hippocampus. Previous work suggests that the anterior part of the hippocampus is preferentially associated with context coding and its signal decays over time while the posterior part of the hippocampus encodes detailed spatial relational information with the activation staying more stable over time (Nadel et al., 2013; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). In addition, the left hippocampus was argued to process context-dependent episodic memory, whereas the right hippocampus has been more strongly associated with spatially locating oneself in the environment (Burgess et al., 2002). By averaging over all triggers in a room, we might average out subregion-specific activation patterns. A subdivision of the hippocampi would therefore be appropriate with the strongest activation and potential differences between patients with PTSD and healthy control subjects to be expected in the left anterior hippocampus.

Context has long been studied in basic neuroscience focusing on the hippocampus as major hub for creating cognitive maps (Epstein, Patai, Julian, & Spiers, 2017; O'Keefe & Nadel, 1978) and has early on also been speculated to play a key role in anxiety disorders (Jacobs & Nadel, 1985; Jacobs et al., 2017; Nadel & Willner, 1980). Here, spatial encoding and recollection of our environment is speculated to provide a much larger function, namely to supply a cognitive space for cognition (Bellmund, Gärdenfors, Moser, & Doeller, 2018). As described above, context includes both internal as well as external aspects (Maren et al., 2013). We argue that a broader approach of studying context processing is needed, increasing

the validity and generalizability of findings in the field of fear learning to, for example, internal cognitive domains like the field of episodic memory (Dunsmoor & Kroes, 2019) or more external domains like the social environment patients with PTSD find themselves interacting in (Maercker & Horn, 2013). Recent studies have associated the hippocampus as well as the vmPFC with navigating social interactions in healthy individuals (Schafer & Schiller, 2018a; Tavares et al., 2015). This fits well with our findings of lower prefrontal white matter and functional activity in patients with PTSD. If context matters in PTSD, it probably does so at different levels of cognition, thereby influencing not only learning and memory processes but attention and social interaction as well. Abnormal social navigation has also been associated with other mental disorders such as schizophrenia, autism or depression (Schafer & Schiller, 2018b). To study and, most importantly, treat the effects of context processing more broadly, we rely on studies focusing on different aspects of context processing.

3.2 Limitations

Several limitations apply to each of the manuscripts and to the work as a whole. Concerning the first study, limitations comprise a) the rather restrictively defined inclusion and exclusion criteria, b) methodologically derived issues with the meta-analytical software applied, and c) the need for future integration of possible mediators and moderators. First, we restricted the systematic review to DTI studies reporting differences in FA, leading to more homogeneous groups. The result, however, was fewer studies within each subgroup (e.g. adult-onset PTSD with trauma experience in adulthood) with smaller sample sizes for each group (patients with PTSD, TCs, HCs). In addition, the meta-analysis was only conducted for the whole-brain studies. By applying this rather restrictive approach, a variety of ROI studies were excluded, which is a particularly widely used approach in studies on underage populations. This leads to the second limitation, which is bound to the usage of the software package *GingerAle* for conducting the meta-analysis. *GingerAle* was originally developed to statistically compare differences in gray matter. However, the analysis space and error distributions are different for the white matter "space", for which toolboxes like for example *Seed-Based d Mapping* (SDM) provide more accurate ways to account for using specific white matter atlases. Third, variables concerning trauma (e.g. trauma type or trauma severity), comorbidity (e.g. depression), imaging (e.g. scanner type), methodology (e.g. software packages used for DTI analysis), outcome (e.g. cluster size with peak value) or demographics (e.g. education) should

be included, as potential mediators or moderators between psychopathology and differences in FA value, in future analyses. Moreover, we need larger sample sizes in each group. Regarding the second study, limitations encompass a) the cross-sectional design of the study and b) specific sample characteristics. The cross-sectional nature of the combined white and gray matter study allows only for limited interpretation of the results. It stays unclear whether these neuroplastic differences in trauma control subjects in comparison to patients with PTSD and HC subjects occur on the basis of pre-existing vulnerabilities or as an effect of the trauma experience. A longitudinal design with measurement points pre- and post-trauma experience would be needed to disentangle these potentially interacting effects. In addition, certain sample characteristics concerning education or trauma type should be controlled for in future studies. Educational level could be included as covariate and larger samples with more heterogeneous groups would allow for comparisons of groups with voluntary (interpersonal) trauma experience to groups with involuntary experiences. In the third study, limitations consist mainly of certain aspects of the a) study design and b) the issue of non-responders. While the novelty and complexity of the study design are the biggest strengths of the study, they come with certain restraints and difficulties concerning drop-outs or non-responders. Participants were wearing MR-suitable goggles during the fMRI session to enhance immersiveness. This, however, led to increased drop-out rates, mainly in patients with PTSD that struggled with increased levels of anxiety due to claustrophobia. In addition, a rather large number of non-responders were observed for the SCR across groups. This was most likely due to measuring the SCR on the left foot of participants instead of the hand, because they received the painful stimulus on the left hand and had the response pad in the right hand. A possible solution would be to record the startle reflect in facial muscles like the masseter or orbicularis oculi muscle. The feasibility of this solution, under the circumstance that participants wear goggles, would have to be tested in future work.

3.3 Outlook

Psychobiological research has sharpened its tools over the past two decades and greatly influenced the way how we perceive, study and treat mental disorders such as PTSD. The next step in this development will show whether our findings of structural and functional differences associated to fear learning and context processing can be a) replicated, refined and b) translated from the laboratory into clinical practice, in particular into psychotherapeutic treatments (Holmes, Craske, & Graybiel, 2014; Holmes et al., 2018; Morris, Rumsey, & Cuthbert, 2014).

3.3.1 Data, Data, Data: Novel approaches for meta-analyses of neuroimaging data

With an estimated amount of over 30,000 neuroimaging papers (Müller et al., 2018), meta-analyses become more common and more essential in cognitive neuroscience. Guidelines for neuroimaging-based meta-analyses have been published only recently on how to report key variables, possible statistical analyses options and risk of bias corrections (Müller et al., 2018). The SDM toolbox (Radua et al., 2012; Radua, Via, Catani, & Mataix-Cols, 2011; Radua & Mataix-Cols, 2009) provides the possibility to meta-analytically investigate white matter differences using a five-step method: 1) extracting the peak coordinate and statistical maps, 2) estimation of lower and upper bounds of possible effect size images and 3) estimation of the most likely effect size along with its standard error, 4) execution of the meta-analysis for each imputed dataset, 5) and running a standard permutation test over recreated subjects images. As mentioned in the limitations, a future meta-analysis on white matter differences in PTSD could benefit from the SDM toolbox by reporting results of either whole-brain, ROI or both approaches, of each study. Our meta-analysis further revealed a large heterogeneity in the provided data and that independently of the software package, the defined contrast groups (e.g. TCs) are essential for the interpretation of the results. Two recent meta-analysis on gray matter differences in adult (Bromis et al., 2018) and underage patients with PTSD (Kribakaran et al., 2020) used SDM and compared patients with PTSD either to TC or HC subjects. They further provided the image files on a freely accessible online platform (http://www.ptsdmri.uk). We have preregistered our own meta-analysis on gray matter differences in PTSD on the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42019135821; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=135821). We chose a combined approach of using *GingerAle* for studies reporting whole-brain data and SDM for studies reporting ROI data. Also, we are planning to subdivide the results in the same categories as previously defined in our white matter analysis with adult-onset PTSD with trauma experience in adulthood (aa), adult-onset PTSD with trauma experience in childhood (ac) and childhood-onset PTSD with trauma experience in childhood (cc). Furthermore, we are planning to provide our final dataset on openly accessible databanks like Neurosynth (https://neurosynth.org/; Yarkoni, Poldrack, & Nichols, 2011) or Sleuth (https://brainmap.org/sleuth/; Laird et al., 2011).

3.3.2 Everything is connected: Network science in PTSD

Recently, structural and functional connectivity have been combined to study complex networks (Bullmore & Sporns, 2009; Bullmore & Vértes, 2013; Kashtan & Alon, 2005; van den Heuvel, Bullmore, & Sporns, 2016). Complex networks have certain topological features, such as high-degree nodes or hubs (Freeman, 1977; Guimerà & Nunes Amaral, 2005; Sporns, 2012). In a large meta-analysis, Crossley et al. (2014) found that brain hubs play a central role in the majority of mental disorders. Brain hubs (richly connected nodes) were more likely to show anatomical abnormalities than non-brain hubs (sparsely connected nodes). These findings are consistent with the idea that densely connected hubs function as major cross-roads between brain regions. Recently, network topologies were studied in patients with PTSD (Suo et al., 2019), the dissociative subtype of PTSD (Sierk et al., 2020) and maltreated youths with PTSD (Sun, Haswell, Morey, & De Bellis, 2019). Studies on neuroplastic differences are particularly valuable to identify potential target hubs, central to the network structure. The forceps minor as "edge of interest" or the anterior insula as "node of interest" would be candidates to study in future work on neural networks. The role of functional brain networks in contextual fear learning has only been studied in rodents so far (Coelho, Ferreira, Kramer-Soares, Sato, & Oliveira, 2018). Similar analyses have been performed with behavioral data, such as symptom severity, where "central symptom hubs" are identified in a particular network of interacting symptom clusters (Borsboom, 2017; McNally, 2016; McNally et al., 2015). Such analyses could also be performed with cognitive dysfunctions in PTSD, with fear learning and context processing as potential central hubs of a network based on symptom clusters. Recent network models consider "simple" forms of associative learning and study how humans learn patterns and form internal networks of these learned patterns (graph-based learning; Karuza, Thompson-Schill, & Bassett, 2016; Lynn & Bassett, 2020). Differences in network properties of learned contexts between patients with PTSD and control subjects could possibly provide valuable information on underlying psychopathological mechanisms of learning. Future research could study learning of environments and differences in graph-based learning of safe and dangerous environments.

3.3.3 Translational Research: From the laboratory into the clinic

The studies reported in this thesis also have potential clinical implications. Whereas the first two studies on structural differences in PTSD could potentially contribute to neuroscience-based treatment approaches (Linhartová et al., 2019; Lubianiker et al., 2019; Nicholson, Rabellino, et al., 2017), the latter could contribute to a better understanding of the

mechanisms behind exposure-based treatments (Bouton, 1988; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). First, neuroscience-based treatments like neurofeedback target mechanism-oriented and personalized neuromodulation (Lubianiker et al., 2019). Findings from studies on structural differences whose results are embedded in psychobiological models are especially valuable in this context for determining regions of interest or connections of interest (e.g. PFC-amygdala) for modulation. Second, trauma-focused exposure therapy, as gold standard of evidenced-based treatment approaches for PTSD (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013; Cusack et al., 2016; Watts et al., 2013), works with the element of contextualization of the traumatic experience, both spatially and temporally (Brewin, 2001; Elbert & Schauer, 2002). One example would be Narrative Exposure Therapy (NET; (Lely, Smid, Jongedijk, Knipscheer, & Kleber, 2019; Schauer, Neuner, & Elbert, 2011; Siehl, Robjant, & Crombach, 2020), an evidence-based, trauma-focused, short-term treatment for survivors of violence and war. Here, elements of context processing are integrated throughout therapy. First, a lifeline is used for the contextualization of the traumatic event within a client's narrative story of his or her life. Second, clients go through multiple sessions of prolonged exposure (Foa, 2011), in which they are exposed, in sensu, to their traumatic memories. The worst scene, the so-called "hot spot", is then contextualized, via the integration of verbal reports about sensory (e.g. smell of burned skin) and environmental elements (e.g. the sun was shining) of the scene. A better and more detailed understanding of fear learning and context processing in PTSD could help to identify moments in which beneficial context processes could be maximized. Enhancing these windows of change would thereby also enhance treatment efficacy.

3.4 Conclusions

In this thesis, structural and functional neuroplasticity of patients with PTSD were assessed, associated with processes of fear learning and context processing and interpreted within a psychobiological model of PTSD. Only very few studies have linked neurobiological differences, in particular in frontal white matter, to behavioral and psychophysiological markers of PTSD. This work provides a large systematic review and meta-analysis on the current findings of diffusion tensor imaging in PTSD, besides an empirical study investigating structural white and gray matter in relation to symptom severity. The results suggest that lower fractional anisotropy in frontal white matter tracts such as the forceps minor, anterior parts of the cingulum and corpus callosum can be associated to difficulties in top-down

control of fear-related symptoms. In addition, long-reaching fiber tracts like the inferior- and superior longitudinal fasciculi, involved in visual spatial attention, show lower fractional anisotropy in patients with PTSD in comparison to trauma control subjects. Furthermore, we found potential evidence of lower BOLD activity in the ventromedial prefrontal cortex but not in the hippocampi or amygdalae, during fear acquisition of an unpredictable context, in patients with PTSD in comparison to two healthy control groups. There were no behavioral or psychophysiological differences between the groups in that condition or during the predictable context. This again suggests that patients with PTSD show an impaired top-down control of fear during contextual fear acquisition. In combination, these results suggest that white matter tracts can be associated to fear- and context related processes in PTSD. A reduced streamline count in frontal white matter as well as lower functional activity within the prefrontal cortex can be associated to deficits in top-down control of contextual fear acquisition in PTSD. In the future, a refined understanding is needed of how important factors such as timing or type of the traumatic experience interact with neurodevelopmental trajectories of individual brain structures. The tools, imaging techniques and paradigms exist to test current psychobiological models of PTSD. The time is ripe to deepen and refine our understanding of the interaction between psychological and neurobiological mechanisms underlying PTSD. Let’s continue.

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