Neurobiological Underpinnings of Trauma-related Psychopathology

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List of Abbreviations

BDI-II	Beck Depression Inventory
CAPS	Clinical Interview for DSM-IV Dissociative Disorders
CDS-30	Cambridge Depersonalization Scale
CSD	Constrained spherical deconvolution
CTQ	Childhood Trauma Questionnaire
DES	Dissociative Experiences Scale
DPD	Depersonalization/Derealization disorder
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM 5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DWI	Diffusion-weighted magnetic resonance imaging
ERQ	Emotion Regulation Questionnaire
FA	Fractional anisotropy
fMRI	functional magnet resonance tomography
IPDE	International Personality Disorder Examination
Lt	Initial-link threshold
MRI	Magnet resonance tomography
NBS	Network-based Statistics
PTSD	Posttraumatic stress disorder
PTSD-D	Dissociative subtype of posttraumatic stress disorder
r-DRT	Revised dual representation theory
ROI	Region of interest
rTMS	Repetitive transcranial magnetic stimulation
SCID-D	Structured Clinical Interview for DSM-IV Dissociative Disorders

SCID-I	Structured Clinical Interview for DSM-IV
STAI-T	State-Trait Anxiety Inventory
VVS	Ventral visual stream

1. Abstract in English and German

1.1 Abstract

The understanding and treatment of trauma-related psychopathology is a crucial challenge in the field of global mental health today. The etiology and mechanisms of two common trauma-related symptoms – intrusive re-experiencing and dissociative symptomatology – are still not well understood. The present work aims to advance the understanding of these phenomena by investigating their neurobiological underpinnings in two disorders: depersonalization/derealization disorder (DPD), in which dissociation depicts the core feature, and the dissociative subtype of posttraumatic stress disorder (PTSD-D), in which dissociative symptomatology and intrusive re-experiencing co-occur and correlate in regard to their severity. Alterations in fiber tract networks in white matter, which are crucial for communicating between brain regions, have not yet been investigated in DPD or PTSD-D. In Study I, white matter network alterations were explored in 23 patients with DPD compared to 23 matched healthy controls. Results yielded relatively lower structural connectivity in left and right temporal regions in DPD, which have previously been associated with dissociative symptomatology in DPD and in other disorders. Furthermore, a trend indicated alterations in a fronto-limbic circuit, which a neurobiological model proposes underlies dissociation in DPD as well as PTSD-D. In Study II, we tested whether fronto-limbic circuits are also altered in PTSD-D (*n*=23) compared to 'classic' PTSD patients (*n*=19) using the same analysis pipeline as in Study I. No respective white matter changes were detected on a network level in PTSD-D. However, subsequent exploratory analyses revealed alterations in two subcortical networks comprising a limbic-thalamic circuit and low-level motor regions, respectively. The limbic-thalamic network is crucial for declarative and spatial mnemonic processes, which according to dual memory models play a crucial role for the development of intrusive memories. We tested the respective memory model in Study III and confirmed for the first time empirically, that spatial-contextual (allocentric) memory ability is negatively associated with severity of intrusive memories in 33 patients with PTSD. The findings of the present work indicate that (1) dissociation in DPD is underpinned by different alterations in structural connectivity than in PTSD-D and (2) dissociative and intrusive memories are associated with aberrations in similar sub-cortical circuits, supporting the notion that in PTSD-D, a lower state of

consciousness exacerbates de-contextualization of the traumatic content, resulting in heightened intrusive symptomatology. Clinical implications of our findings are discussed.

1.2 Zusammenfassung

Eine der wichtigsten Herausforderungen im Rahmen globaler Gesundheit ist das Verständnis und die Behandlung Trauma-assoziierter Psychopathologien. Die Ätiologie und zugrundeliegenden Mechanismen zweier häufig auftretender Trauma-assoziierter Symptome – intrusives Wiedererleben und dissoziative Symptomatologie – sind bis heute nicht eindeutig geklärt. Die vorliegende Arbeit zielt darauf ab, durch die Untersuchung neurobiologischer Mechanismen in zwei Störungen das Verständnis dieser Phänomene zu verbessern: In der Depersonalisation/Derealisation Störung (DPD), in der Dissoziation die Kernsymptomatik darstellt, und im dissoziativen Subtyp der Posttraumatischen Belastungs-störung (PTSD-D), in welchem dissoziative Symptome und intrusives Wiedererleben gemeinsam auftreten und hinsichtlich ihrer Schwere miteinander korrelieren. Netzwerkveränderungen der zerebralen Nervenbündel, die kritisch für die Kommunikationen zwischen Gehirnregionen sind, wurden bislang weder in der DPD noch in der PTSD-D untersucht. In Studie I wurden strukturelle Netzwerkveränderungen in 23 Patienten mit DPD im Vergleich zu 23 gesunden Kontrollen exploriert. Die Ergebnisse zeigten eine relativ verringerte strukturelle Konnektivität in DPD Patienten innerhalb des linken sowie des rechten Temporallappens, die bereits zuvor mit dissoziativer Symptomatik in der DPD und in anderen Störungen assoziiert wurden. Des Weiteren fand sich ein Trend, der auf Alterationen in einem frontal-limbischen Netzwerk hindeutet, von dem neurobiologische Modelle annehmen, dass hiesige Dysfunktionen der Dissoziation sowohl der DPD als auch der PTSD zugrunde liegen. In Studie II wurde anhand des gleichen Analyseprozesses wie in Studie I getestet, ob frontal-limbische Schaltkreise auch in PTSD-D Patienten (*n*=23) relativ zu Patienten der „klassischen“ PTSD (*n*=19) verändert sind. Es zeigten sich keine entsprechenden relativen Netzwerkveränderungen in der weißen Masse in der PTSD-D. Eine anschließende explorative Analyse zeigte jedoch Alterationen in zwei subkortikalen Netzwerken, die limbisch-thalamische bzw. basale motorische Regionen umfassen. Limbisch-thalamische Verbindungen spielen eine wichtige Rolle bei deklarativen und räumlichen Gedächtnisprozessen, von denen duale Gedächtnismodelle annehmen, dass

sie eine zentrale Rolle bei der Entstehung von intrusiven Erinnerungen spielen. Wir testeten in Studie III das entsprechende theoretische Modell und konnten erstmals empirisch nachweisen, dass die räumlich-kontextuelle (allozentrische) Gedächtnisleistung mit der intrusiven Symptomschwere in 33 PTBS-Patienten negativ assoziiert ist. Die Ergebnisse der vorliegenden Arbeit deuten darauf hin, dass (1) Dissoziation in der DPD mit unterschiedlicher strukturelle Konnektivität assoziiert ist im Gegensatz zur PTSD-D und dass (2) dissoziative und intrusive Symptome mit ähnlichen subkortikalen Netzwerkveränderungen assoziiert sind. Dies unterstützt die Annahme, dass in der PTSD-D ein verringerter Bewusstseinszustand die De-kontextualisierung traumatischer Inhalte verstärkt und eine erhöhte intrusive Symptomatik nach sich zieht. Klinische Implikationen der Ergebnisse werden diskutiert.

2. Introduction

Most people will experience at least one traumatic event in their life, ranging from a singular event, such as the death of a loved one or witnessing a motor vehicle accident, to events affecting entire communities over several years like war and conflict. Whereas the experience of a traumatic event is usually processed healthily (cf. Bonanno, 2004), some individuals go on to develop psychopathologies. Various biological, psychological, and social factors are suggested to play a role in the type of pathological development and its maintenance (cf. Priebe, Schmahl, & Stiglmayr, 2013). This thesis aims to contribute to the understanding of the complex etiology by examining the neurobiology that may underlie two common trauma-related symptoms: dissociation and intrusive memories.

Dissociation is a heterogenic phenomenon and can refer to alterations in various human domains, such as identity, consciousness, memory, or perception, while intrusive memories refer to dysfunctional mnemonic processes and describe the re-experiencing of a past event (APA; American Psychiatric Association, 2000). Current research suggests a strong link between traumatic experiences and the occurrence of dissociative phenomena (Dalenberg et al., 2012) as well as intrusive memories (Brewin, 2015). While transient dissociative and intrusive symptoms may be adaptive during or in the aftermath of trauma, persistent dissociation as well as recurrent intrusive memories have been related to psychopathology (APA, 2013). Intrusions depict one of the hallmark symptoms of posttraumatic stress disorder (PTSD), which develops after at least one traumatic event. Individuals with PTSD, who experience additional dissociative symptomatology may be diagnosed with the dissociative subtype of PTSD (PTSD-D). Some studies have shown that patients with PTSD-D display higher symptom severity, mediated by heightened intrusive symptomatology (Stein et al., 2013; Wolf et al., 2012).

A debate exists on how intrusive memories arise. Whereas a unitary memory model considers intrusive memories to be ordinary yet strong autobiographical memories (Rubin, Berntsen, & Bohni, 2008), dual memory accounts consider trauma memories to be ‘special’ (Brewin, Dalgleish, & Joseph, 1996; Brewin, Gregory, Lipton, & Burgess, 2010; following Nadel & Jacobs, 1998). They assume intrusions arise due to an imbalance between two distinct

memory representations: sensory and contextual representation. Brewin et al. (2010) postulate that during peritraumatic processing, sensory representations are upregulated via activity in early sensory areas (insula and amygdala), while contextual representations are only weakly formed following decreased activity in the hippocampal formation – a structure crucial for declarative (Tulving & Markowitsch, 1998) and spatial memory (King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002). Accordingly, in patients with PTSD, sensory cues trigger involuntary retrieval of those de-contextualized images 'bottom-up', whereas in healthy memory, voluntary recall of a traumatic event is formed in the hippocampal system controlled 'top-down' via prefrontal brain structures (cf. Bisby & Burgess, 2017). Brewin et al. (2010) propose that dissociation in the traumatic moment ('peritraumatic') impedes the disintegration of sensory with its corresponding contextual representation by interrupting conscious processing of the trauma. Congruently, meta-analyses have identified peritraumatic dissociation as the strongest predictors for the development of PTSD (Breh & Seidler, 2007; Ozer, Best, Lipsey, & Weiss, 2003). In contrast, some studies emphasize the role of posttraumatic dissociation in the development of PTSD (e.g. Murray, Ehlers, & Mayou, 2002) and it is possible that both play a role, in that peritraumatic dissociation obstructs contextualizing the scene in the traumatic moment while posttraumatic dissociation impedes recovery from trauma by continuously hindering the integration of the event into the autobiographical memory base, leading to the chronification of PTSD via persistent intrusive symptomatology. If so, it still remains unclear how peri- and posttraumatic dissociation relate to intrusive memory experience on a neurobiological level.

In dissociative disorders, persistent or repeated episodes of dissociation constitute the core feature, whereas intrusive symptomatology is not part of the diagnostic criteria (APA, 2013). Yet, memory disturbances in form of amnesia depicts the hallmark symptom of dissociative amnesia and has also been reported to be present in dissociative identify disorder (Laddis, Dell, & Korzekwa, 2017). Research has shown that trauma plays a crucial role in the development of dissociative amnesia and dissociative identity disorder (Spiegel et al., 2011). However, inconsistent findings exist regarding the link between trauma and the etiology of depersonalization/derealization disorder (DPD; cf. Hunter, Phillips, Chalder, Sierra, & David, 2003; Simeon, Guralnik, Schmeidler, Sirof, & Knutelska, 2001). In dissociative disorder, individuals experience recurrent episodes of feeling detached from themselves

(depersonalization) and/or their environment (derealization). These dissociative symptoms are also present in patients with PTSD-D (APA, 2013). Congruently, neurobiological models seeking to explain dissociative symptomatology in either disorder do partially overlap. In DPD, two neurobiological models of dissociation have received attention in the literature: An early theory, which attributes a crucial role to the temporal lobe (Penfield & Rasmussen, 1950) and a more recent one, that proposes emotional processes (underpinned by limbic structures in the brain) to be overregulated by structures involved in cognitive control (i.e. prefrontal cortices; Sierra & Berrios, 1998). The model of fronto-limbic inhibition, but not the temporal-lobe hypothesis, is in line with neurobiological models proposed for PTSD-D (Lanius et al., 2010). Yet, empirical evidence supporting these neurobiological models is scarce. In DPD, functional imaging studies suffer from small sample sizes and – like structural imaging accounts – have solely focused on neural alterations in locally distinct brain areas. However, theoretical models suggest dysfunctional interaction of multiple structures in DPD (Sierra & Berrios, 1998; also see Edelman & Tononi, 2000). Novel neuroimaging and analysis tools enable the investigation of brain connectivity, which can refer to networks of anatomical links ("structural connectivity") or to temporal correlations of neural activity ("functional connectivity") between distinct brain regions (Rubinov & Sporns, 2010). In PTSD-D, studies did investigate functional connectivity and results demonstrated tentative support for the model of fronto-limbic inhibition (cf. Lanius et al., 2010), though various shortcomings remain. First, the results are highly inconsistent regarding the precise frontal and limbic structures involved. Second, only connectivity proceeding from pre-defined structures have been examined (so called “seed-based analyses”), while no whole brain analysis has been conducted thus far; and thirdly, no study to date has examined structural connectivity in PTSD-D.

The present thesis tries to address the aforementioned empirical shortcomings by using novel neuroimaging analysis techniques as well as behavioral experiments across three single studies. The objective is to examine the structural connectome, that is, the architecture of the white matter fiber bundles of the brain that interconnect distinct brain regions, in patients with DPD (Study I) and PTSD-D (Study II). Furthermore, implications of the neurobiological model regarding intrusive symptomatology will be tested across patients with PTSD and PTSD-D (Study III). Results will provide indications on whether dissociation is hard-wired in DPD and

PTSD-D and if so, whether structurally connectivity associated with dissociation may be distinct in these disorders. Results will provide valuable contributions to conceptualizing dissociation in DPD and PTSD-D. Furthermore, testing implications of the dual representation account regarding intrusive memory development will strengthen theory building and inform novel clinical interventions for PTSD patients. Finally, findings on hard-wired changes in PTSD-D could enable an integrative discussion within the context of the tested neurobiological model of intrusive symptomatology, advancing the understanding of the empirical link found between dissociative and intrusive symptomatology in PTSD-D.

3. Theoretical Background

3.1 Dissociation and Trauma

3.1.1 Definition and transdiagnostic perspective

Terminologically, dissociation means the opposite of association and describes a state of disconnection between entities that are usually linked with each other. In psychology, dissociation refers to the dysfunction of the normal integration of identity, consciousness, memory, and perception of one's environment (DSM-IV; APA, 2000). Psychological dissociative symptoms can further comprise disturbances in the integration of cognitive and emotional processes, while dissociations that relate to neurophysiology, encompass the fragmentation of sensory and motor functions (World Health Organization, 1992).

Dissociative symptoms occur in nearly all mental disorders with dissociative identify disorder demonstrating the highest symptom severity, followed by PTSD, borderline personality disorder, and conversion disorder (Lyssenko et al., 2018). Dissociation can be experienced comorbidly, that is, it is not part of the diagnostic criteria of the primary disorder, but may be experienced transiently, as in schizophrenia (Ross & Keyes, 2004) or obsessive-compulsive disorder (Rufer, Fricke, Held, Cremer, & Hand, 2006). Furthermore, dissociative phenomena can be part of the diagnostic criteria of a primary disorder, like in PTSD (Daniels et al., 2012), in which they *may* be present, or in borderline personality disorder (Spitzer, Effler, & Freyberger, 2000), in which they *have to be* present for the diagnosis to be given. Finally, dissociative symptomatology constitutes the core feature of dissociative disorders, in which mostly single dissociative symptom clusters have manifested themselves (Spiegel, 1993; Spiegel et al., 2011).

Dissociation is a heterogenic phenomenon and can refer to different entities of the human cognitive, emotional, and physical domain. Within the scope of this thesis, only the characteristics of dissociative experiences relevant for the present work will be outlined: (a) dysfunction of identity and (b) dysfunction of memory. (a) Disturbances of one's identity refers to any miscomprehension of oneself or its boundaries to the external world. The dissociative symptoms depersonalization and derealization are dissociative symptoms that

refer to an altered sense of identity (Priebe et al., 2013), although they have also been conceptualized as alterations of consciousness (Cardeña & Weiner, 2004). Depersonalization describes the subjective experience of feeling detached from one's own self. Sufferers may describe their experience like watching themselves from outside of their body or feeling like a robot (Priebe et al., 2013). Derealization refers to the sensation of being detached from the environment. Sufferers may experience the world or the people around them as unreal or as they are viewing life from behind glass (APA, 2013). Disruption of identity also refers to the experience of more than one personality state or identity to be present, as in dissociative identity disorder. Dissociative identity disorder is the most severe and chronic form of dissociation and has been linked to severe childhood trauma (Ellason, Ross, & Fuchs, 1996). (b) Disturbances in memory comprise any form of impairments in encoding and recalling information or experiences. The dissociative disorder 'dissociative amnesia' describes the inability to recall autobiographical information, which often refers to a traumatic or stressful event (Staniloiu & Markowitsch, 2014). Patients with dissociative amnesia may not be able to recall time periods of a few hours, days or several years, while memory loss can also affect a specific category of information, for example the family or a location (cf. Spiegel et al., 2011). Dissociative amnesia has also been described in patients with dissociative identity disorder (Laddis et al., 2017) and is part of the diagnostic criteria of PTSD (APA, 2013). Another dissociative phenomenon that relates to dysfunctional memory processes are flashbacks (APA, 2013). Flashbacks are involuntarily recalled memories, in which an individual re-experiences a past event or fragments of an experience. In its pathological form, as experienced by patients with PTSD, the mnemonic content of a flashback refers to a traumatic experience (APA, 2013; Brewin, 2015).

As already indicated in the previous paragraph, dissociation has been associated with aversive or traumatic experiences. One of the first to describe a link between dissociation and trauma, and to investigate this systematically, was Pierre Janet in the 19th century. He conceptualized dissociation as a complete loss of conscious controls over behavior or memory and described dissociative reactions as a psychological defense mechanism against overwhelming traumatic experiences. According to Janet (1907), the pathological mechanism of dissociation refers to the detachment of sensory processes from consciousness. While Janet's proposed link between trauma and dissociation still holds in modern age, researchers today are debating

on how dissociation should be conceptualized (for review see Holmes et al., 2005). A concept that has been put forward entails that dissociation lies on a single continuum, with non-pathological and pathological dissociation on either end (cf. Braude, 2009). According to this notion, all dissociative phenomena are similar in quality, differing only in their degree. This unitary concept has been challenged by other authors arguing that dissociative phenomena are qualitatively different from each other (Allen, 2001; Brown, 2002; Putnam, 1997). For instance, Allen (2001) proposed two distinct forms of dissociation, that is 'detachment', which comprises depersonalization and derealization, and 'compartmentalization', which entails more dramatic forms of dissociative phenomena, such as amnesia or dissociative identity disorders. Empirical evidence regarding either concept stems mainly from factor analyses of the most commonly used measurement instruments of dissociation – the Dissociative Experiences Scale (DES; Carlson & Putnam, 1993). The majority of studies in clinical and non-clinical populations indicate that the DES comprises three factors: (1) depersonalization/derealization (2) dissociative amnesia and (3) absorption (e.g. Ross, Ellason, & Anderson, 1995; Sanders & Green, 1994; Stockdale, Gridley, Balogh, & Holtgraves, 2002). Since most researchers consider absorption to be a non-pathological phenomenon of dissociation (Spiegel et al., 2011), the factor analyses support the dichotomy model of detachment (depersonalization/derealization) and compartmentalization (amnesia) as qualitatively distinct forms of pathological dissociation. In contrast, some studies found one-factor solutions of dissociation, which would be in line with the unitary model of dissociation (e.g. Fischer & Elnitsky, 1990; Holtgraves & Stockdale, 1997). However, these studies were solely run in non-clinical populations, leaving it unclear whether a one factor model would also apply to pathological forms of dissociation. Generally, it should be noted that the validity of these factor analyses is limited as they are based on a single measurement instrument, which may not assess all forms and severity of dissociative phenomena. For instance, the DES does not measure conversion symptoms (e.g. disembodiment; the German version FDS has added respective items; Spitzer, Mestel, Klingelhöfer, Gänsicke, & Freyberger, 2003). Hence, conceptualizing the phenomenon dissociation based on measurement items that are derived from a pre-defined idea of what dissociation should measure, may not capture all forms of dissociative symptoms and detect respective qualitative differences.

Non-pathological dissociation is considered an adaptive mechanism to acute or chronic psychological trauma and has been suggested to ensure survival in situations of persistent threats or inescapable captivity (cf. Spiegel et al., 2011). Models on adaptive defense mechanism in humans are mostly based on animal models and dissociation has been described to be a homologue of 'freezing' in animals – a condition of tonic immobility (cf. Lanius, Paulsen, & Corrigan, 2014). In an overview, Hagenaars, Oitzl, and Roelofs (2014) differentiate between two states of freezing, both characterized by tonic immobility. The first one is characterized by heightened muscle tone, which is assumed to occur while the animal is still able to escape, while the other is associated with a loss of voluntary motor function, which is thought to occur during direct contact with the perpetrator without any chance of escape. Though findings in animal studies are not conclusive, they suggest that during the first process, both parasympathetic and sympathetic systems are activated, which is often indicated by reduction in heart rate and increase in heart rate variability (as a marker for parasympathetic control). Respective patterns have been found in humans during acute dissociative symptomatology (Griffin, Resick, & Mechanic, 1997; Lanius et al., 2001).

This evolutionary mechanism is considered as an adaptive response to acute or chronic psychological trauma and has been suggested to ensure survival in situations of inescapable captivity (cf. Spiegel et al., 2011). Yet, persistent dissociation in the absence of threat has been associated with trauma-related psychopathology (Bremner & Marmar, 2002; Diseth, 2006; Dutra, Bureau, Holmes, Lyubchik, & Lyons-Ruth, 2009; Lynn et al., 2014). Advocates of the 'fantasy model' deny this relationship and claim that trauma histories are largely confabulations resulting from fantasy proneness and suggestibility in dissociative individuals (e.g. Giesbrecht, Lynn, Lilienfeld, & Merckelbach, 2008). However, empirical evidence strongly supports an association between trauma and dissociation, even if suggestibility is controlled for (Dalenberg et al., 2012). Studies have shown that the type of trauma (e.g. interpersonal or natural disaster), length of trauma (e.g. singular or persistent) as well as the age at trauma (e.g. childhood or adulthood) contribute differently to the development of dissociative symptomatology. Studies found that interpersonal traumatization, compared to natural disaster or motor vehicle accidents, constitutes a heightened risk for the occurrence and development of dissociation, specifically, if it occurs at an early age (cf. Carlson, Dalenberg, & McDade-Montez, 2012). Childhood maltreatment (e.g. physical, emotional or

sexual abuse or neglect) has been associated with greater levels of dissociative symptomatology, for example in 554 young healthy adults (Teicher, Samson, Polcari, & McGreenery, 2006), 98 female psychiatric impatient (Chu & Dill, 1990), in 167 male survivors of sexual abuse (Yiaslas et al., 2014), 47 institutionalized adolescents (Sanders & Giolas, 1991), and in 134 patients with posttraumatic stress disorder (Steuwe, Lanius, & Frewen, 2012). These findings suggest that traumatic stress during sensitive periods in neurodevelopment may cause the developing brain to organize in accordance to the used threat response (cf. Perry, Pollard, Blakley, Baker, & Vigilante, 1995). A lower risk to develop dissociation after non-interpersonal trauma or trauma in adulthood is compromised if length of trauma is considered. For instance, so called type-II traumata, which refer to long-term and persistent traumatization, such as torture or political imprisonment, which may or may not be of interpersonal nature, can lead to heightened dissociation. Warren, Loper, and Komarovskaya (2009) investigated 203 detained women, who experienced multiple traumatic experiences in their life. Approx. half of them fulfilled criteria for posttraumatic stress disorder (cf. section 3.2.2) and within this subgroup, 92.2% of women reported feelings of dissociation. It has been suggested that chronic trauma exposure may lead to heightened reliance on dissociation as a coping mechanism, which in turn can impede behavioral adaptation and emotion regulation of the traumatic experience (Cook et al., 2017). Taken together, it is possible that these two mechanisms intertwine, in that dissociation presents a passive automatic response to acute threat, whereas after long-term exposure to threat, dissociation can turn into a conscious coping mechanism.

3.1.2 Dissociation in posttraumatic stress disorder

PTSD is a psychological disorder that can develop as a consequence of one or more traumatic events. Dissociative symptomatology may occur in this condition, which will be outlined below, but does not depict a core feature as it does in DPD. In western societies, PTSD has a life time prevalence of 5.7% in the general population (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012), which increases to 15.3% in persons who have experienced interpersonal trauma (Kilpatrick et al., 2013) and can rise to 69%-92% in populations affected by war and torture (Kolassa, Kolassa, Ertl, Papassotiropoulos, & De Quervain, 2010; Moisander & Edston, 2003).

In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM 5; APA, 2013) PTSD is listed under the new chapter, trauma- and stressor related disorders'. A traumatic event in the DSM 5 is defined as a direct or indirect confrontation with death or threatened death, actual or threatened serious injury, or actual or threatened sexual violence (Diagnostic criterion A). The clinical phenotype of PTSD is characterized by the following four groups of symptoms (cluster B-E): Persistent intrusive symptoms (cluster B), which refer to the re-experiencing of the traumatic event. According to the DSM 5 individuals must have at least one symptom of trauma-associated re-experiencing (e.g. intrusive memories or nightmares). Cluster C comprises the avoidance of internal (e.g. thought or feelings) or external (e.g. places or objects) trauma-relevant stimuli. At least one avoidance symptom must be present. Cluster D refers to negative thoughts or feeling, such as exaggerated self-blame or the inability to recall key aspects of the trauma. Cluster E – trauma-related arousal and reactivity – refers to symptoms such as aggressive behavior, hypervigilance or sleep disturbances. For a PTSD-diagnosis to be given, at least two symptoms of cluster D and E must be fulfilled.

Within these symptom groups, two dissociative symptoms are entailed: (1) Dissociative re-experiencing (e.g. flashbacks), which is assumed to exist on a continuum from short intrusive episodes to complete loss of consciousness and (2) partial dissociative amnesia, that is, the inability to remember important aspects of the trauma. Additionally, some patients report symptoms of depersonalization and derealization (for review see Carlson et al., 2012). In the past years, indication accumulated that pronounced dissociative symptoms are not represented dimensionally in PTSD but can be attributed to a distinct subgroup of PTSD patients, leading to the DSM 5 to include the dissociative subtype of PTSD. For this diagnosis to be given, patients must fulfil all diagnostic criteria for classic PTSD while reporting additional symptoms of depersonalization and derealization. In support of this novel sub-distinction, different research groups conducted latent class analyses in different PTSD samples (e.g. Armour, Karstoft, & Richardson, 2014; Blevins, Weathers, & Witte, 2014; Steuwe et al., 2012; Tsai, Armour, Southwick, & Pietrzak, 2015; Wolf et al., 2012). Across twelve studies, Hansen, Ross, and Armour (2017) found the prevalence of PTSD-D ranged from 6% in the sample of military veterans and their intimate partners to 44.6% in victims of incest. The mean prevalence of D-PTSD across studies was 20.35%. Most studies found that

patients with PTSD-D displayed higher symptom severity mediated by higher intrusive symptomatology. How these two phenomena are theoretically and clinically linked will be outlined in section 3.2.2.

3.1.3 Dissociation in depersonalization/derealization disorder

Depersonalization/derealization disorder (DPD) is a dissociative disorder and thus, dissociation constitutes the core entity of this condition. Individuals with DPD experience persistent or recurrent episodes of depersonalization and/or derealization. Alongside these core diagnostic features, sufferers may report distortions and impairments in affective (e.g. emotional numbing), cognitive (e.g. impaired concentration), and somatosensory (e.g. disembodiment) functioning (Baker et al., 2003; Michal et al., 2016; Sierra, 2009). These experiences are not delusional in that patients with DPD are aware that these phenomena are subjective and not an objective reality.

Episodes of dissociative symptoms in DPD are recurrent or persistent and cause significant distress to the people affected. The prevalence of DPD in the general population is estimated to lie between 1 and 2% (Hunter, Sierra, & David, 2004). This deviates immensely from the 12-months prevalence of .007 based on the diagnosis given by clinicians, which has been found in a German study (Michal, Beutel, & Grobe, 2010), suggesting DPD to be severely underdiagnosed (Michal et al., 2010). The onset of DPD is often sudden and lies in early adolescence (cf. Baker et al., 2003; Hunter et al., 2003). The cause of DPD is not well understood. As outlined in section 3.1.1, strong empirical support exist for a relationship between the experience of aversive events in childhood and dissociative symptomatology. However, in DPD, a clear link between childhood trauma and the presence of DPD has not been consistently established. Baker et al. (2003) found that only 14% reported childhood trauma (physical/sexual abuse) as a contributing factor for depersonalization. In a case study of 223 cases of DPD versus 1129 cases of major depression disorder, DPD patients reported more often a family history of anxiety disorders, but less often physical and sexual abuse in childhood as opposed to depressive patients (Michal et al., 2016). Reports of emotional neglect and abuse as well as physical neglect and abuse did not differ between groups. On the contrary, Simeon et al. (2001) found childhood trauma to be highly predictive of the condition and of dissociative symptoms in 49 patients with DPD. The authors identified

emotional abuse as the most significant predictor of DPD. Daniels, Gaebler, Lamke, and Walter (2015), reported significantly higher rates of childhood physical neglect in a DPD cohort of 25 patients compared to 23 individuals in the control group. In addition, non-significant trends pointed towards relatively higher emotional neglect and abuse in the DPD sample (Daniels et al., 2015). It may be that emotional abuse and/or neglect might contribute to the development of DPD rather than physical or sexual abuse. Alternatively, DPD might not relate to trauma as clearly as the other dissociative disorders. Emphasizing this alternative explanation is Hunter et al. (2003), who proposed to conceptualize DPD as an anxiety disorder. Despite the non-established link between trauma and DPD, the authors point towards the high comorbidity between DPD and anxiety as well as panic disorders and claim that after a certain threshold, symptoms of anxiety diverge into a state of depersonalization and/or derealization (Hunter et al., 2003). Apart from the debate regarding the causal model of childhood abuse, studies have shown that DPD can also develop as a result of drug use, mainly cannabis consumption (Medford et al., 2003). One study has shown that a history of social phobia and anxiety may precede the triggering of DPD via drug use (Hurlimann, Kupferschmid, & Simon, 2012), which may provide indirect support for the link between anxiety and DPD development, as proposed by Hunter et al. (2003).

3.1.4 Contrasting dissociation in PTSD and DPD

Quantitatively, it is evident that dissociation depicts the core feature of DPD, whereas in PTSD-D, dissociative symptoms are experienced transiently and alongside classic PTSD symptoms, i.e. intrusions, avoidance, and hyperarousal (APA, 2013). It is less clear whether dissociative symptoms in DPD and PTSD differ qualitatively from each other. Considering the diagnostic criteria as well as the clinical phenotype described in the literature, patients with DPD and PTSD seem to present overlaps regarding their experience of depersonalization and derealization. In addition, patients with DPD report emotional numbing and so do patients with PTSD. This may not be surprising considering emotional numbing has been regarded as a form of depersonalization (Spiegel & Cardeña, 1991). Furthermore, somatoform dissociation has been described in patients with DPD (cf. Sierra, 2009) and also in patients with PTSD (El-Hage, Darves-Bornoz, Allilaire, & Gaillard, 2002; Kienle et al., 2017). Dissociative symptoms that differ between DPD and PTSD-D refer to dissociative amnesia and dissociative

re-experiencing (i.e. flashbacks) in regard to a traumatic event, which unlike to patients with PTSD, DPD patients do not experience (Baker et al., 2003). The question arising is whether these phenomena are qualitatively different between these two disorders, if the dichotomy of detachment and compartmentalization is considered (cf. section 3.1.1). Regarding dissociative amnesia, it has been suggested that voluntary memory deficits for the traumatic event in PTSD are the result of peritraumatic detachment that causes inadequate encoding of the traumatic event (cf. section 3.2.2; Brewin et al., 2010; Ehlers & Clark, 2000; but also see Rubin et al., 2008). However, it is also possible, that amnesia for parts of the trauma reflect a retrieval deficit that prevents fully stored memories from accessing consciousness, and thus presents a form of compartmentalization (Foa, Molnar, & Cashman, 1995). Flashbacks have been more clearly categorized as detachment. Nonetheless, it is difficult to entangle whether peritraumatic dissociation is re-experienced as part of the intrusive memory or whether re-experiencing itself generates feelings of detachment (cf. Holmes et al., 2005). In conclusion, it may be possible that in both disorders, detachment (i.e. depersonalization and derealization) and compartmentalization (e.g. amnesia in PTSD-D and somatosensory distortion in DPD) co-exist. However, whether or not the different forms of dissociative symptoms observed in DPD and PTSD-D are qualitative different between disorders, remains unclear.

3.2 Memory and Trauma

3.2.1 Intrusive re-experiencing in PTSD

PTSD has been conceptualized as a disorder of memory, in which voluntary memory for the traumatic event can be fragmented and part of the trauma involuntary re-experienced in form of intrusive memories or flashbacks. Intrusive memories are memories that are retrieved involuntarily and are not deliberately or consciously recalled. They can occur in various modalities (e.g. visual, auditory, olfactory) and in different forms (e.g. nightmares, flashbacks). Intrusive imagery has been observed in a variety of mental disorders (for review see Brewin et al., 2010), e.g. anxiety disorder (Clark, 1999), obsessive-compulsive disorder (Lipton, Brewin, Linke, & Halperin, 2010), social phobia (Wild, Hackmann, & Clark, 2007), and eating disorders (Somerville, Cooper, & Hackmann, 2007). In this thesis, the focus lies on

visual intrusive memories in patients with PTSD. Intrusive visual memories in PTSD have been found to hold distinct qualities including a high degree of sensory information (van der Kolk & Fisler, 1995), sense of nowness and a lack of temporal and spatial context (Ehlers, Hackmann, & Michael, 2004). Intrusive memories are common immediately after traumatic events and are considered vital for processing the trauma emotionally (Ehlers et al., 2002). However, in patients with PTSD, intrusive memories are persistent and highly distressing and as a consequence, sufferers avoid trauma-reminders that may trigger intrusive memories (Brewin et al., 2010).

There is a debate on whether traumatic memories are 'special'. Some cognitive psychologist argue that traumatic memories are not any different from ordinary autobiographical memories and no special mechanism is needed (Berntsen, 2001; Rubin et al., 2008). In their so called Autobiographical Memory Theory of PTSD, Rubin, Dennis, and Beckham (2011) propose three mechanisms that are involved in autobiographical memory: individual differences (e.g. low vs. high emotional arousal to an event), the memory itself (e.g. more vs. less emotional or often vs. rarely retrieved), and emotion regulation at recall (e.g. low vs. high). The authors argue that these three factors vary across all types of memories, irrespective of whether they traumatic or not, and that PTSD develops due to an increase in these three mechanisms. Empirical support for this model stems from studies showing patients with PTSD rate the quality (emotional arousal, frequency and centrality to one's life) of involuntary, intrusive trauma memories not differently to non-intrusive trauma memories (Rubin et al., 2011; Rubin, Feldman, & Beckham, 2004). These findings contrast with work, in which PTSD patients wrote a trauma narrative and were able to point out parts or words that had different quality, e.g. characterized by a sense of re-living (Halligan, Michael, Clark, & Ehlers, 2003).

In contrast to the Autobiographical Memory Theory of PTSD, other authors argue for a special mechanism to underlie traumatic memories and propose a dual form of memory representation (Brewin et al., 1996; Conway, 2009; Ehlers & Clark, 2000; Nadel & Jacobs, 1998). An influential model is the *revised Dual Representation Theory* (r-DRT; Brewin et al., 2010), which is highly relevant for the present work and will be elaborated in more detail as follows. The r-DRT postulates two connected types of memory to be involved in storing and retrieving intrusive images: (1) contextualized representations, which are responsible for

storing the spatiotemporal context of a specific scene and (2) sensory-bound representations, which carry the respective sensory-perceptual features. Neurobiologically, contextualization of mental imagery is assumed to be formed hierarchically through the ventral visual stream to the hippocampal formation, allowing integration with other autobiographical memories (cf. Brewin, 2015). Sensory representations are proposed to rely on the insula and dorsal visual stream areas, mediated by processes in the amygdala. While the dorsal visual stream is associated with creating images of the environment from a viewer-dependent perspective (egocentric), appropriate contextual encoding additionally requires allocentric processing (viewer-independent). In their r-DRT, Brewin et al. (2010) presume an amygdala-mediated strengthening of egocentric sensory representations during the peritraumatic encoding while a hippocampus-dependent allocentric representation is only weakly formed. According to this model, the rise of intrusive imageries after trauma reflect an imbalance between strong emotion-laden sensory memories and weak associative and contextual representations.

Empirically, the r-DRT has found support in studies with patients and healthy individuals. A common approach to investigate intrusive memories in the laboratory is the trauma film paradigm (for review see James et al., 2016), in which healthy controls watch at least one traumatic video and report the experience of intrusions in a diary over the subsequent days. Researchers have used the trauma film paradigm to manipulate trauma processing either before, during, or after encoding of the traumatic material. Relevant for the r-DRT are findings showing a decrease of intrusive images by deploying a visuospatial task either during encoding (Bourne, Frasquilho, Roth, & Holmes, 2010; Brewin & Saunders, 2001; Holmes, Brewin, & Hennessy, 2004) or directly thereafter (Holmes, James, Coode-Bate, & Deeprose, 2009; Holmes, James, Kilford, & Deeprose, 2010), with preliminary translational evidence in survivors of a motor vehicle accident (Iyadurai et al., 2017). The interpretation of these findings, aligned with the r-DRT, is that visuospatial tasks compete for perceptual resources, which leads to an attenuation of the sensory representation and thus, to less intrusive memories (cf. Brewin, 2014; Stuart, Holmes, & Brewin, 2006). In contrast, a few studies did not detect differences between the visuo-spatial task and no-task condition (e.g. Marks, Steel, & Peters, 2012), though this may have been due to essential differences in the task design.

Studies on individual cognitive differences in healthy individuals have supported implications of the r-DRT by showing contextual or allocentric spatial processing to be inversely related to intrusive memories (Bisby, King, Brewin, Burgess, & Curran, 2010; Meyer, Krans, van Ast, & Smeets, 2017; Meyer et al., 2013). Meyer et al. (2017) tested memory contextualization of learning abilities using a contextual cueing paradigm in 81 individuals. With the trauma film paradigm, the authors found a negative correlation between memory contextualization performance and visual intrusive memories, but not verbal intrusive thoughts (Meyer et al., 2017). Congruently, Bisby et al. (2010) assessed allocentric spatial memory in 48 healthy controls and found that participants' performance correlated negatively with frequency of intrusive memories in the week following the traumatic film. The authors tested further implications of the r-DRT by suppressing hippocampal-dependent memory during traumatic encoding via the administration of alcohol (low/high dosage versus placebo). Consistent with the model, a low dosage of alcohol was linked to reduced allocentric spatial memory performance and resulted in the development of more intrusions. However, a high dosage was associated with lower intrusive memories, which was not clearly interpretable.

In clinical populations, empirical studies that relate directly to the r-DRT are scarce, yet indirect support is present. Reduced hippocampal volume has been reported by numerous studies in PTSD (cf. O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015) and was recently confirmed by the largest neuroimaging study in PTSD today (ENIGMA-PGC consortium study involving 1868 subjects, comparing 794 patients with PTSD to trauma-exposed controls; Logue et al., 2018). Building on these findings, Smith, Burgess, Brewin, and King (2015) investigated allocentric spatial processing and allocentric spatial memory ability in 29 patients with PTSD and 30 trauma-exposed controls. The authors found both hippocampus-dependent allocentric spatial processing and memory to be selectively impaired in PTSD, while egocentric spatial memory was spared. Reduced spatial processing abilities in PTSD compared to trauma-controls have also been reported in other work (Gilbertson et al., 2007; Miller, McDougall, Thomas, & Wiener, 2017; Tempesta, Mazza, Iaria, De Gennaro, & Ferrara, 2012). Yet, in these studies frequency or intensity of intrusive memories have not been acquired in isolation or have not been reported (only overall PTSD symptom severity), and it remains unclear whether the relationship between intrusive

memories and allocentric spatial memory found in healthy cohorts also holds for clinical populations.

3.2.2 Linking dissociative and intrusive symptomatology

As indicated in section 3.1.2, numerous studies have reported an association between dissociative and intrusive symptomatology. Stein et al. (2013) analyzed data from the World Mental Health Surveys of the WHO, which was conducted in 16 countries with 25,018 individuals, and found that patients with PTSD, who have been assessed as dissociative (14.4%), displayed greater intrusive symptom severity. Similarly, Wolf et al. (2012) examined two cohorts of traumatized war veterans and found that PTSD patients with dissociation compared to those without, were characterized by a particular severe intrusive symptomatology.

Clinically, intrusive memories and dissociation are not so clearly distinguishable and can be experienced simultaneously. For instance, patients in the present work have reported re-experiencing parts of the trauma in form of intrusive memories and feeling detached thereby or immediately thereafter. A similar phenomenon was observed in a case series of patients with PTSD, in which feelings of dissociation were commonly reported as part of intrusive memories (Holmes, Grey, & Young, 2005). As already mentioned in section 3.1.4, it is possible that peritraumatic dissociation is re-experienced as part of the intrusive memory, given that dissociation occurred during the traumatic moment. On the other hand, re-experiencing itself might generate feelings of detachment (cf. Holmes et al., 2005). In the DSM 5, as well as the proposed *International Classification of Diseases 11th Revision*, flashbacks are existing on a continuum from involuntary traumatic memories to complete loss of consciousness – a state, which is dissociative in itself. As outlined in the previous section, there is a debate on whether 'dissociative re-experiencing' (i.e. flashbacks according to the DSM 5) is qualitative or quantitatively different from voluntary traumatic memories. According to clinical studies and the dual representation theory, the difference is qualitative (Brewin et al., 2010), whereas cognitive psychologists argue that it is quantitative (Rubin et al., 2008).

Authors in support of the qualitative distinction have suggested that peritraumatic dissociation (mainly detachment) interferes with declarative, contextual processing in the

traumatic moment, leading to poor integration of the traumatic event into autobiographical memory and thus, to the development of intrusive memories (Brewin et al., 2010; Brewin & Holmes, 2003; Ehlers & Clark, 2000). Within the dual representation model, Brewin et al. (2010) propose that the reduction in consciousness caused during dissociation leads to weaker contextual representation to be formed and impedes the integration of sensory and contextual representations. This view has found empirical support in studies with healthy individuals using the trauma-film paradigm, in which peritraumatic dissociation positively predicted the frequency of intrusive memories in the subsequent week (Holmes, Brewin, & Hennessy, 2004; Laposa & Rector, 2012). Specifically, lower heart rate, as an indicator of dissociative responses (Griffin et al., 1997; Sack, Cillien, & Hopper, 2012), during the encoding phase of the film has also been associated with frequency of intrusions (Chou, La Marca, Steptoe, & Brewin, 2014; Holmes et al., 2004) and recognition memory of details (Chou et al., 2014). In the study by Chou et al. (2014), the association between lower heartrate and intrusive memories was only evident in a subgroup of individuals who showed both an atypical sudden reduction in heart rate after a startle stimulus and higher trait dissociation. Alternative models consider reduction in heart rate as an indicator for increased orientation within the early stages of freezing (cf. Adenauer, Catani, Keil, Aichinger, & Neuner, 2010) and it is possible that heightened alertness to the traumatic content of the film increased intrusive symptomatology. Yet, clinical studies with PTSD patients support the view that not heightened levels of alertness, but clinically relevant dissociation is associated with intrusive symptomatology. A meta-analysis of 68 prospective studies (Ozer et al., 2003) identified dissociation during and immediate after the trauma as the strongest predictor for the development of PTSD symptoms (among seven measured predictors). These finding were confirmed by another meta-analysis of 20 quasi-prospective and 15 retrospective studies, respectively (Breh & Seidler, 2007). However, as these meta-analyses are based on overall posttraumatic symptom severity it is not clear whether intrusive symptomatology or potentially other PTSD symptom cluster drive this relationship. Moreover, in most studies, data on posttraumatic dissociation was not collected or reported, and since peritraumatic dissociation highly correlates with posttraumatic dissociation (Daniels et al., 2012; Peltonen, Kangaslampi, Saranpää, Qouta, & Punamäki, 2017), it remains unclear whether dissociation interferes with encoding during the traumatic event or inhibits successful integration into the autobiographical memory base thereafter. Daniels et al. (2012), who investigated acute as

well as peritraumatic dissociation scores (retrospectively), found activation in the right fusiform and lingual gyrus to be associated with peritraumatic dissociation (if controlled for acute dissociation), which are structures involved in the ventral visual stream. This finding supports the notion that peritraumatic detachment directly inhibits contextualization of mental imagery during the traumatic moment. Congruently, Peltonen et al. (2017) showed in a recent longitudinal study with 197 children in the Gaza Strip, that the quality of trauma-related memories mediated the predictive capacity of peritraumatic dissociation on higher levels of posttraumatic symptoms nine months after trauma. In contrast, Murray et al. (2002) found in two samples of 27 and 176 motor vehicle accidents, that persistent dissociation four weeks post trauma was identified as the strongest predictor for the development of PTSD and Briere, Scott, and Weathers (2005) found in two civil cohorts of trauma survivors that the correlation between peritraumatic dissociation and PTSD symptoms dissolves if persistent dissociation is controlled for. Other studies found that peri- (4%) as well as posttraumatic dissociation (8%) contributed to the explained variance (Werner & Griffin, 2012). Disentangling the influence of both phenomena is exacerbated by the fact that severity ratings of peritraumatic dissociation vary over time (David, Akerib, Gaston, & Brunet, 2010), yet most studies measure peritraumatic dissociation retrospectively.

In sum, results indicate that both mechanism may intertwine, in that peritraumatic dissociation interferes with memory encoding in the traumatic moment, while posttraumatic dissociation impedes integration of the traumatic event into autobiographical memory post trauma, leading to the chronification of PTSD via intrusive symptomatology. It should be noted however, that dissociation during or after the traumatic event does not present a pre-requisite for the development of PTSD. Numerous individuals who develop PTSD do not report having experienced dissociative symptomatology during or after trauma (Harvey & Bryant, 2002; also see Bryant, 2011), suggesting that intrusive memories are not solely a product of peri- or posttraumatic dissociation, respectively.

3.3 Neurobiology of Intrusive and Dissociative Symptomatology[1]

3.3.2 Neurobiology of intrusive re-experiencing and dissociation in PTSD

Among researchers, a relative consensus exists regarding functional neurobiological mechanism of 'classic' PTSD symptomatology, that is, without additional profound dissociative symptoms. A recent meta-analysis on 36 functional neuroimaging studies in PTSD has reported hyper-responsiveness of the amygdala and hypo-responsiveness of the medial prefrontal cortex (Patel, Spreng, Shin, & Girard, 2012). The studies included in this meta-analysis varied in regard to their experimental design and thus, the findings may reflect classic PTSD symptomatology rather than intrusive re-experiencing. Another meta-analysis focussed on the reaction to trauma-related stimuli versus a control condition (Sartory et al., 2013) and found that across 19 studies PTSD patients showed heightened activation of the retrosplenial cortex and precuneus in response to trauma-related stimuli. The retrosplenial cortex has been suggested to be involved in a range of cognitive functions, including episodic memory, navigation, and imagination (Vann, Aggleton, & Maguire, 2009) while the precuneus is thought to be crucial for visuo-spatial imagery and episodic memory retrieval (Cavanna & Trimble, 2006). These findings may relate specifically to intrusive memories and compliment the assumptions of the r-DRT. In regard to structural neurobiological alterations associated with intrusive re-experiencing, evidence is scarce as most studies in this field focused on general PTSD symptom severity instead of distinct symptom clusters (cf. Karl et al., 2006). One study has reported reduced volume in the bilateral inferior temporal cortex, which is part of the ventral visual stream and involved in processing the context of visual objects and scenes, to be associated with increased re-experiencing (Kroes, Rugg, Whalley, & Brewin, 2011). Two others reported negative correlations between re-experiencing symptoms and left hippocampal volume in PTSD (Lindauer, Olff, van Meijel, Carlier, & Gersons, 2006; Villarreal et al., 2002).

[1] *Note:* Neurobiology can be divided into neurochemistry, neuroendocrinology, structural and functional neuroanatomy. Within the scope of this thesis, section 3.3 will provide an overview about the structural and functional neurobiological underpinnings of intrusive and dissociative symptomatology in PTSD/PTSD-D and DPD, respectively. However, the interaction of neurochemistry and neuroendocrinology plays an important role in the understand of intrusive and dissociative experiences. For a comprehensive overview on these factors in PTSD see the review article by Rasmusson and Shalev (2014). Gebauer provides a respective overview regarding dissociative symptomatology in her book chapter (Gebauer & Daniels, 2017).

The underlying neurobiological changes associated with dissociative symptoms in PTSD are also still unclear. It has been suggested that dissociative states in PTSD are associated with physiological and neural activation patterns distinct from states of re-experiencing (Lanius et al., 2010). Psychophysiological studies have not been conclusive, but indicate that non-dissociative patients with PTSD display heightened heart rate during trauma-exposure (for review see Bedi & Arora, 2007), while dissociative PTSD patients display unaltered or slightly lower heart rate during acute dissociation (Griffin et al., 1997; Sack et al., 2012; also see Zaba et al., 2015). A neurobiological model put forward by Lanius et al. (2010) postulates that in PTSD, dissociative symptoms arise due to an overregulation of prefrontal cortices on emotional (limbic) structures, while classic PTSD is characterized by hyperactive limbic regions due to insufficient inhibition from frontal regions. The working group around Lanius have used fMRI during symptom provocation ('script-driven imagery') and post hoc correlational analyses with dissociative symptom questionnaires to underpin these assumptions empirically. To demonstrate their degree of overlap, the results will be described in detail here. During acute dissociation, the researchers found positive associations between dissociative symptomatology and regional cerebral blood flow in the left medial frontal gyrus, right superior temporal gyrus (Hopper, Frewen, van der Kolk, & Lanius, 2007), left middle frontal and right superior frontal gyrus (Daniels et al., 2012) and negative correlations with right anterior insula, right inferior frontal, left superior temporal (Hopper et al., 2007), amygdala, left putamen, right anterior cingulate cortex, left superior frontal gyrus (Mickleborough et al., 2011). In very broad terms, these studies taken together indicate heightened blood flow in frontal regions, which are necessary for cognitive control and decreased blood flow in regions responsible for emotion regulation (e.g. amygdala and insula), supporting the model of fronto-limbic inhibition. However, the results are inconsistent regarding the exact activation sights in frontal and limbic areas, while one study also found decreased blood flow in a frontal region (left superior frontal) to be associated with dissociation (Mickleborough et al., 2011). Moreover, the studies have solely performed so called seed-based analyses, in which connectivity from pre-defined structures is examined. No whole brain analysis has been conducted thus far.

Nevertheless, if we assume fronto-limbic inhibition is indeed associated with dissociative symptomatology in PTSD and fronto-limbic disinhibition with classic PTSD symptomatology,

then these opposing neuronal patterns of emotional over- and underegulation co-exist in patients with PTSD-D per definition. This would imply that dissociation may be underpinned by dynamic neural processes in PTSD-D. Yet, two studies have reported correlations between brain morphology and dissociative symptom severity in PTSD. Daniels, Frewen, Theberge, and Lanius (2016) found increased volume of the right precentral and fusiform gyri and reduced volume in the right inferior temporal gyrus in patients with PTSD-D compared to patients with classic PTSD. Dissociative symptoms severity was positively associated with grey matter volume of the right middle frontal gyrus. Nardo et al. (2013) found positive correlations between trait dissociation and grey matter volume of the right medial superior frontal gyrus, and right middle temporal pole in a subclinical sample when correcting on a cluster-level (i.e. across PTSD patients and trauma-controls). Their uncorrected results (voxel-level) expanded to positive correlations between trait dissociation and volume of left middle and superior temporal pole, right angular gyrus (in the parietal lobe) and negative correlation with volume of the right putamen. These findings indicate that emotional overregulation in PTSD-D may be underpinned by differences in grey matter brain anatomy, which could either reflect pre-morbid biological risk factors for dissociative responses or adaptations to their development. However, these structural aberrations only refer to locally distinct areas and no interaction with brain circuits can be inferred from these studies.

3.3.1 Neurobiology of dissociation in DPD

Psychophysiological and neuroimaging research suggests that DPD is underpinned by alterations within neurobiological circuits. In an early model, the neurologist Wilder G. Penfield postulates the 'temporal lobe hypothesis' of depersonalization (Penfield & Rasmussen, 1950). By stimulating parts of the temporal lobe, Penfield was able to induce states of dissociation. He postulated that during dissociation assimilated memories of sensory experiences are disrupted, which rely on temporal regions. The temporal lobe hypothesis has been supported by studies in patients with temporal lobe epilepsy (Hollander et al., 1992; Locatelli, Bellodi, Perna, & Scarone, 1993) and two neuroimaging studies on DPD, which found decreased metabolic rates in the right temporal lobe (Simeon et al., 2000) and less cortical thickness in the right middle temporal gyrus (Sierra et al., 2014). In addition, Mantovani et al. (2011) reported significant symptom reduction in 6 out of 12 participants after three weeks

of low frequency repetitive transcranial magnetic stimulation (rTMS) on the right temporal-parietal junction with the strongest improvement observed in anomalous body experiences (71% improvement in responders; Christopeit et al., 2014).

A more recent theory by Sierra and Berrios (1998) proposes a fronto-limbic dysbalance in DPD. The authors assume that hyperactive prefrontal cortices inhibit emotional, limbic structures, which is in line with theories proposed for the dissociative subtype of PTSD (Daniels et al., 2012; Lanius et al., 2010), described in section 3.2.2. Empirically, studies have used functional magnetic resonance imaging (fMRI) to test this model by using the presentation of affective stimuli (e.g. sad or fearful faces) to show indications of in- or decrease in neural activity. Unfortunately, all fMRI studies to date suffer from very small DPD sample sizes (*n*=9-14). Although this severely limits their validity, the findings will still be listed in the following to provide indications of their overlap. Phillips et al. (2001; *n*=6 DPD patients) found decreased signal in DPD compared to healthy controls in limbic structures, such as the left insula, the bilateral cingulate gyrus, but also in the lingual gyrus, superior temporal gyrus, and left inferior parietal and inferior occipital lobule. Increased relative activity in response to aversive stimuli in DPD patients was found in the right inferior frontal gyrus and right middle temporal gyrus. With a similar task design, Lemche et al. (2008; *n*=9 DPD patients) found 14 clusters activated in DPD patients and emphasized their findings on decreased activation in limbic regions (right amygdala, right hypothalamus) and relative increases in dorsolateral prefrontal regions. The authors also found earlier peaks in haemodynamic response to emotionally salient faces in DPD relative to healthy controls. Medford et al. (2016; *n*=14 DPD patients) reported increased blood flow in DPD to aversive relative to neutral stimuli in the right ventrolateral prefrontal cortex and bilateral medial prefrontal cortex. In an emotional Stroop task, Lemche et al. (2016; *n*=10 DPD patients) found DPD patients to differ from healthy controls in the location of the parietal region involved (inferior vs. superior lobule) and reported that DPD co-activated the dorsomedial prefrontal cortex and posterior cingulate cortex in contrast to healthy controls. Finally, in a treatment study, Medford et al. (2016; *n*=10 for pre/post effects) administered the anticonvulsant Lamotrigine and found that before pharmacotherapy, DPD patients displayed lower activity in the left anterior insula compared to healthy controls while after treatment, the responder of the DPD group (*n*=5) showed increased activity in this region compared to the non-responders (*n*=5).

In conjunction, these studies do overlap regarding their findings of frontal hyper- and limbic hypo-responsiveness to aversive stimuli, yet similar to the empirical evidence regarding the model of fronto-limbic inhibition in PTSD-D, studies in DPD differ immensely in regard to the exact frontal structures involved. Moreover, one study did not find any activation differences between DPD and healthy individuals during encoding of emotional stimuli (Medford et al., 2006; *n*=10).

As criticized at the beginning of this section, the low sample sizes in the fMRI studies limits generalization of these results. In contrast, two recent studies that have investigated cerebral grey matter in DPD are well-powered. The findings showed less cortical thickness in the right middle temporal region (Sierra et al., 2014 *n*=20 DPD patients) and reduction of grey matter volume in the right caudate, right thalamus and right cuneus as well as well as a volume increase in the left dorsomedial prefrontal cortex and right somatosensory region in individuals with DPD compared to healthy controls (Daniels et al., 2015 *n*=25 DPD patients). In the latter, the authors reported an association between all structural alterations and dissociative symptom severity (Daniels et al., 2015). Thus, these studies indicate that DPD might be underpinned by hard-wired changes in the brain. However, all neuroimaging studies to date (except in a single case study; Sedeño et al., 2014), investigated local aberrations in distinct brain areas, although theoretical models propose that DPD symptomatology is underpinned by dysfunctional interaction of multiple brain areas (Sierra & Berrios, 1998; also see Edelman & Tononi, 2000, p. 67, l. 9-12).

4. Aim of Thesis

The overall aim of this thesis is to advance the understanding of neurobiological mechanisms in trauma-related psychopathology by using novel neuroimaging techniques and analysis tools. The focus lies on the trauma-related symptoms (a) dissociation and (b) intrusive re-experiencing as well as on (c) the attempt to relate these phenomena on a neurobiological level.

(a) Based on the existing empirical evidence when this thesis was planned, the neurobiological mechanisms of dissociative symptomatology was still not well understood. First, it remained unclear whether dissociation in DPD, a dissociative disorder, is conceptually and neurobiologically distinct from dissociation in the trauma-related disorder PTSD. Second, valid empirical evidence regarding the neurobiological underpinnings in either disorder is still scarce. Group studies on the underlying neural mechanisms of dissociative symptomatology in DPD have solely focused on locally distinct brain areas, albeit neurobiological models suggest dysfunctional neurocircuitry, which involves multiple structures. In PTSD-D, studies did examine functional connectivity between regions, though inconsistent results on the structures involved limits the validity, while a whole brain approach is outstanding. Thus, the objective of this work is to examine dissociation in DPD and PTSD by analyzing the structural connectome in these patient populations, that is, their neural connectivity in the white matter of the brain. Hence, in Study I, structural connectivity will be explored in a cohort of DPD patients and compared to a group of matched healthy controls. In Study II, white matter network alterations will be examined in patients of the dissociative subtype of PTSD relative to patients with classic PTSD.

(b) In the study of intrusive symptomatology in PTSD, empirical evidence has confirmed impairments in hippocampus-based contextual (allocentric) memory in patients with PTSD and an inverse relationship between allocentric spatial memory and intrusive memories in healthy individuals. However, no systematic investigation of the relationship between allocentric spatial memory, brain morphology, and intrusive memories in PTSD exist and shall be addressed in Study III in this work. The specific aim is to test implications of the dual

representation model and examine whether an association between allocentric memory performance and intrusive memory severity is evident in a clinical population.

(c) Finally, the relationship between trauma-related dissociative and intrusive symptomatology will be discussed by drawing upon potential overlapping neurobiological characteristics.

5. Methods

5.1 Clinical Diagnostics

Clinical interviews or clinical diagnostics, respectively, enable a trained clinician to employ an accurate diagnosis regarding the presence of a mental illness or pathological symptom. For a specific description of the clinical interviews undertaken in Study I, II, and III, please see the method sections in the respective study appendix, as the procedure in Study I differed from the one in Study II and III (note that the sample of Study III derived from Study II). In all studies, participants were invited for a diagnostic assessment by a licensed clinical psychologist before study inclusion. In total, German versions of four standardized clinical interviews were administered to establish the diagnosis of DPD (Study I) and classic PTSD (Study II+III), respectively. To establish the diagnosis of DPD in Study I, the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D; Gast, Zündorf, & Hofmann, 2000) was employed. In Study II, the Clinician-administered PTSD Scale (CAPS-IV; Schnyder & Moergeli, 2002) was implemented to diagnose PTSD. For the diagnosis of axis I disorders, which were partly subject to exclusion (see respective studies for specific exclusion criteria), the Structured Clinical Interview for DSM-IV (SCID-I; Wittchen, Zaudig, & Fydrich, 1997) was administered. To determine whether personality disorders were present the International Personality Disorder Examination (IPDE; Mombour et al., 1996) was used in Study I and the Structured Clinical Interview for DSM-IV axis II (Fydrich, Renneberg, Schmitz, & Wittchen, 1997) was employed in Study II+III.

5.2 Self-report Questionnaires

Self-report questionnaires provide a measure of psychological state or trait characteristics that relies on the individual's own report. Apart from providing a thorough sample characterization, self-report questionnaires are abundant to verify that potentially detected group differences are not based on differences on a symptom level that is not of interest, such as levels of depression or anxiety symptoms. In the present work, almost all self-reports

were gathered using a paper-and-pencil format and all were administered in their German version. In the following, only those are listed that have been implemented in all three studies; for further information, please refer to the method sections of each study in appendix A. We employed the Beck Depression Inventory (BDI-II, Hautzinger, Keller, & Kühner, 2006), the Emotion Regulation Questionnaire (ERQ; Abler & Kessler, 2009), the State-Trait Anxiety Inventory (STAI-T; Laux & Spielberger, 2001), and the Childhood Trauma Questionnaire (CTQ; Wingenfeld et al., 2010). To assess state and trait dissociative symptoms, participants filled out the 30-item and 22-item Cambridge Depersonalization Scale (CDS-30; Michal et al., 2004), respectively as well as the Dissociative Experiences Scale (DES; Spitzer et al., 2003). The German versions of both CDS and DES showed good reliability and internal consistency: The CDS displayed high internal consistency and reliability (*alpha*=0.95 and *Guttman Split-half*=0.95; Michal et al., 2004) and the DES showed a test-retest reliability of *rtt*=0.88 and an internal consistency of *alpha*=0.93 (Freyberger et al., 1998). Finally, we measured information processing speed and executive functions using the Trail Making Test version A and B (Stanczak, Lynch, McNeil, & Brown, 1998), respectively.

5.3 Neuroimaging

5.3.1 Structural magnet resonance imaging

Magnetic resonance imaging (MRI) is a non-invasive biomedical imaging technique that is a widely used research method in neuroscience to acquire an anatomical image of the human brain. Through a strong oscillating magnetic field (in human research usually 1 or 3 Tesla), spinning hydrogen atoms in the human body discharge radio waves, which are detected by a radiofrequency head coil and are used to generate two and three-dimensional images of the brain (cf. Huettel, Song, & McCarthy, 2004).

In all three studies, anatomical MRI scans of the brain, i.e. T1-weighted images, were acquired on a 3 Tesla Siemens Tim Trio scanner (Siemens, Erlangen, Germany) equipped with a 12-channel head coil. Firm foam paddings were placed around the head to minimize head movement during the scan. The structural T1-weighted images were obtained with a magnetization-prepared rapid acquisition with gradient echo sequence using the following

parameters: Repetition time=1.9ms, echo time=2.52ms, inversion time=900ms, flip angle=9°, field of view=256mm, 192 slices, 1mm isovoxels, 50% distancing factor. Measurements of cortical thickness and volume of cortical and subcortical regions, respectively, were acquired using the default settings in *FreeSurfer* v5.3 (Study I) and version v6.0 (Study II and III), respectively.

FreeSurfer is an open-source brain imaging software package to analyze MRI data and to obtain morphometric measurements of distinct brain areas, such as subcortical volume or cortical thickness. A detailed description of all processing steps is described by Fischl and Dale (2000). Important preprocessing steps include intensity normalization, skull stripping, segmentation of subcortical white matter and deep grey matter volumetric structures, and parcellation of the cerebral cortex. In all studies, each output was inspected visually for quality insurance. If the automated segmentation or parcellation was not accurate, it was corrected manually, and the respective processing step rerun in *FreeSurfer*. An example of a T1-weighted image as well as the respective *FreeSurfer* parcellation is provided in Figure 1A and 1B, respectively.

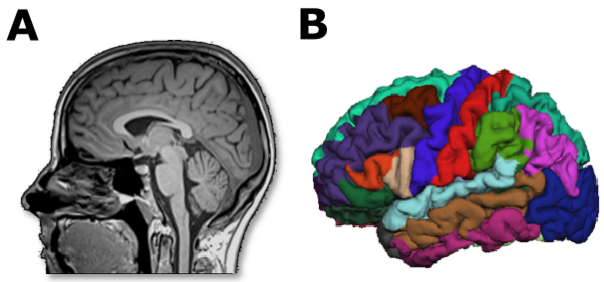

Figure 1. An example of a T1-weighted image and the respective *FreeSurfer* parcellation **A:** A T1-weighted image, that is, an anatomical brain scan. **B:** Example of the cortical parcellation performed by *FreeSurfer*.

5.3.2 Diffusion weighted magnetic resonance imaging

Diffusion-weighted magnetic resonance imaging (DWI) is a non-invasive technique that uses the diffusion of water molecules to image the characteristics of the neuronal white matter (Assaf & Pasternak, 2008). Due to their thermal energy, water molecules are moving constantly, that is, diffuse in the human body. They may diffuse randomly (‘isotropic’), which

is the case in the grey matter of the human brain. In white matter, water molecules diffusivity is restricted to the myelin of axonal fiber bundles. As they cannot diffuse perpendicular to the myelin sheath, they diffuse along the orientation of fiber bundles ('anisotropic'), which enables inferences regarding the course of the major fiber tracts (Beaulieu, 2002). The most commonly used parameter indicating the degree of diffusivity is fractional anisotropy (FA). FA is sensitive to microstructural changes of white matter and thus, may provide indication for pathologic changes or altered structural connectivity (Hasan, Alexander, & Narayana, 2004). Anatomical connections between brain regions can also be measure using diffusion tractography, which has been implemented in the present work as this allows subsequent network analyses of white matter connectivity. Tractography is a modelling technique that uses specific algorithm to reconstruct the pathways of major fiber bundles in the brain (Mukherjee, Chung, Berman, Hess, & Henry, 2008).

In the present work, the preprocessing of the DWI data was performed using the default settings in *ExploreDTI*, version 4.8.6 (http://www.exploredti.com; Leemans, Jeurissen, Sijbers, & Jones, 2009), which runs in MATLAB (MATLAB Release 2014b, https://mathworks.com). Specifically, data was corrected for subject motion using 'Rekindle' methods (Tax, Otte, Viergever, Dijkhuizen, & Leemans, 2015), eddy current induced geometric distortions (Leemans & Jones, 2009), as well as EPI distortions (Irfanoglu, Walker, Sarlls, Marenco, & Pierpaoli, 2012). Subsequently, constrained spherical deconvolution whole brain tractography was performed (Jeurissen, Leemans, Jones, Tournier, & Sijbers, 2011; Tax, Jeurissen, Vos, Viergever, & Leemans, 2014) for each subject. The individual outputs were visually expected for quality insurance. Figure 2A and 2B provides examples of a diffusion weighted image before and after preprocessing, respectively. Figure 2C displays a two-dimensional tractography image.

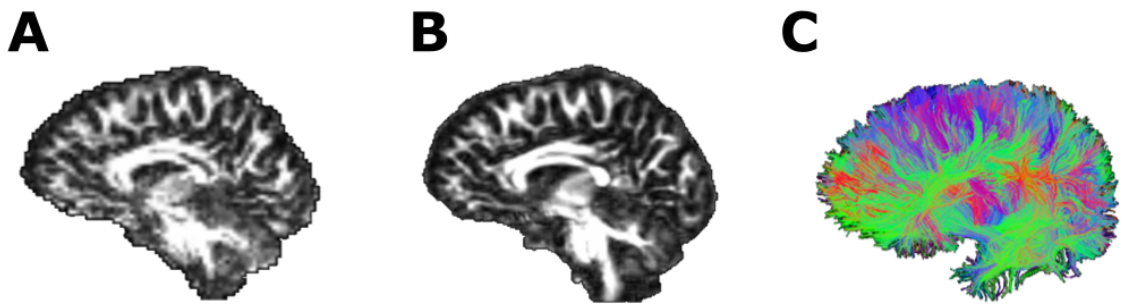

Figure 2. Examples of diffusion weighted images before and after preprocessing. **A:** A diffusion weighted brain scan before any corrections are made. **B:** Diffusion weighted image after correction for subject motion, eddy current induced geometric distortions, and EPI distortions. **C:** Reconstructed fiber tracts after performing while brain tractography. The color scheme represents the orientation of the diffusion directions of the water molecules. Blue is superior-inferior (top-bottom), red is left-right, and green is anterior-posterior (front-back).

5.3.3 Network analysis

Structural connectivity between brain regions can be described by defining networks, which comprise brain regions of interests ('nodes') and interregional structural connections, that is fiber tracts ('edges'). Graph theory is a mathematical approach for the analysis of complex networks, such as the human brain. By applying graph theory to data of diffusion MRI tractography, anatomically localized sub-networks can be identified that are related to a particular effect of interest, such as a psychopathological condition or symptom (Zalesky et al., 2010). In recent years, graph theory has been successfully employed to detect sub-networks associated with neuronal alterations in psychiatric conditions (Bullmore & Sporns, 2009; Fornito, Zalesky, & Breakspear, 2013; Griffa, Baumann, Thiran, & Hagmann, 2013; Zalesky, Fornito, & Bullmore, 2010). In the present thesis, this approach is employed to identify differences in structural connectivity on a network level between patients with DPD and healthy controls (Study I) and between PTSD-D and classic PTSD (Study II).

Specifically, in Study I and II, Network-based statistics (NBS) is performed, which is a nonparametric statistical method developed by Zalesky and coworkers (Zalesky et al., 2010) to identify graph components within a network that are associated with an external variable,

while controlling the family wise error rate (FWER). Within NBS, statistical thresholding is carried out in two steps: first, the hypothesis of interest (*here:* group differences) is tested independently at every connection within a network using so called initial-link thresholds (lt). Adjacent supra-threshold links may ultimately form graph components (i.e. sub-networks). The statistical significance of these graph components at the network level is determined by comparing their size against the occurrence of differently sized graph components generated from random data (i.e. from a null model distribution). In the present work, a corresponding null-model distribution was generated by employing 10,000 permutations and the resulting graph component was considered statistically significant with an FWER-corrected p-value of p_{FWER}<.05.

It is important for the present thesis that variations in initial-link thresholding can be informative regarding the nature of any observed group difference: effects found only at liberal thresholds (e.g. p_{lt}<.05) are expected to be subtle and topologically extended, whereas effects evident at conservative thresholds (e.g. p_{lt}<.001) are likely to reveal strong focal differences between groups (Zalesky et al., 2010). Thus, depending on the a priori hypothesis regarding the network topology, initial-link thresholds may be determined beforehand (e.g. from p_{lt}=.05 or p_{lt}=.001) or if an exploratory analysis is performed (as in Study I), multiple initial-link threshold may be applied.

Although NBS improves power due to its stringent control of false positives (cf. Zalesky et al., 2010), only the network as a whole can be regarded as significant and thus, can only be interpreted as such. Another approach presents the *link-based controlling procedure* (Zalesky et al., 2010), in which a test statistic and a respective p-value is computed for each network link while controlling the false discovery rate (FDR; Genovese & Wasserman, 2002). Hence, the null hypothesis is tested based on individual links, while controlling the ratio of false positive connections among all positive connections. In contrast, NBS allows rejecting the null hypothesis at the level of cerebral networks by controlling the FWER, that is, the probability of false positive networks. In the GraphVar toolbox (Kruschwitz, List, Waller, Rubinov, & Walter, 2015), which was used in the present work, a FDR correction algorithm (Benjamini & Yekutieli, 2001) is carried out with respect to a designated alpha level. In Study I, we performed a link-based controlling procedure in addition to using NBS. The objective to do so derived from the exploratory nature of that study, as FDR correction can provide additional

information on focal effects concerning individual connections. We applied a FDR corrected threshold of p_{FDR}=.05 and tested against random groups using 100,000 permutations.

6. Summary of Studies

6.1. Study I: White matter network alterations in patients with depersonalisation/derealisation disorder

Citation: Sierk*, A., Daniels*, J. K., Manthey, A., Kok, J., Leemans, A., Gaebler, M., Lamke, JP, Kruschwitz, J., Walter, H. White matter network alterations in patients with depersonalisation/derealisation disorder. *J Psychiatry Neurosci*. 2018; 1-11. DOI:10.1503/jpn.000000

Background. Depersonalization/derealization disorder (DPD) is a distressing pathological condition estimated to affect 1-2% of the general population (Hunter et al., 2004). Individuals with DPD undergo recurrent episodes of feeling detached from oneself (depersonalization) and/or the external world (derealization) and may also experience emotional numbing and somatosensory distortions (Baker et al., 2003; M. Michal et al., 2016). Neurobiological models suggest DPD to be underpinned by alterations within neurobiological circuits: an early model emphasizing the role of the temporal lobes (Penfield & Rasmussen, 1950), while a more recent theory proposes a fronto-limbic dysbalance in DPD (Sierra & Berrios, 1998), which is congruent with theories proposed for the dissociative subtype of PTSD (Lanius et al., 2010). Some neuroimaging studies have provided indications for structural and functional alterations in a variety of distinct brain regions in patients with DPD. Yet, the theoretical models propose that DPD symptomatology is underpinned by dysfunctional interaction of multiple brain areas (Sierra & Berrios, 1998; also see Edelman & Tononi, 2000, p. 67, l. 9-12) and it is possible that local changes are mediated by altered interregional white matter connections. DWI allows to image the human brain connectome non-invasively and the application of graph theory to DWI data has made it possible to analyze structural connectivity on a network level. Thus, the aim of this study was to investigate structural connectivity on a network level in patients with DPD. Albeit existing theories on the underlying neurobiology of DPD, empirical evidence is scarce. Moreover, being the first study to investigate white matter anatomy in DPD, we chose to employ a strictly exploratory approach aimed at theory building.

Methods. The sample comprised 23 patients with DPD patients and 23 healthy individuals (18 female each, age 30±7.6ys), matched for age and education. All participants underwent German versions of three standardized interviews (SCID-I, SCID-D, IPDE). The SCID-D was employed to establish the diagnosis of DPD, according to the criteria in DSM-IV. Patients were included if DPD was established as the primary diagnosis and participants were only included in the control group when no mental disorder had been identified. All subjects completed several self-report questionnaires to measure state and trait characteristics, such as depression and anxiety. To assess symptom severity of depersonalization and derealization, participants completed the German versions of the 30-item Cambridge Depersonalization Scale (CDS-30; Michal et al., 2004).

Diffusion tensor imaging (64 gradient orientations, TE=86ms) and T1-weighted images (TR=1.9ms, TE=2.52ms) were acquired on a 3T Siemens scanner. *FreeSurfer* v5.3 was used to extract 85 pre-defined regions of interest (ROI) from the T1-weighted scans. DWI data was preprocessed with *ExploreDTI* v4.8.6. Data was corrected for subject motion, eddy current induced geometric distortions, and EPI distortions. Subsequently, constrained spherical deconvolution (CSD) whole brain tractography was performed. The output of each processing step was checked for quality. The 85 ROI files derived from *FreeSurfer* were combined with the CSD files and existent connections between any two ROIs examined, resulting in 85x85 connectivity matrices for each subject. Mean fractional anisotropy (FA) was used as an edge weights between any two ROIs to get an indicator for their strength of association or structural connectivity, respectively.

Age, sex, and handedness were included as covariates in all network analyses. To assess group differences, we performed NBS and a link-based controlling procedure. NBS is a nonparametric statistical method developed by Zalesky and coworkers (Zalesky et al., 2010) to identify graph components within a network that are associated with an external variable, while controlling the family wise error rate (FWER). Due to the exploratory nature of this analysis, we determined supra-threshold links by applying descending initial link thresholds from p_{lt}=.05 to p_{lt}=.001 in steps of .005. As an additional analysis, we use the false discovery rate (FDR; Genovese & Wasserman, 2002) to also explore focal effects concerning individual connections. Non-parametric permutation tests (10,000 for NBS and 100,000 for link-based controlling procedure) were used for group comparisons and subnetworks were considered

significant at p_{FWER}=.05 and p_{FDR}=.05, respectively. To obtain indications whether potential group differences are specific to DPD symptomatology, we additionally performed partial correlation analyses with dissociative symptom severity, as measured by the CDS-30 (controlling for age, sex, and handedness), using both controlling methods.

Results. DPD patients did not differ from HC regarding age (*t(44)*=0.289, *p*=.774), handedness (*t(44)*=1.542, *p*=.130), level of education (Mann–Whitney *U*=245.5, *p*=.662), information processing speed (*t(40)*=-.150, *p*=.882), and executive functions (*t(40)*=-.355, *p*=.725). Patients with DPD reported significantly higher physical neglect in childhood (*t(43)*=-2.241, *p*=.032). Moreover, the DPD group differed from healthy controls on various self-report questionnaires (see original study in the appendix A), which in turn correlated highly with dissociative symptom severity in DPD.

In the network analyses, our main finding refers to lower FA values within left temporal and right temporal-parietal regions in DPD compared to healthy controls when using link-based controlling procedure. Specifically, DPD patients displayed lower FA values than healthy individuals between the left temporal pole and left superior temporal gyrus (p_{FDR}<.001) and between the right middle temporal gyrus and right supramarginal gyrus (p_{FDR}<.002). These links were also significantly associated with dissociative symptom severity and could not be explained by anxiety or depression scores. Using NBS, no significant group differences in graph components between brain regions were detected. However, at an initial-link threshold of p_{lt}=.005, a trend was found indicating group differences regarding one sub-network, which comprised frontal and subcortical limbic regions. Within this network, DPD patients displayed higher FA values compared to healthy controls between the left superior frontal gyrus, right medial orbitofrontal cortex and its connection to the right amygdala and lower FA values relative to controls between the right amygdala, brain stem and left caudate (p_{FWER}=.084). Dissociative symptom severity was not significantly correlated with this sub-network.

Discussion: Our prominent results using link-based controlling procedure compliment previous findings that highlighted the role of temporal regions in DPD and support the temporal-lobe hypothesis. In previous studies, patients with DPD relative to controls showed reduced cortical thickness in the right medial temporal gyrus (Sierra et al., 2014) and lower metabolic rate in the right middle and superior temporal gyrus (Simeon et al., 2000) while the supramarginal gyrus has been associated with dissociation in the context of PTSD

(Harricharan et al., 2017). Furthermore, functional aberrations in left temporal lobe regions have been linked to dissociation in DPD (Hollander et al., 1992; Sierra et al., 2014), panic disorder (Hayashi, Makino, Hashizume, Nakano, & Tsuboi, 2010; Locatelli et al., 1993), and temporal lobe epilepsy (Devinsky, Putnam, Grafman, Bromfield, & Theodore, 1989). In healthy individuals, left and right temporal regions have been mainly attributed a role in transmodal integration (Mesulam, 1998; Visser, Jefferies, Embleton, & Ralph, 2012) and cross-modal spatial attention (Macaluso, Frith, & Driver, 2000), respectively. Patients with DPD frequently report symptoms that imply dysfunctional integration of sensory modalities (i.e. detachment) and somatosensory distortions. Hence, reduced connectivity in left and temporal regions may reflect the neural underpinnings of dysfunctional association of multimodal information and failed sensory integration necessary for an intact body perception in space.

No group differences were detected using network-based statistics. Yet, in one sub-network, a trend pointed towards higher FA between frontal regions and projections to the amygdala and lower FA values between the amygdala, brain stem and left caudate in DPD relative to healthy controls. This finding is in line with the model of fronto-limbic inhibition (Sierra & Berrios, 1998), which is proposed to underlie emotional numbing observed in DPD. Furthermore, functional synchronization between amygdala, caudate, and medial prefrontal cortex has been suggested to serve active coping with threat (cf. Hagenaars et al., 2014). Thus, our findings suggest that structural alterations in fronto-limbic-striatal circuits may contribute to abnormal fear responses observed in DPD. However, as dissociative symptom severity was not significantly correlated with this network's FA values, future studies should carefully explore its role.

6.2. Study II: The dissociative subtype of posttraumatic stress disorder is associated with white matter network alterations

Citation: Sierk, A., Manthey, A., Brakemeier, E.-L., Walter, H., Daniels, J. K. (submitted for publication at *Psychological Medicine*) The dissociative subtype of posttraumatic stress disorder is associated with white matter network alterations.

Background. Posttraumatic stress disorder (PTSD) is characterized by intrusions, avoidance and hyperarousal, while patients of the dissociative subtype (PTSD-D) experience additional symptoms of depersonalization and derealization. Based on latent class analyses, it has been suggested that on average around 20% of patients belong to this subtype (Hansen et al., 2017). PTSD-D has been associated with higher symptom severity, mediated by higher intrusive symptomatology (Stein et al., 2013; Wolf et al., 2012). A neurobiological model proposes hyper-inhibition of limbic structures mediated by prefrontal cortices to underlie dissociation in PTSD (Lanius et al., 2010). This presents an opposing neural pattern to intrusive re-experiencing, which has been associated with defective prefrontal inhibition leading to heightened limbic activation (Garfinkel & Liberzon, 2009). These neuronal patterns of emotional over- and under-regulation co-exist in patients with PTSD-D per definition, suggesting dissociation may be underpinned by dynamic neural processes. Yet, two studies have reported correlations between brain morphology and dissociative symptom severity in PTSD (Daniels et al., 2016; Nardo et al., 2013), indicating emotional overregulation in PTSD-D to be underpinned by differences in brain anatomy. Yet, these studies only describe structural aberrations in locally distinct areas and no interaction with brain circuits can be inferred. To test whether the proposed neural model of fronto-limbic inhibition may indeed be underpinned structurally in PTSD-D, we applied graph theoretical analyses on data of diffusion MRI tractography to identify sub-networks with altered structural connectivity associated with this condition.

Methods. The sample comprised 23 women with PTSD-D and 19 women with classic PTSD (age 40.0±9.8ys). All participants underwent three standardized interviews (CAPS-IV, SCID-I, SCID-D). The PTSD diagnosis was established using the German versions of the CAPS-IV while participants were allocated to the PTSD-D subgroup based on predefined cut offs in the SCID-

D, CDS-state, CDS-30, and DES. If presented as the secondary diagnosis, we included comorbid depressive and anxiety disorders, eating disorders, borderline personality disorder, and substance abuse disorders to ensure ecological validity.

Diffusion weighted imaging (64 gradient orientations, TE=86ms) and T1-weighted images (TR=1.9ms, TE=2.52ms) were acquired on a 3T Siemens scanner. Using default settings in *FreeSurfer*, we extracted 87 pre-defined ROIs from the T1-weighted scans. The preprocessing of the DWI data was performed with *ExploreDTI*. Data was corrected for subject motion, eddy current induced geometric, as well as EPI distortions and CSD whole brain tractography performed thereafter. 87 ROI files derived from *FreeSurfer* were combined with the CSD files, resulting in 87x87 connectivity matrices for each subject. We thresholded the connectivity matrices by a minimum number of streamlines (maximum number of tracts in each subject * .001), which curbs the effect of spurious streamlines (cf. Rubinov & Sporns, 2010). Mean FA was used as an edge weight between any two ROIs and thus presented an indicator for structural connectivity.

NBS were performed with *GraphVar* (Kruschwitz et al., 2015). We applied two initial-link thresholds (p_{lt}<.005 and p_{lt}<.001) and used non-parametric permutation tests (10,000) for group comparisons. To test for significant group differences in structural connectivity between brain regions implicated in the proposed model of fronto-limbic inhibition, limbic and prefrontal start points were selected (for exact structures, see Appendix A). In addition, we performed an exploratory whole-brain analysis of network-level FA differences between the PTSD-D and the classic PTSD group aimed for theory building. In order to obtain indication whether potential group differences are related to dissociative symptomatology, we performed a partial correlation analysis (controlling for age) between FA values and dissociative symptom severity, as measured by the CDS-30.

Results. Regarding demographics, no group differences were detected concerning age (*t(40)*=0.12, *p*=.908), level of education (Mann–Whitney *U*=192.00, *p*=.423), information processing speed (TMT-A; *t(40)*=0.74, *p*=.461), and executive functions (TMT-B; *t(40)*=0.57, *p*=.570). In addition, patients with PTSD-D did not differ from classic PTSD regarding depressive symptoms (i.e. BDI-II scores), trait anxiety (i.e. STAI-T scores), emotion regulation (i.e. ERQ scores), and childhood trauma experiences (i.e. CTQ scores). As expected, PTSD-D patients scored significantly higher than patients with classic PTSD on measures of trait

dissociation (DES, *t(40)*=-3.21, *p*=.003), current dissociation (CDS-30, *t(37)*=-7.11, *p*<.001; MDI, *t(37)*=-4.11, *p*<.001), and state dissociation (CDS-state, *t(39)*=-4.30, *p*<.001).

Using NBS, no significant group differences were detected on a network level in fronto-limbic circuits, that is, between any of the pre-defined frontal and limbic structures. In the exploratory analysis, two sub-networks were identified at an initial-link threshold of p_{It}<.005, for which patients with PTSD-D displayed altered FA compared to patients with classic PTSD (p_{FWER}=.026). Within the first sub-network, the PTSD-D group showed relatively lower FA between the left amygdala and the left hippocampus as well as between the left hippocampus and left thalamus and higher FA values between the left thalamus and the brain stem. Within the second network, patients with PTSD-D displayed higher FA values compared to patients with classic PTSD between the left ventral diencephalon, the left putamen, and left pallidum. Dissociative symptoms severity, but not anxiety or depression scores, correlated with FA in all three sub-networks. No group differences were identified at an initial-link threshold of p_{It}<.001.

Discussion. No group differences in structural connectivity were detected between frontal and limbic structures, which may indicate that fronto-limbic inhibition in PTSD-D present a dynamic neural process, which is not hard-wired via white matter tracts. Alternatively, our null-finding suggests that frontal structures play a less central role than previously assumed. Our exploratory results indicate altered fiber tract communication in a limbic-thalamic circuit, which include regions responsible for contextualization of mnemonic content, emotional processing (Carlesimo, Lombardi, & Caltagirone, 2011; Gilboa et al., 2006) and sensory integration (Blumenfeld, 2012). These different neural underpinnings of patients with PTSD-D compared to classic PTSD, may underlie (a) an initial strong emotional reaction to trauma reminders before conscious regulatory processes are enabled and (b) deficits in early sensory and mnemonic processing. Moreover, alterations in structural connectivity in subcortical motor regions may present neural correlates for dissociation as a passive threat-response (i.e. freezing; Hagenaars et al., 2014).

6.3. Study III: Allocentric spatial memory ability predicts the experience of intrusive memories in posttraumatic stress disorder

Citation: Sierk, A., Manthey, A., King, J., Brewin, C., Bisby, J., Walter, H., Burgess, N., Daniels, J. K. (submitted for publication at *Neurobiology of Learning and Memory*) Allocentric spatial memory ability predicts the experience of intrusive memories in posttraumatic stress disorder.

Background. One of the hallmark symptom of Posttraumatic stress disorder (PTSD) are recurrent involuntary memories of the traumatic event. For visual intrusions, the revised dual representation model (r-DRT) proposes that intrusive memories arise from poor contextual encoding due to an up-regulation of sensory representations in the traumatic moment (Brewin et al., 2010). The contextual representation is assumed to rely on the hippocampal formation and is thought to be coded within the ventral visual stream, allowing integration with other autobiographical memories (cf. Brewin, 2015). Sensory representations are thought to rely on egocentric encoding (viewer-dependent), while appropriate contextual encoding additionally requires allocentric processing (viewer-independent). In their r-DRT, Brewin and colleagues (2010) presume an amygdala-mediated strengthening of egocentric sensory visual representations during the traumatic moment in the context of a weak hippocampus-dependent allocentric representation. Concordantly, impaired allocentric spatial processing ability (Gilbertson et al 2007; Smith et al., 2015; Tempesta et al. 2012) as well as reduced hippocampal volume (Logue et al., 2018) has been reported for patients with PTSD, but has only been linked to the occurrence of intrusions in healthy cohorts (Bisby et al., 2010, Meyer et al. 2017). Here we tested for the first time the implications of the r-DRT, that neuronal aberrations in structures of the ventral visual stream, the hippocampus, as well as allocentric memory performance are associated with intrusive memory severity.

Methods. 33 women with PTSD due to childhood trauma (age 39.67±10.16ys.) participated in the study. A licensed clinical psychologist established the PTSD diagnosis using the German version of the CAPS-IV. Egocentric and allocentric spatial memory ability was assessed with the Town Square task, which makes use of a virtual environment. To isolate allocentric spatial memory performance, while controlling for confounding differences in egocentric spatial processing, we subtracted egocentric memory from the allocentric memory score. In

addition, general visuo-spatial ability and working memory were assessed to control for their potential influence on allocentric spatial memory performance. To assess intrusive symptom severity, we employed the script-driven imagery paradigm (Lanius et al., 2002) to provoke intrusive memories. Upon completion, participants were asked "*During Trial X, did you re-experience part of the trauma involuntarily (intrusions)?"*. The response was given on a 7-point-Likert scale from 0 (not at all) to 6 (very strong). T1-weighted images (TR=1.9ms, TE=2.52ms) were acquired on a 3T Siemens scanner. ROIs were limited to the left and right hippocampus and the following bilateral areas within the ventral visual stream: lateral occipital gyrus, fusiform gyrus, lingual gyrus, sulcus of the pericalcarine gyrus, middle temporal gyrus, inferior temporal gyrus, temporal pole, and parahippocampal gyrus. The respective subcortical volumes and cortical thickness measurements were acquired using the default settings of *FreeSurfer* version v6.0. Based on significant bivariate correlations with intrusive memory severity, we selected predictive variables of intrusive symptom severity to be entered into a planned multiple regression analysis.

Results. Controlling for working memory performance and general visuo-spatial ability, the allocentric memory score negatively correlated with intrusive memory severity (r=-.474, p=.009). In addition, cortical thickness of the left lingual gyrus correlated negatively with intrusive memory severity (r=-.37, p=.035).[2] Hence, these two variables were entered in the multiple linear regression model as predictors of intrusive memory severity. The results indicated that the two variables explained a significant amount of variance in intrusive symptom severity (R^2=.19, $F(2,32)$=4.81, p=.015). Only lower allocentric memory performance significantly predicted higher intrusive memory severity (β=-.35, p=.048), while cortical thickness of the left lingual gyrus did not provide a unique contribution (β=-.24, p=.161). In post hoc analyses, we confirmed that the relationship between allocentric spatial memory performance and intrusive memory severity could not be explained by age, depressive symptom severity, and trait anxiety (r=-.43, p=.025). Furthermore, we tested for potential effects of duration of symptoms and found a significant negative correlation between age since index trauma and left hippocampal volume (r=-.36, p=.027, uncorrected; n=41).

[2] Note that the allocentric memory score also correlated with cortical thickness of the left lingual gyrus (r=.40, p=.032), in that a higher allocentric memory score was associated with greater cortical thickness.

Discussion. To our knowledge, this is the first study to report a relationship between allocentric spatial memory ability and intrusive symptomatology in PTSD. Our findings support the r-DRT, which emphasizes the role of contextual processing in the development of intrusive symptomatology. Moreover, the results complement previous studies, which reported a selective impairment of allocentric spatial memory in PTSD (Gilbertson et al., 2007; Smith et al., 2015) and stronger allocentric processing to be associated with fewer intrusive memories in healthy subjects following an analogue trauma (e.g. Bisby et al., 2010). Our findings have relevant clinical implications for psychological intervention, specifically for trauma-focused therapy in PTSD (e.g. Ehlers & Clark, 2000), which are discussed in section 7.3.

7. General Discussion and Prospects

7.1. General Discussion

The aim of this thesis was to contribute to the understanding of two trauma-related symptoms – dissociation and intrusive re-experiencing – by investigating their neurobiological underpinnings in two psychological disorders. In Study I, dissociation was investigated by examining white matter network alterations in patients with DPD compared to healthy individuals. Using the same analysis, we then examined structural connectivity in PTSD-D relative to classic PTSD in Study II. In Study III, a neurobiological model of the etiology of intrusive symptomatology was tested across patients with PTSD-D and PTSD. In this section, the results of Study I, II and III are being discussed in relation to each other. Specifically, the way in which dissociation in DPD differs from dissociation in PTSD-D on a neurobiological level and how this informs conceptualizations of detachment in either disorder. Further, it will be discussed how theoretical models on the relationship between dissociation and intrusive symptomatology can be informed from our neurobiological findings.

The neurobiology of dissociation in DPD and PTSD-D

In Study I, a trend was found when using NBS that pointed towards higher structural connectivity between frontal regions (left superior frontal gyrus and right medial orbitofrontal) and amygdala as well as lower structural connectivity between amygdala, brain stem and caudate in patients with DPD relative to healthy controls. This finding provides tentative support for the model of fronto-limbic inhibition (Sierra & Berrios, 1998), suggesting that frontal inhibition of limbic structures are underpinned by white matter alterations in DPD. However, dissociative symptom severity did not correlate with FA values within this sub-network. Having used an exploratory whole brain approach in the DPD sample in Study I, we tested the model of fronto-limbic inhibition hypothesis-driven in a PTSD-D cohort in Study II. We did not find any structural differences in fronto-limbic regions between patients with PTSD-D and patients with classic PTSD. This null-finding taken together with the weak support in Study I leads to the assumption that overregulation of emotions by frontal structures may play less of a central role in transdiagnostic dissociation than previously assumed. An

alternative explanation is that fronto-limbic inhibition may not be underpinned by structural network alterations, but presents a dynamic neural process in PTSD-D and potentially also in DPD, albeit our findings would tentatively suggest otherwise. Support for this notion is found in fMRI studies suggesting heightened activity in frontal structures and lower connectivity in limbic regions in patients with PTSD-D (Daniels et al., 2012; Hopper et al., 2007; Lanius et al., 2010; Mickleborough et al., 2011). However, the overlap regarding the exact activation sites among these studies is poor, while they are based solely on post hoc correlational analyses rather than group contrasts as in the present work. Future studies should carefully explore the role of fronto-limbic dysbalance in PTSD-D by considering functional resting state connectivity, for instance. NBS can be used to test group differences in regard to functional connectivity on a network level, which would enable to test whether fronto-limbic inhibition may indeed present a dynamic neural process in PTSD-D. Applying this procedure in further exploratory analyses is warranted for theory building.

Using a link-based controlling procedure in Study I, we found that DPD patients, relative to heathy controls, displayed lower structural connectivity between left temporal pole and superior temporal gyrus and between right middle temporal and supramarginal gyrus, which correlated with dissociative symptom severity (i.e. CDS-30 scores). These findings support the temporal-lobe hypothesis (Penfield & Rasmussen, 1950) and compliment previous studies in DPD that reported functional alterations in temporal areas (Hollander et al., 1992; Locatelli et al., 1993; Mantovani et al., 2011; Sierra et al., 2014; Simeon et al., 2000). Our results suggest that these functional alterations are at least partly due to fiber tract aberrations. Derived from studies on healthy functioning of these structures (Macaluso, Frith, & Driver, 2000; Mesulam, 1998; Patterson, Nestor, & Rogers, 2007; Visser et al., 2012), white matter alterations between right middle temporal and supramarginal gyrus may underlie disembodiment (e.g. somatosensory distortion), while lower FA values between left temporal pole and superior temporal gyrus may underlie disintegration of sensory modalities (i.e. depersonalization and derealization), which is the core symptom of DPD and also experienced in PTSD-D. Unlike in Study I, no differences in structural connectivity in temporal regions was found in PTSD-D compared to classic PTSD in Study II, though it ought to be noted that no link-based controlling procedure was used in addition to NBS. Nevertheless, the results suggest that structural interconnectivity in the temporal lobe may not play a comparably

crucial role for detachment in PTSD-D than in DPD. In contrast, one study that found a negative association between acute dissociation and activation of the left superior temporal gyrus in patients with PTSD (Hopper et al., 2007). To our knowledge, no structural aberrations in left temporal areas have been associated with PTSD-D. Yet, two studies indicated morphometric alterations in right temporal areas, but structural aberrations were not correlated with dissociative symptom severity (Daniels et al., 2016) or were only present in a subclinical sample (Nardo et al., 2013), respectively. Hence, it is possible that, unlike in DPD, depersonalization and derealization (i.e. detachment) is not hard-wired in PTSD-D, but may present a dynamic neural process in PTSD-D. An alternative explanation is that detachment in PTSD-D differs qualitatively from detachment in DPD, which is reflected by distinct white matter network alterations in DPD and PTSD-D, as found in the present work.

In Study II, two altered subcortical networks in PTSD-D (relative to classic PTSD) were identified, comprising connections between (1) the left amygdala, hippocampus, and thalamus as well as links between (2) the left ventral diencephalon, putamen, and pallidum, respectively. Dissociative symptom severity (i.e. CDS-30 scores) in the PTSD-D group correlated with FA values within both networks. The nodes of the second sub-network refer to low-level motor regions and may present neural correlates for dissociation as a passive threat-response (cf. Hagenaars et al., 2014). The first sub-network mainly comprises regions along the white matter fiber bundle fornix, which connects the amygdala and hippocampus to the anterior nuclei of the thalamus (Catani, Dell'acqua, & Thiebaut de Schotten, 2013). Interconnections between these structures have been suggested to be crucial for emotional and mnemonic processing (Carlesimo et al. 2011; Gilboa et al., 2006) as well as altered consciousness (Blumenfeld, 2012). Hence, lowered structural connectivity between these regions in PTSD-D may underlie emotional dysregulation observed in PTSD-D. Within this context, studies showing that aversive stimuli need to be processed consciously to elicit limbic overregulation in PTSD-D, should be considered (Felmingham et al., 2008; Klimova, Bryant, Williams, & Felmingham, 2013). When fearful faces were presented subliminally (i.e. below the perceptual threshold) instead of supraliminally, PTSD-D patients showed increased activity in the amygdala and parahippocampus (Felmingham et al., 2008), which is in line with our findings of alterations in a limbic-thalamic circuit. Hence, our results suggest that individuals with subcortical alterations in limbic-thalamic and low-level motor circuits may be

prone to experience dissociation due to their initially heightened (preconscious) arousal in the traumatic moment as well as their predisposition to freeze. The heightened arousal may lead to conscious overregulation of limbic structures in the traumatic moment, eliciting feelings of detachment. Over time, this detachment response may be adopted as a conscious coping mechanism in response to distress or trauma reminders. Alternatively, it can reflect re-experiencing of peritraumatic dissociation and thus, is a phenomenon that is not detachment in itself, like in DPD. Either concept, detachment as a coping mechanism and detachment as re-experiencing of peritraumatic responses, entails a clear link between threat and dissociation, which is also supported by reliable provocation of acute dissociation via exposure to trauma reminders (cf. Lanius et al., 2010).

A respective association, that is, between trauma and dissociation, has not been clearly established in DPD. Emotional abuse in childhood has been identified as a strong predictor for the development of DPD in one study (Simeon et al., 2001), whereas childhood trauma was not a clear etiological factor in others (Baker et al., 2003; Michal et al., 2016), although here, only physical and sexual abuse were measured. In 554 healthy individuals, Teicher et al. (2006) found emotional abuse to be strongest associated with dissociative symptomology, ahead of physical and sexual abuse. In our sample, patients with DPD reported significantly more physical neglect and a trend pointed towards more emotional abuse. This leads to the suggestion that unlike in PTSD, maltreatment associated with DPD constitutes less of a threat to one's integrity, but refers to emotional abuse or neglect (for an opposing view see Hunter et al., 2003). In line with our findings, Teicher (2002) emphasizes the impact of childhood maltreatment on left temporal regions. In an earlier study, the author and this colleagues reported an equally developed right hemisphere in 104 abused patients (regardless of primary diagnosis) compared to controls, but detected extensive abnormality throughout the left hemisphere in patients, with the temporal regions being the most affected (Ito et al., 1993). The results of Study I complement these findings by emphasizing the role of altered fiber tract communications in temporal areas in DPD. Furthermore, it is worth considering white matter development and the age of onset in DPD, which lies in adolescence (Baker et al., 2003). Subcomponents of neuronal white matter constantly undergo dynamic changes throughout adolescence (Barnea-Goraly et al., 2005; Casey, Jones, & Hare, 2008), making this an important phase for brain network development. Amongst other regions, Nagy,

Westerberg, and Klingberg (2004) found age-related FA-differences within the left temporal white matter cluster in a group of healthy 8-18-year-olds. Thus, it is possible, that emotional abuse or respective emotional responses in sufferers during sensitive times affect the development of fiber tracts in temporal areas, causing persistent disturbances in structural connectivity and contribute to the development of DPD. This assumption cannot be directly confirmed by our study, as we did not find a correlation between FA values within the temporal graph components and symptom duration (i.e. years since onset). Yet, this may have been due to the bimodal distribution that arose, because most patients reported either a short or a long symptom duration. An alternative explanation to the causal model of childhood maltreatment is that lower structural connectivity in temporal regions presents a predisposed risk factor for the development of DPD (after childhood maltreatment or after drug use, for instance). On the basis of the present cross-sectional study, we cannot infer which explanation ought to be weighted. Longitudinal studies are warranted to shed light on the causality between temporal lobe aberrations and the development of DPD.

In sum, what did Study I and II in conjunction imply regarding the comparison between dissociation in DPD and PTSD-D? Our distinct neurobiological findings in patients with DPD (Study I) and patients with PTSD-D (Study II) support the clinical observation that detachment in these disorders differ in quantity, that is, it depicts a core and persistent feature in DPD whereas it is transient phenomenon in PTSD-D. Our findings suggest that this quantitative distinction may be underpinned by differences in the underlying neurobiology, in that detachment is hard-wired in temporal areas in DPD, yet presents a dynamic neural process in PTSD-D. Additionally, the present work suggests that detachment in DPD may also be qualitatively different to detachment in PTSD-D. Two possible qualitative differences have been discussed, which are not mutually exclusive: (a) Detachment in PTSD-D is a direct response to threat and individuals with altered structural connectivity in limbic-thalamic circuits are prone to show this response in the traumatic moment. In contrast, detachment in DPD presents a secondary effect of neurobiological changes in temporal regions due to childhood emotional abuse; (b) detachment is re-experienced as part of intrusive memories and does not depict detachment in itself like in DPD. Thus, patients with PTSD-D do not present altered connectivity in temporal regions, which underlies detachment. It would be

intriguing to test these proposed distinctions scientifically in future studies, as important clinical implications may be drawn from these in the long term (cf. section 7.3 and 7.4).

Dissociative and intrusive symptomatology in PTSD

The present section will discuss Study II and III in relation to each other while trying to inform the relationship between intrusive and dissociative symptomatology from a neurobiological perspective. The r-DRT proposes that during the traumatic moment the amygdala mediated sensory representation is strengthened, disconnected from contextual, hippocampus-dependent allocentric representation, which is only poorly formed (Brewin et al., 2010). The authors presume that the resulting imbalance between strong emotion-laden traumatic memories and weak associative and contextual representations gives rise to trauma-related intrusive memories. in Study III, we investigated the predictive capacity of allocentric spatial memory performance, cortical thickness of ventral visual stream structures, and hippocampal volume for intrusive memory severity in patients with PTSD. Using a planned multiple linear regression model, we found that higher allocentric memory performance significantly predicted lower intrusive memory severity. These outcome complements previous findings, which reported a selective impairment of allocentric spatial memory in PTSD (Gilbertson et al., 2007; Smith et al., 2015) and stronger allocentric processing to be associated with fewer intrusive memories in healthy subjects following an analogue trauma (Bisby et al., 2010). To our knowledge, this is the first study to have demonstrated an association between allocentric spatial memory ability and intrusive memory severity in a clinical population. Hence, it provides unique empirical support for the r-DRT and emphasizes the role of contextual processing abilities for intrusive symptomatology in PTSD. Due to our cross-sectional study design, we can only speculate whether impaired allocentric memory ability presents a risk factor for the development of posttraumatic intrusive memories or a consequence of traumatic stress. Allocentric processing is assumed to be hippocampal-dependent (Hartley et al., 2007; King et al., 2002) and reduced hippocampal volume has been associated with childhood abuse (Teicher et al., 2017) as well as cumulative stress exposure (Hanson et al., 2015). Congruently, we found a negative correlation between left hippocampal volume and years since index trauma. Considering severity of re-experiencing symptoms have been associated with smaller left hippocampal volume in PTSD (Lindauer et al., 2006; Villarreal et al., 2002), we would assume that hippocampal-dependent allocentric memory ability

presents a risk factor for the development of intrusive symptomatology and not a consequence of traumatic stress. However, in the present work, no association between hippocampal volume and intrusive memory severity was detected. Neither did we find a significant correlation between allocentric spatial memory performance and hippocampal volume. It is possible, that these unexpected null-findings were caused by the lack of power in Study III (n=33). Alternatively, other structures may play a crucial role in contextualization mental imagery, which allocentric spatial memory is necessary for.

We hypothesized that structures of the ventral visual stream predict intrusive memory severity. In Study III, reduced cortical thickness of the left lingual gyrus correlated significantly with intrusive memory severity, but did not remain a significant predictor of intrusive memory severity in the multiple regression model. Yet, as reduced cortical thickness of the left lingual gyrus was also associated with lower allocentric memory performance, it might be worth considering its role in mnemonic processing of affective stimuli. It has previously been linked to visual as well as crossmodal spatial attention (Driver & Spence, 2000; Macaluso et al., 2000) and has been associated with visual memory (Bogousslavsky, Miklossy, Deruaz, Assal, & Regli, 1987). Studies in women with PTSD due to childhood abuse reported reduced cortical thickness in the right lingual gyrus compared to trauma controls (Tomoda, Navalta, Polcari, Sadato, & Teicher, 2009) and increased blood flow during re-experiencing (Bremner et al., 1999). Also, altered connectivity between the bilateral lingual gyrus and the left dorsal anterior cingulate cortex has been associated with resilience to childhood maltreatment (van der Werff et al., 2013). Interestingly, Daniels et al. (2012) found activation in the right fusiform and lingual gyrus to be associated with peritraumatic dissociation (controlled for acute dissociation), which are both structures of the ventral visual stream. These findings support the notion that peritraumatic dissociation directly inhibits contextualization of mental imagery during the traumatic moment (Brewin et al., 2010; Brewin & Holmes, 2003; Ehlers & Clark, 2000). It further leads to speculate that visual information, running hierarchically through the ventral visual stream to the hippocampal formation, may get disrupted via dissociative responses before reaching the hippocampus, in which the spatio-temporal context is formed. In fact, it is still unclear within the r-DRT how the hippocampal formation in the traumatic moment gets “downregulated”. The hippocampus is sensitive to stress-related atrophy caused by the stress hormone cortisol acting on glucocorticoid receptors

(Payne, Nadel, Britton, & Jacobs, 2004; Watanabe, Gould, & McEwen, 1992). However, in the traumatic moment, the cortisol reaction would be too slow to directly impede hippocampal functioning (cf. Dickerson & Kemeny, 2004). Hence, instead of the idea that all information of the traumatic scene reaches the hippocampus but is not properly processed there, it may be that respective information gets manipulated in early visual mnemonic structures, reaching the hippocampal formation in inadequate format, which ultimately obstructs coherent declarative processing. The proposed idea is highly speculative, but it may be worth testing it in a controlled experiment. One possibility presents examining this effect in healthy subjects with low and high trait dissociation. Using the trauma film paradigm in the fMRI environment, while monitoring the heart rate, the objective could be to test whether blood flow in ventral visual stream areas is related to lowered heart rate (as an indicator for dissociation) as well as intrusive memories.

The neurobiological findings from Study II further inform the relationship between intrusive and dissociative symptomology. Clinically, these two phenomena are related in that patients with PTSD who report profound dissociation display heightened intrusive symptomatology (Stein et al., 2013; Wolf et al., 2012). In Study II, we found that patients with PTSD-D relative to patients with classic PTSD display lower structural connectivity in regions necessary for early motor, emotional, and mnemonic processes. Since the two groups did not differ regarding their reports on childhood trauma, it is unlikely that these alterations were caused by cumulative stress exposure. According to the r-DRT, connections between the amygdala and the hippocampus present the neural correlate of the connection between sensory bound and contextual bound representation. Thus, alterations in this circuit may present a predisposed risk factor in some individuals for inadequate emotional memory processing of the traumatic event (cf. Carlesimo et al., 2011; Gilboa et al., 2006), leading to the development of intrusive memories. Moreover, as outlined in the previous section, individuals with alterations in limbic-thalamic connectivity may be prone to dissociative as a reaction to threat (expressed by peritraumatic detachment), aggravating de-contextualization of the traumatic content, potentially via ventral visual stream structures. This assumption is supported by a study in healthy controls using the trauma film paradigm. Chou et al. (2014) found that lower heart rate during viewing of a trauma film, as an indicator for peritraumatic dissociation, was only predictive of intrusive memory frequency in a

subgroup of participants. These individuals showed an abnormal sudden reduction in heart rate after a startle stimulus and displayed high trait dissociation, fear, and anxiety.

The findings of Study II and III in conjunction suggests that (a) peritraumatic dissociation may directly inhibit contextualization via areas of the ventral visual stream, leading to intrusive memory development and that (b) some individuals are more at risk to respond to trauma with a lower state of consciousness (e.g. detachment, freezing) due to alterations in areas crucial for emotional memory processing. This biological risk factor may contribute to the development of a severe form of PTSD after trauma, which is characterized by profound dissociation and heightened intrusive symptomatology (i.e. PTSD-D).

7.2. Limitations

Several limitations need to be considered that apply to each study as well as to the interpretation of the results in relation to each other.

First, methodological limitations are evident regarding the resolution of the data and the relatively broad subdivision of the *FreeSurfer* parcellation. For instance, we cannot ascertain which specific subnuclei of the thalamus or which part of the superior temporal gyrus is involved in the detected circuits in Study I and II, respectively. Within the course of this thesis, improved parcellation schemes have been developed, which ensure improved neuroanatomical precision regarding the structural and functional organization of the human brain (e.g. Glasser et al., 2016). Future studies should use novel parcellation schemes to enable precise localization of structural or functional alterations. Furthermore, general methodological issues apply regarding the graph theoretical analysis of diffusion MRI tractography performed in Study I and II. Challenges of the tracking algorithm, such as modelling distinctive fiber geometries, may increase false-positive streamlines and thus present a limitation. It should also be considered that weighting the connectivity matrices with the diffusion parameter FA does not allow strong inferences of the state of the anatomical connection. Considering FA is modulated by a variety of microstructural factors, lower or higher FA between regions does not imply the degree of structural connectivity (Jones, Knosche, & Turner, 2013).

Second, the results of Study I and II stem from exploratory analyses. Hence, the results are a product of a purely data driven approach and need to be replicated in a confirmatory study (i.e. with a priori hypotheses). They should only be used for theory building and ought to be replicated with pre-registration (cf. Szucs & Ioannidis, 2017).

Third, when putting the results of Study I and II in relation, it needs to be considered that in Study I we compared DPD patients with healthy individuals, while in Study II we contrasted PTSD-D with classic PTSD patients. Thus, the latter presents a more restrictive approach in that the control group presented a comparable degree of psychopathology, while the groups mainly differed regarding their dissociative symptomatology. This is in contrast to Study I, in which the control group did not display any psychopathologies compared to the DPD patients. This variance between studies gives rise to the possibility that differences in the structural connectivity in DPD compared to PTSD-D are not specific to dissociative symptomatology. However, this is rather unlikely, as we controlled for comorbidities and the network alterations found in Study I and II both correlated with dissociative symptomatology, but not with depression or anxiety scores. Nevertheless, a follow up study should address this limitation by, for instance, replicating the results of Study I by adding a psychopathological control group, consisting of patients with different psychological disorder (e.g. obsessive-compulsive disorder, general anxiety disorder, depressive disorder etc.).

Fourth, the PTSD-D sample in Study II comprised patients with childhood trauma. The majority of patients reported more than one trauma and we consider the patient's experience to be categorized as type-II-trauma. We did not measure another control group, comprising patients who experienced only one trauma and developed subsequent PSTD-D. Therefore, we cannot ascertain whether the identified subcortical alterations have been caused by repetitive posttraumatic dissociation or whether it presents a biological risk factor to dissociate in the traumatic moment. An additive relationship of these two mechanisms may also be possible and should be tested for in future studies with longitudinal study designs.

Fifth, limitation derive from the sample recruited in Study II and III. The results cannot be generalized to men or to women with traumatization during adulthood, as our sample consisted exclusively of women with a history of childhood trauma. In addition, we did not exclude patients with certain comorbidities and those taking selected psychotropic mediation, which applies to Study I as well. Consequently, in all studies, the patient sample

presented a high degree of comorbidity, which limits the specificity of the effects being attributable to the variable of interest. Nonetheless, including these patients is inevitable if ecological validity is aimed for and in all studies comorbidity and medication was controlled for in post hoc analyses.

Finally, it is important to keep in mind that it remains unclear whether the observed effects in Study I, II and III present a risk factor or a consequence of the disorder due to the cross-sectional design of all studies. As mentioned above, longitudinal studies are crucial to overcome this limitation.

7.3 Clinical implications

Several clinical implications can potentially be drawn from this work in the long term, given that replications and confirmatory findings arise.

Regarding interventions for dissociative symptomatology in DPD, our results emphasize the need to strengthen multimodal integration and embodiment in DPD. These functions rely on left and right temporal regions, respectively, in which we found structural connectivity to be low. An interesting approach in doing so presents rTMS above temporal and temporal-parietal regions. In a first clinical trial, Mantovani et al. (2011) administered low frequency rTMS for three weeks on the right temporal-parietal junction and reported significant symptom reduction in 6 out of 12 participants with DPD. The strongest improvement was observed in distorted body experiences (71% improvement in responders; Christopeit et al., 2014). Further trials deploying rTMS above the left superior gyrus, for instance, may present a promising way to test whether improvements in detachment can be measured in patients with DPD.

The present work further indicates that interventions for dissociative symptomatology in PTSD-D should not focus on temporal regions as in DPD, but rather consider (potentially pre-disposed) alterations in low-level sensory, mnemonic and motor processes. The findings of Study II in conjunction with Study III support new avenues of interventions for PTSD-D patients, in which toleration of dissociation is supported to allow processing of the traumatic memories. In two case studies, Kaur, Murphy, and Smith (2016) showed that walking patients through the imaginal scene outdoors while viewing the scene from multiple perspective, that

is, facilitating contextualization of the memory (cf. Bisby & Burgess, 2017; Brewin et al., 2010), reduced dissociation and enabled cognitive reappraisal. This approach might be a promising asset to suggested interventions for PTSD-D, in which emotion regulation strategies are strengthened before trauma-focused therapy is implemented to treat intrusive symptomatology (Cloitre, Koenen, Cohen, & Han, 2002; Cloitre, Petkova, Wang, & Lu Lassell, 2012; Steil, Dyer, Priebe, Kleindienst, & Bohus, 2011).

Furthermore, this work holds relevant clinical implications for psychological intervention for intrusive symptomatology in PTSD, specifically for trauma-focused therapy (cf. Ehlers & Clark, 2000). Patients are typically asked to relive their trauma via imagery and update negative appraisals. In the standard procedure, patients are asked to imagine the traumatic scene in front of their eyes and thus, reconstruct their egocentric representation (Bisiach & Luzzatti, 1978). As outlined in the aforementioned case studies, imagining the scene from multiple perspectives may strengthen the allocentric representation, which according to the r-DRT should facilitate the integration of contextual details, and thus, reduce intrusive re-experiencing. The results of Study III, which yielded an inverse relationship between allocentric spatial memory ability and intrusive memory severity, suggest that patients with severe intrusive memories will have more difficulty creating an allocentric representation and may need specific guidance. Potentially, by first training allocentric spatial memory ability using a neutral task and then moving on to the traumatic content. Future trials should investigate whether such a module would be effective at reducing the frequency and intensity of intrusive memories and how strengthening an allocentric representation may be implemented to a maximum effect. The findings of Study III also imply that a strong premorbid allocentric memory ability could present a resilience factor for the development of posttraumatic intrusive memories, which is particularly relevant for populations who are at greater risk for traumatic exposure, such as first responders or soldiers. Further studies testing this implication are needed.

7.4 Prospect

As outlined in the limitations, the results from Study I and II stem from exploratory analyses and future studies should replicate these findings in pre-registered confirmatory analyses.

The same refers to the confirmatory Study III, considering the replication crisis (cf. Szucs & Ioannidis, 2017).

Apart from replication studies, further work is warranted to advance the understanding of dissociation in DPD and PTSD-D. Building on this work, it would be informative to investigate resting state connectivity, that is functional connectivity at rest, and see whether alterations in functional connectivity on a network level compliments our hard-wired findings. A respective analysis is currently performed in the present DPD sample, however, a respective investigation in a new study population would increase validity. Moreover, regarding DPD, prospective studies should pursue the temporal lobe hypothesis further, in particular by using rTMS in clinical trials as discussed earlier. Thus far, the study by Mantovani et al. (2011) presents the only clinical trial using this method, stressing that more research in this area is warranted to test this potentially promising approach. Furthermore, longitudinal studies starting in early childhood can shed light on whether DPD is indeed related to emotional abuse and how alterations in inter-connectivity in temporal areas present a biological risk factor for the development of DPD.

In regard to PTSD-D, future studies should not only focus on fronto-limbic inhibition but consider dysfunctional low-level initial-threat responses, for example, by investigating subliminal exposure. Longitudinal studies can examine whether alterations in initial sensory encoding depict a risk factor for mnemonic fragmentation and overregulation of emotions and how this may inform advances for psychotherapeutic pre- and interventions for those effected. Respective experiments may also be informative in subclinical samples with high levels of dissociation. Furthermore, studies should aim to disentangle proneness to react with acute dissociation in the traumatic moment, and the effect that persistent dissociation after trauma has on the functional and structural neurobiology. Addressing this question would require multiple patient groups: a PTSD-D group and a classic PTSD group, who have both experienced repetitive type-II traumata and two comparable groups, who have experienced a single traumatic event and have developed PTSD-D and classic PTSD thereafter.

Finally, studies should examine dissociative and intrusive symptomatology in conjunction and consider the way in which proneness to dissociate in response to threat presents a risk factor to develop a severe form of PTSD (i.e. PTSD-D). Our findings suggest that it is worth testing whether contextualization in structures of the ventral visual stream get manipulated by

dissociative responses before they reach the hippocampal formation. Implementing fMRI in healthy subjects during the trauma film paradigm with an adequate manipulation may present a feasible way of testing this hypothesis. As already mentioned, a concrete possibility could be to show healthy subjects traumatic video footage in the fMRI environment while monitoring their heart rate, as an indicator for dissociation. Considering the findings by Chou et al. (2014), it would be worth choosing subjects with low and high trait dissociation scores. Subsequently, one could test whether reduced blood flow in ventral visual stream areas is related to lower heart rate (i.e. dissociation) as well as intrusive memories and whether this relationship is only evident in the 'high dissociative' subgroup, who show an atypical sudden reduction in heart rate after a startle stimulus.

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9. Appendix

A. Study I

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Research Paper

White matter network alterations in patients with depersonalization/derealization disorder

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Background: Depersonalization/derealization disorder (DPD) is a chronic and distressing condition characterized by detachment from oneself and/or the external world. Neuroimaging studies have associated DPD with structural and functional alterations in a variety of distinct brain regions. Such local neuronal changes might be mediated by altered interregional white matter connections. However, to our knowledge, no research on network characteristics in this patient population exists to date. **Methods:** We explored the structural connectome in 23 individuals with DPD and 23 matched, healthy controls by applying graph theory to diffusion tensor imaging data. Mean interregional fractional anisotropy (FA) was used to define the network weights. Group differences were assessed using network-based statistics and a link-based controlling procedure. **Results:** Our main finding refers to lower FA values within left temporal and right temporoparietal regions in individuals with DPD than in healthy controls when using a link-based controlling procedure. These links were also associated with dissociative symptom severity and could not be explained by anxiety or depression scores. Using network-based statistics, no significant results emerged. However, we found a trend for 1 subnetwork that may support the model of frontolimbic dysbalance suggested to underlie DPD symptomatology. **Limitations:** To ensure ecological validity, patients with certain comorbidities or psychotropic medication were included in the study. Confirmatory replications are necessary to corroborate the results of this explorative investigation. **Conclusion:** In patients with DPD, the structural connectivity between brain regions crucial for multimodal integration and emotion regulation may be altered. Aberrations in fibre tract communication seem to be not solely a secondary effect of local grey matter volume loss, but may present a primary pathophysiology in patients with DPD.

Introduction

Depersonalization/derealization disorder (DPD) is a dissociative disorder[1] estimated to affect 1%–2% of the general population.[2] However, a German study found a 12-month prevalence of 0.007 based on diagnoses given by clinicians, which suggests DPD is severely underdiagnosed, making research challenging in this population.[3] Individuals with DPD experience recurrent episodes of feeling detached from oneself (depersonalization) and/or the external world (derealization). Other clinical phenomena of DPD include emotional numbing and somatosensory distortions.[4,5] Shorter episodes of depersonalization or derealization can also occur in the context of other disorders, such as temporal lobe epilepsy,[6] schizophrenia,[7] or posttraumatic stress disorder (PTSD).[8] Psychophysiological and neuroimaging research suggests DPD to be underpinned by alterations within neurobiological circuits: an early model emphasizing the role of the temporal lobes[9] has been supported by studies with epileptic patients[10,11] and 2 neuroimaging studies on DPD.[12,13] A more recent theory proposes a frontolimbic dysbalance in individuals with DPD, assuming hyperactive prefrontal cortices to inhibit limbic structures,[14] which is also congruent with theories proposed for the dissociative subtype of PTSD.[8,15] Most functional MRI (fMRI) studies on DPD used affective stimuli to test this model and reported hypoactivity in limbic regions[16,17] and hyperactivation in prefrontal regions in individuals with DPD compared with healthy controls,[17, 18] (but also see Medford and colleagues[19]). Unfortunately, all fMRI studies published to date had very small DPD sample sizes (n = 6–14), which severely affects their

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validity. Two recent structural MRI studies with larger samples of patients with DPD and healthy controls suggest that grey matter alterations underlie DPD symptomatology.[12,20] One of them (n = 20 patients with DPD) found less cortical thickness in the right middle temporal gyrus,[12] while the other (n = 25 patients with DPD) found reductions of grey matter volume in the right caudate, right thalamus and right cuneus as well as volume increases in the left dorsomedial prefrontal cortex and right somatosensory regions.[20] In the context of other disorders, dissociation has also been associated with altered functional connectivity.[21] Edelman and Tononi[22] suggest that disturbed neuronal interaction might underlie the cognitive and emotional disconnect characteristic of dissociation. As dissociative symptoms constitute the hallmark of DPD, one may hypothesize that disturbed integration of neuronal information underlies DPD symptomatology as well. However, to our knowledge, no study to date has analyzed functional connectivity (except in a single case study[23]) or structural connectivity (i.e., white matter anatomy) in patients with DPD.

Diffusion tensor imaging (DTI) allows the human brain connectome to be imaged noninvasively.[24,25] Applying graph theory to DTI data has made it possible to analyze structural connectivity on a network level.[26] Graph theory is a mathematical approach for the analysis of complex networks constructed of "nodes" (i.e., in our case brain regions of interest), which are interconnected via "edges." Graph theory has emerged as a powerful tool for identifying anatomically localized subnetworks associated with neuronal alterations in psychiatric conditions.[27–30] By applying an exploratory graph theoretical analysis on diffusion MRI tractography data, we sought to identify networks with different structural connectivity between patients with DPD and matched healthy controls. Thus, the research question of the present study is whether DPD is associated with altered structural connectivity on a network level.

Despite existing theories on the underlying neurobiology of DPD, empirical evidence is scarce. Being the first group, to our knowledge, to investigate structural connectivity in patients with DPD, we sought to provide an unbiased investigation. To this end, we chose to use a strictly exploratory approach aimed at theory-building rather than hypothesis-testing as discussed with regard to the replication crisis.[31]

Methods

Participants

We acquired DTI scans in patients with DPD and healthy controls, who were a subset of the sample analyzed for volumetric changes in grey matter in an earlier study by our group.[20] Participants were recruited via advertisements posted online and in public spaces as well as in mental health in- and outpatient clinics. We obtained written informed consent from all individuals before participation. All participants were interviewed using German versions of 3 standardized clinical interviews: the Structured Clinical Interview for Dissociative Disorders (SKID-D),[32] the Structured Clinical Interview for DSM-IV (SKID)[33] and the International Personality Disorder Examination (IPDE).[34] The SKID-D was used to establish the diagnosis of DPD according to the criteria in DSM-IV (300.6) as well as the criteria of the depersonalization-derealization disorder according to ICD-10 (F48.1). The DPD diagnosis established in the present work is still valid, as the relevant criteria have not changed in DSM-5. Patients were excluded from the study if they had a history of lifetime psychotic disorders, substance addiction in remission for less than 6 months, or current PTSD. Patients with comorbid PTSD were excluded to avoid diagnostic ambiguity, considering that symptoms of the dissociative subtype of PTSD strongly overlap with DPD symptoms.[1]

Participants were included in the control group only when no mental disorder had been identified. General exclusion criteria were lifetime neurologic disorders, serious head injury, current use of benzodiazepines or opioids, insufficient knowledge of the German language, and MRI incompatibilities. The study was approved by the research ethics board at the Charité – Universitätsmedizin Berlin.

Questionnaires and tasks

All participants completed several self-report questionnaires. To assess symptom severity of depersonalization and derealization, participants completed the German versions of the 30-item Cambridge Depersonalization Scale (CDS-30)[35] and the Dissociative Experiences Scale (DES).[36] Patients with a score of at least 60 on the CDS-30 (α = 0.981) were invited for clinical diagnostics. In addition, the Beck Depression Inventory (BDI-II),[37] the State-Trait Anxiety Inventory (STAI),[38] the Liebowitz Social Anxiety Scale (LSAS),[39] the Toronto Alexithymia Scale (TAS-20),[40] the Emotion Regulation Questionnaire (ERQ),[41] the Kentucky Inventory of Mindfulness Skills,[42] the questionnaire for functional and dysfunctional self-focused attention,[43] the Sheehan Disability Scale,[44] and the short version of the Childhood Trauma Questionnaire[45] were used for sample characterization. Information processing speed and executive functions were measured using the Trail Making Test versions A and B (TMT),[46] respectively.

MRI acquisition

We acquired the MRI data using a 3 T Siemens Tim Trio scanner equipped with a 12-channel head coil. Diffusion tensor imaging was performed with a single-shot echo-planar imaging sequence using the following parameters: repetition time (TR) 7500 ms, echo time (TE) 86 ms, 61 slices, voxel size 2.3 × 2.3 × 2.3 mm^3, slice thickness 2.3 mm, field of view (FOV) 220 × 220 mm^2, 64 diffusion directions, b value = 1000s/mm^2. We acquired T_1-weighted images using a magnetization-prepared rapid acquisition with gradient echo sequence (TR 1.9 ms, TE 2.52 ms, inversion time (TI) 900 ms, flip angle 9°, FOV 256 × 256 mm^2, 192 slices, 1 mm isotropic voxel sizes, 50% distancing factor).

Preprocessing

The preprocessing pipeline for the structural network analysis is shown in Figure 1. We processed the T_1-weighted MRI scans using the default settings implemented in FreeSurfer

version 5.3 (https://surfer.nmr.mgh.harvard.edu/). Important processing steps include skull stripping, segmentation of subcortical white matter and deep grey matter volumetric structures, intensity normalization, definition of the grey matter–white matter boundary, and parcellation of the cerebral cortex into units with respect to gyral and sulcal structures.[47] Each output was visually inspected for quality control. Five scans had to be manually corrected and (partially) rerun. The final results yielded a proper distinction of each surface and subcortical ROIs in all participants.

The preprocessing of the DTI data was performed with ExploreDTI, version 4.8.6 (www.exploredti.com)[48] in MATLAB (Release 2014b; https://mathworks.com) using default settings. Specifically, data were corrected for participant motion using "Rekindle" methods,[49] eddy current–induced geometric distortions[50] and EPI distortions.[51] Subsequently, constrained spherical deconvolution (CSD) whole brain tractography was performed[52,53] for each participant. Following visual inspection, 1 participant was excluded as the fibre tracts could not be reconstructed adequately.

Connectivity matrices

Connectivity matrices were constructed based on 85 predefined anatomic regions of interest (ROIs) derived from FreeSurfer. The ROIs encompassed all cortical regions from the Desikan Killiany atlas (34 areas) plus the bilateral subcortical structures hippocampus, amygdala, thalamus, caudate, pallidum, putamen, accumbens area, ventral diencephalon and brainstem. The cerebellum was excluded as it was not fully captured in a number of scans. The 85 ROI files were combined with the streamline files from ExploreDTI, resulting in 85×85 connectivity matrices for each participant. It is inevitable when using deterministic tractography that not all fibre tracts can be reconstructed in all participants.[54,55] As this may vary between groups, we included only links in the network analyses for which streamlines had been generated successfully for all participants (i.e., 1153 links).

Statistical analysis

We included age, sex, and handedness as covariates in all network analyses; although they did not differ significantly between groups, subtle changes in these variables have been shown to impact structural brain connectivity.[56] We used the streamlines between each pair of nodes as a mask, within which we calculated mean fractional anisotropy (FA), a commonly used parameter that reflects tissue organization in cerebral white matter.[57] Mean FA values were used as edge weights between any 2 ROIs and thus presented an indicator for their strength of association or structural connectivity, respectively. Note that not all included ROI pairs are linked via direct anatomic connections (only homotopic regions are directly connected via fibre bundles) as tractography accounts for indirect connections. All second-level network analyses (i.e., network-based statistics, link-based false discovery rate [FDR] analysis, and correlational analyses with symptom scores) were performed using GraphVar version 1.0 (www.nitrc.org/projects/graphvar/).[58]

Network-based statistics: group comparison

Network-based statistics (NBS) is a nonparametric statistical method developed by Zalesky and colleagues[30] to identify graph components within a network that are associated with an external variable, while controlling the family wise error (FWE) rate. Within NBS, statistical thresholding is carried out in 2 steps: first, the hypothesis of interest is tested independently at every connection within a network using link thresholds. Adjacent suprathreshold links may ultimately form

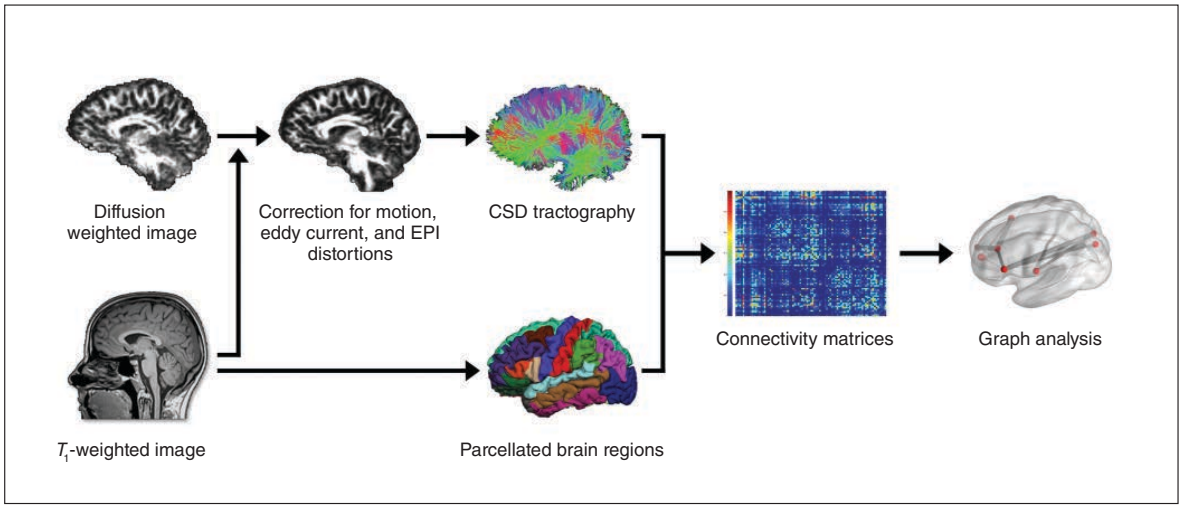

Fig. 1: Flowchart of the preprocessing pipeline using FreeSurfer (https://surfer.nmr.mgh.harvard.edu) and ExploreDTI (www.exploredti.com). CSD = constrained spherical deconvolution; EPI = echo-planar imaging.

graph components. Subsequently, the significance of these graph components at the network level is determined by comparing their size against the occurrence of differently sized graph components derived from random data (i.e., by performing FWE correction). In accordance with this procedure, we performed a series of t tests to identify links between any of the 85 ROIs for which the DPD and control group showed significant differences in FA values. To determine suprathreshold links, we applied descending initial link thresholds (lt) from $p_{lt} = 0.05$ to $p_{lt} = 0.001$ in steps of 0.005. This procedure (i.e., no fixed initial link threshold) was chosen because variations in thresholding can be informative regarding the nature of any observed group difference: effects found only at liberal thresholds (e.g., $p_{lt} < 0.05$) are expected to be subtle and topologically extended, whereas effects evident at conservative thresholds (e.g., $p_{lt} < 0.001$) are likely to reveal strong focal differences between groups.[30] Significance of the resulting graph components was determined by generating a corresponding null-model distribution, using 10 000 permutations. For the present analysis, we considered an identified graph component (i.e., subnetwork) as statistically significant with an FWE-corrected $p < 0.05$. However, owing to the explorative nature of this study, significant results are used purely for theory-building and should be replicated with preregistration.[31]

Network-based statistics: correlational analysis
To obtain indications of whether the previously described NBS group differences are specific to DPD symptomatology, we subjected the connectivity matrices of all participants (control and DPD) to an NBS partial correlation analysis with dissociative symptom severity, as measured by the CDS-30 (controlling for age, sex and handedness). Specifically, instead of using group-wise t tests, we applied partial correlations for mass univariate testing in every cell of the connectivity matrix to determine sets of suprathreshold links. Again, significance of the resulting graph components was determined by generating a corresponding null-model distribution with 10 000 random permutations of CDS-30 scores.

Link-based analysis using FDR: group comparison
As an additional analysis, we used FDR[59] to explore individual connections between any ROI pair within a network that may be altered in individuals with DPD. Although NBS improves power, as it is a more stringent control of false positives, only the network as a whole can be regarded as significant and, thus, can be interpreted only as a whole. The objective of performing a link-based controlling procedure[30] in addition to using NBS derives from the exploratory nature of the present study; FDR correction may provide additional information on focal effects concerning individual connections. Using FDR, a test statistic and a respective p value is computed for each network link, which in this case refers to the FA-based connection for which streamlines have successfully been generated in all participants. Therefore, the null hypothesis is tested based on individual links while controlling the ratio of false-positive connections among all positive connections. In contrast, NBS allows rejecting the null hypothesis at the level of cerebral networks by controlling the FWE rate (i.e., the probability of false-positive networks). In the GraphVar toolbox,[58] an FDR correction algorithm[60] is carried out with respect to a designated α level. We applied an FDR-corrected threshold of $p_{FDR} = 0.05$ and tested against random groups using 100 000 permutations.

Link-based analysis using FDR: correlational analysis
Link-based analysis was performed to explore the association of symptom severity as measured by the CDS-30 with the individual connections between any ROI pair within a network. Again, we computed partial correlations controlling for age, sex and handedness. We applied an FDR-corrected threshold of $p = 0.05$ and tested against a random distribution of CDS-30 scores using 100 000 permutations.

Results

Final sample

We enrolled 24 patients with DPD (18 women) and 23 healthy controls (18 women; Table 1) in the present study; 1 patient had to be excluded owing to inadequate fibre reconstruction, leaving a final sample of 23 patients in the DPD group. Seventeen patients had current comorbid disorders, mainly anxiety disorders, and 9 used psychotropic medication (Table 2).

Demographics

Patients with DPD did not differ from controls in age ($t_{44} = 0.289$, $p = 0.77$), handedness ($t_{44} = 1.542$, $p = 0.13$), level of education (Mann–Whitney $U = 245.5$, $p = 0.66$), information processing speed, or executive functions (Table 1). Patients with DPD differed significantly from controls on various self-report questionnaires (Table 1), which in turn correlated highly with DPD symptom severity (Appendix 1, Table S1, available at jpn.ca/170110-a1). No significant differences between patients with and without psychotropic medication were detected. Information regarding age at symptom onset was available for 21 of 23 patients with DPD. Based on retrospective reports, the mean age at symptom onset was 18.2 ± 6.17 years. At the time of the scan, patients had been living with DPD on average for 12.43 ± 10.20 (range 0.5–36) years. In most cases, symptoms had been chronic since their onset, with either no or only brief interruptions.

Network-based statistics

Group comparison
No significant group differences in graph components (i.e., subnetworks) between brain regions were detected with any of the initial link thresholds. However, a trend was found at an initial link threshold of $p_{lt} = 0.005$, which indicated group differences regarding 1 subnetwork ($p_{FWE} = 0.08$ at the network level, controlled for age, sex and handedness). This network comprised 5 nodes and 4 links between frontal and subcortical regions. Within this network, patients with DPD

showed higher FA values than controls between the left superior frontal gyrus, right medial orbitofrontal cortex and its connection to the right amygdala and lower FA values than controls between the right amygdala, brainstem and left caudate (Fig. 2).

Partial correlation analyses

For 1 patient, no questionnaire data were available, leaving 45 participants for the partial correlation analysis (controlling for age, sex and handedness). No significant correlation between CDS-30 scores and interregional FA values in the links identified using the initial link threshold of $p_{it} = 0.005$ was found using NBS.

Link-based analysis using FDR

Group comparison

We found that 9 individual graph components significantly differed between patients with DPD and controls when using the link-based controlling procedure (Table 3). Components for which patients with DPD showed lower FA values than controls concerned connections between the left temporal pole and left superior temporal gyrus ($p_{FDR} < 0.001$), between the right middle temporal gyrus and right supramarginal gyrus ($p_{FDR} = 0.002$), between the brainstem and left caudate ($p_{FDR} < 0.001$), between the right medial orbitofrontal cortex and the right caudal anterior cingulate cortex ($p_{FDR} < 0.001$) and between the right inferior temporal gyrus and the right lingual cortex ($p_{FDR} < 0.001$). Higher FA values for patients with DPD than controls were found for the connection linking the right superior temporal gyrus and the right banks of superior temporal sulcus ($p_{FDR} < 0.01$). Each of the remaining

Table 2: Current and lifetime comorbid disorders in patients with DPD (*n* = 23)

Disorder	Current, *n*	Lifetime, *n*
Anxiety disorders	11	11
Social anxiety disorder		
Panic disorder	2	3
Specific phobia	2	2
Obsessive–compulsive disorder	2	2
Generalized anxiety disorder	1	1
Mood disorders	2	10
Major depressive disorder		
Personality disorders	1	1
Emotionally unstable – impulsive type		
Emotionally unstable – borderline type	1	1
Anxious avoidant	1	1
Dependent	1	1
Other	0	1
Posttraumatic stress disorder		
Conversion disorder	0	1
Impulse control disorder	1	1
Eating disorder	0	3
Substance abuse disorder	0	1
Total comorbidity	17	19

DPD = depersonalization/derealization disorder.

Table 1: Demographic characteristics and clinical measures

	DPD		Control			
Characteristic	*n*	Mean ± SD	*n*	Mean ± SD	2-tailed *t* test	*p* value
Age, yr	23	30.61 ± 7.31	23	29.96 ± 7.99	$t_{44} = 0.289$	0.774
Handedness	23	0.76 ± 0.50	23	0.92 ± 0.15	$t_{44} = -1.542$	0.135
CDS-30	22	148.14 ± 43.10	23	9.61 ± 12.04	$t_{43} = 14.543$	< 0.001
CDS-State	23	926.96 ± 383.52	22	173.64 ± 254.40	$t_{43} = 7.796$	< 0.001
DES	22	442.27 ± 217.95	23	36.09 ± 39.05	$t_{43} = 8.610$	< 0.001
BDI-II	22	20.32 ± 11.27	23	2.48 ± 3.41	$t_{43} = 7.120$	< 0.001
STAI-T	22	56.23 ± 11.80	23	34.00 ± 11.37	$t_{43} = 6.434$	< 0.001
LSAS	22	442.27 ± 217.95	23	36.09 ± 39.05	$t_{43} = 3.738$	0.001
TAS-20	22	55.59 ± 8.66	23	52.00 ± 7.07	$t_{43} = 5.785$	< 0.001
ERQ	22	42.68 ± 8.98	23	39.52 ± 9.62	$t_{43} = 1.138$	0.262
KIMS	22	86.68 ± 19.71	23	124.39 ± 13.43	$t_{43} = -7.531$	< 0.001
DFS	22	70.36 ± 9.52	23	61.65 ± 9.24	$t_{43} = 3.119$	0.003
CTQ_sum	22	52.32 ± 17.52	23	44.22 ± 10.33	$t_{43} = 1.878$	0.069
CTQ_PA	22	6.36 ± 2.68	23	5.91 ± 1.91	$t_{43} = 0.652$	0.518
CTQ_PN	22	5.50 ± 2.76	23	4.00 ± 1.54	$t_{43} = 2.241$	0.032
CTQ_EA	22	11.00 ± 4.04	23	5.91 ± 1.91	$t_{43} = 1.765$	0.086
CTQ_EN	22	6.91 ± 5.86	23	4.57 ± 5.27	$t_{43} = 1.411$	0.165
CTQ_SA	22	6.45 ± 2.30	23	5.65 ± 1.72	$t_{43} = 1.119$	0.269
TMT-A	21	24.62 ± 5.52	21	24.90 ± 6.80	$t_{40} = -0.150$	0.882
TMT-B	21	51.38 ± 14.20	21	53.19 ± 18.59	$t_{40} = -0.355$	0.725

BDI = Beck Depression Inventory; CDS = Cambridge Depersonalization Scale; CTQ = Childhood Trauma Questionnaire; DES = Dissociative Experiences Scale; DFS = Questionnaire for functional and dysfunctional self-focused attention; DPD = depersonalization/derealization disorder; EA = emotional abuse; EN = emotional neglect; ERQ = Emotion Regulation Questionnaire; KIMS = Kentucky Inventory of Mindfulness Skills; LSAS = Liebowitz Social Anxiety Scale; PA = physical abuse; PN = physical neglect; SA = sexual abuse; SD = standard deviation; STAI-T = State-Trait Anxiety Scale, trait version; TAS = Toronto Alexithymia Scale, TMT = Trail Making Test.

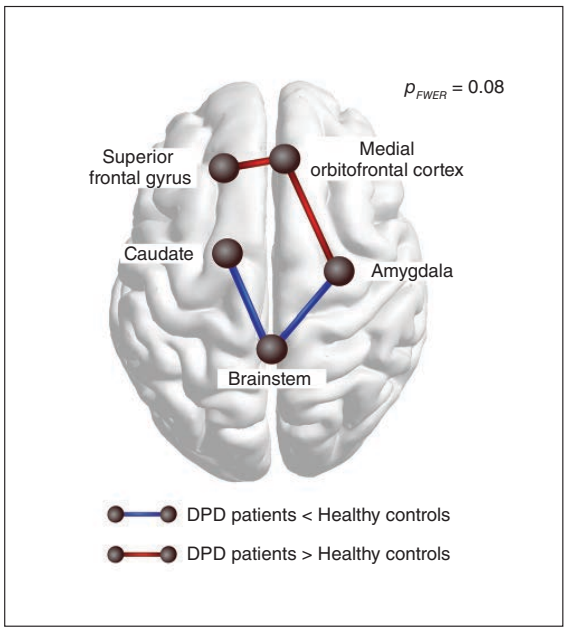

Fig. 2: Visualization of the trend found in the group comparison when using network-based statistics. At an initial-link threshold of p_{tt} = 0.005, a subnetwork was identified for which patients with depersonalization/derealization disorder (DPD) displayed lower fractional anisotropy (FA) (blue edges) as well as higher FA (red edges) than healthy controls (p_{FWE} = 0.08). Patients showed relatively lower FA values between the left caudate, brainstem and the right amygdala, and higher FA between the left superior frontal gyrus, right medial frontal cortex and the right amygdala. FWE = family-wise error.

3 components encompassed 3 brain regions connected via 2 edges. Patients with DPD showed lower FA values between the left insula, left pars triangularis and the left lateral orbitofrontal cortex (p_{FDR} < 0.01), while showing higher FA values between the left isthmus of the cingulate cortex, right cuneus and left superior parietal cortex (p_{FDR} < 0.01). Finally, within 1 component of 3 nodes, patients with DPD showed lower FA values than controls between the left caudal anterior cingulate cortex and the left medial orbitofrontal cortex and higher FA values than controls between the latter and the right superior frontal gyrus (p_{FDR} < 0.01).

Partial correlation analyses

As 1 patient with DPD did not complete the CDS-30 questionnaire, data from 45 participants were analyzed with partial correlation analysis (controlling for age, sex and handedness). The link-based analysis yielded a significant negative correlation between DPD symptoms, as measured by the CDS-30, and FA values of 5 components (Appendix 1, Table S2). Four of these components match those identified in the group contrast for which patients with DPD showed lower FA values than controls when using a link-based controlling procedure (Table 3). In light of the high intercorrelations between questionnaires assessing anxiety, depression and dissociation, we tested whether this effect was driven by dissociation severity by performing additional partial correlation analyses with STAI-T scores and BDI scores. Using these as exclusive masks, we determined that mean FA between the left superior temporal gyrus and temporal pole (corrected α level p_{FDR} < 0.001) as well as mean FA between the right middle temporal gyrus and right supramarginal gyrus (corrected α level p_{FDR} < 0.001) correlate solely with dissociation severity. These results are shown and the respective scatterplots provided in Figure 3A–D.

Table 3: Group comparison using link-based controlling procedure, controlled for age, sex and handedness*

Negative correlation between symptom scores and FA values				
BDI	STAI-T	CDS	Significant components DPD ≠ HC†	p_{FDR} value
—	—	√	Left temporal pole – – Left superior temporal gyrus	< 0.001
—	—	√	Right middle temporal gyrus – – Right supramarginal gyrus	0.002
—	√	√	Brain stem – – Left Caudate	< 0.001
√	√	√	Right medial OFC – – Right caudal ACC	0.001
—	√	—	Right inferior temporal gyrus – – Right lingual cortex	< 0.001
—	—	—	Right superior temporal gyrus + + Right banks of superior temporal sulcus	< 0.01
—	—	—	Left insula – – Left pars triangularis – – Left lateral OFC	< 0.01
—	—	—	Left caudal ACC – – Left medial OFC + + Right superior frontal gyrus	< 0.01
—	—	—	Left isthmus of the cingulate cortex + + Right cuneus + + Left superior parietal cortex	< 0.01

ACC = anterior cingulate cortex; BDI = Beck Depression Inventory; CDS = Cambridge Depersonalization Scale; DPD = depersonalization/derealization disorder; FA = fractional anisotropy; FDR = false discovery rate; HC = healthy controls; STAI-T = State-Trait Anxiety Scale, trait version; OFC = orbitofrontal cortex.
*All components for which patients with DPD and controls displayed significantly different FA values are listed along with the respective *p* value. Ticks mark components for which a significant correlation was found with dissociative symptoms scores (CDS-30), trait anxiety (STAI-T), or depression (BDI).
†Minus signs between brain regions (– –) represent connections for which patients with DPD displayed lower FA values than controls; plus signs between regions (+ +) represent connections for which patients displayed higher FA values than controls.

Additional post hoc analyses

We performed additional post hoc analyses to control for potential effects of psychotropic medications, which were taken by 9 patients. We repeated the group comparison with medication as a covariate (in addition to age, sex and handedness) using NBS (p_{it} = 0.005) and a link-based controlling procedure. Our main findings remained the same, even when medication effects were partialed out (Appendix 1, Table S3 and Table S4). Furthermore, we ran post hoc correlations within the patient group for age at symptom onset as well as duration of symptoms to verify whether components found in the group comparison could be further explained by these variables. In addition, we contrasted a subsample of patients without comorbid disorders (n = 11) with healthy controls (n = 23) to test whether FA values between certain regions might be associated exclusively with the DPD diagnosis. None of our post hoc analyses yielded any overlap between the subnetwork and graph components identified in the group comparison.

Discussion

To our knowledge, this is the first study exploring aberrations in structural connectivity in patients with DPD. Two statistical correction methods for multiple comparisons were used to identify potential group differences in an explorative approach. Using link-based analysis, significant group differences were found for 9 links. Connections between the left superior temporal gyrus and the left temporal pole as well as

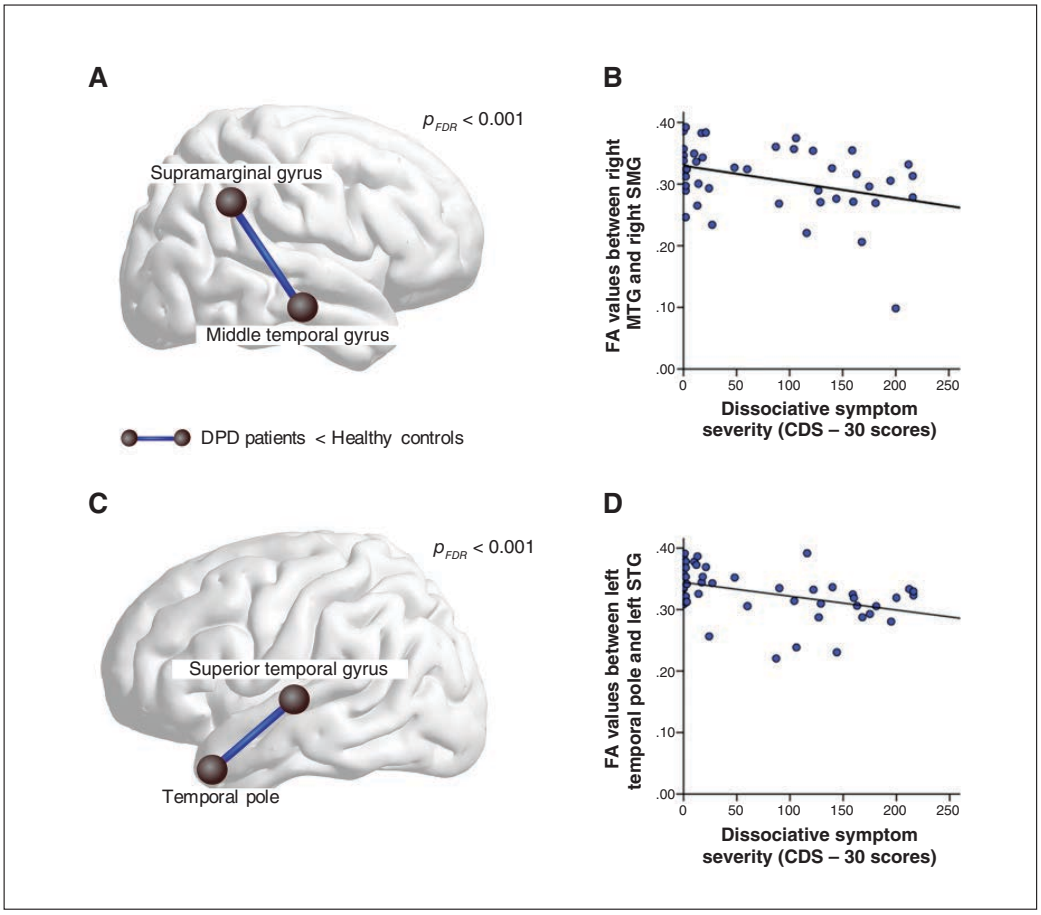

Fig. 3: Visualization of the 2 most outstanding results of the group comparison when using a link-based controlling procedure. First, (**A**) patients with depersonalization/derealization disorder (DPD) showed significantly lower fractional anisotropy (FA) between the right middle temporal gyrus and the right supramarginal gyrus. (**B**) The FA values within this connection were negatively correlated with dissociative symptom scores across groups, as measured by the CDS-30. Second, (**C**) relative to controls, patients with DPD showed significantly lower FA values between the left temporal pole and the left superior temporal gyrus. (**D**) Dissociative symptom severity correlated negatively with FA values of this connection. CDS = Cambridge Depersonalization Scale; FDR = false discovery rate; MTG = middle temporal gyrus; SMG = supramarginal gyrus; STG = superior temporal gyrus.

between the right middle temporal gyrus and the right supramarginal gyrus are characterized by lower mean FA values in the DPD group, which correlate with dissociative symptom severity, but not with anxiety or depressive symptom severity. The remaining 7 links do not correlate with dissociation severity exclusively; some showed significant correlations with both dissociation severity and anxiety or depression scores, whereas others did not correlate with either. Using NBS, a trend-level finding points toward connectivity alterations in a circuit comprising frontolimbic as well as subcortical striatal–brainstem connections, which partially overlap with connections identified when using link-based statistics.

The results from the link-based controlling procedure are discussed first. Altered structural connectivity (lower FA) in patients with DPD relative to controls was found between the right middle temporal gyrus (MTG) and the right supramarginal gyrus (SMG). In previous studies, lower metabolic rate[13] and reduced cortical thickness were reported for the right MTG in patients with DPD relative to controls,[12] whereas the SMG has previously been associated with dissociation in the context of PTSD.[61] As part of the somatosensory association cortex in the parietal lobe, the SMG receives input from visual, auditory, somatosensory and limbic structures; the right hemispheric SMG has been associated with cross-modal spatial attention[62] and sense of agency.[63] The function of the MTG is still unclear. It has been associated with conceptual processing[64,65] and transmodal integration,[66,67] but also with social anxiety[68] and hallucinations in schizophrenia.[69,70] Considering patients with DPD frequently report symptoms related to impaired integration of different sensory modalities as well as somatosensory distortions, alterations in fibre pathways between the right MTG and right SMG may represent the neuronal underpinnings of failed sensory integration necessary for, for example, an intact body perception in space.

Our second prominent finding using link-based analysis indicates lower structural connectivity between the left temporal pole and the left superior temporal gyrus, which is also in relative concordance with previous findings. Hollander and colleagues[10] found increased theta slowing in left temporal areas in a case study of DPD, and Sierra and colleagues[12] reported a significant correlation between dissociative symptom scores in DPD with the left inferior temporal gyrus. Furthermore, depersonalization symptoms have been associated with temporal lobe epilepsy, more often with left-sided foci,[6] and with electroencephalography abnormalities above the temporal lobe within the context of panic disorder.[11,71] The results of the present study extend these findings by highlighting the role of anatomic connections between the left superior temporal gyrus and the left temporal pole. In healthy individuals, the left superior temporal gyrus has been confirmed to play a role in auditory processing and language comprehension.[72] The temporal pole has been suggested to be an amodal "semantic hub," which is crucial for forming associations across distinct attributes.[73] It is possible that reduced connectivity between these 2 temporal structures underlies dysfunctional association of multimodal information observed in patients with DPD. In conjunction, these explorative findings suggest that the temporal lobe model of DPD[9] is worth pursuing further.

Moreover, potentially lower structural connectivity between the right medial OFC and right caudal ACC found in patients was associated with dissociative, anxiety and depressive symptoms and thus might be of particular interest from a transdiagnostic perspective. Finally, we further found 5 components pointing toward altered structural connectivity in right temporal regions, bilateral frontal and limbic areas as well as in left parietal and occipital cortices in patients with DPD relative to controls. However, no correlations between interregional FA values and symptom severity emerged, so these links seem to be less central to any neurobiological model of DPD.

Patients also showed relatively lower FA than controls between the brainstem and the left caudate, which was associated with dissociative scores as well as anxiety scores. This finding seems particularly important as it was also identified using NBS: this subnetwork was characterized by higher FA between frontal regions and projections to the amygdala and lower FA values between the amygdala, brainstem and left caudate (Fig. 2). According to the model of frontolimbic dysbalance,[14,15] prefrontal cortices are assumed to overregulate limbic structures,[14] resulting in the emotional numbing observed in patients with DPD. Albeit only approaching statistical significance in the current sample, this finding supports the frontolimbic dysbalance theory, as we found a trend toward higher structural connectivity (i.e., higher FA) within the left superior frontal gyrus and the right orbitofrontal cortex (OFC) and higher connectivity strength between the OFC and the amygdala in the DPD group. The OFC and the basolateral nucleus of the amygdala are important nodes in the limbic corticostriatal loop and share many reciprocal connections that have been associated with regulating emotional responses.[74] Frontolimbic inhibition has been reported in functional connectivity studies in PTSD and its dissociative subtype[15] and was confirmed in task-based fMRI in DPD, yet so far only in small samples.[17–19] Interestingly, the identified subnetwork also comprised connections in which patients with DPD showed lower mean FA values (between the brainstem to the right amygdala and the left caudate, respectively). Functional synchronization between the amygdala, caudate and medial prefrontal cortex has been suggested to subserve active coping with threat.[75] Accordingly, altered functional connectivity due to altered structural connectivity can be hypothesized to underlie passive responses to threat, such as dissociation. The primary control centre for internal and external stressors in the brainstem is the periaqueductal gray. Its connectivity with the central nucleus of the amygdala is suggested to play a role in freezing, a passive threat response, which is suggested to be the homologue of dissociation in animals.[76] Convergently, dissociation in PTSD has been linked to reduced functional connectivity between the periaqueductal gray and the amygdala,[77] while activation of the caudate and the amygdala has been associated with specific dissociative identity states.[78] These distinct brain aberrations may be mediated by altered white matter on a network level. Thus, our findings suggest that

structural alterations in frontolimbic–striatal circuits may contribute to abnormal fear responses (e.g., emotional numbing) observed in DPD. However, as dissociative symptom severity was not significantly correlated with this network's FA values, future studies should carefully explore its role.

As for the question whether the reported group differences are best considered a diathesis for or a result of the disorder, we can only speculate. We could not confirm a relationship between FA values and duration of illness, but cannot rule out that this is due to the bimodal distribution of the duration of illness in our sample. Finally, as our results do not overlap with findings in the same cohort on grey matter alterations,[20] we assume that altered structural connectivity is best understood as a primary pathophysiology and not merely a secondary effect of local grey matter volume loss in patients with DPD.

Limitations

The following limitations need to be considered. First, the present study is of a purely exploratory nature; that is, it represents a data-driven approach aimed at theory-building. Second, to ensure ecological validity, we did not exclude patients with comorbid disorders or patients taking psychotropic medication. It remains unclear whether the observed alterations in white matter fibre connections represent a risk factor or a consequence of the disorder due to the cross-sectional nature of this study. Finally, general methodological issues concerning the graph theoretical analysis of diffusion MRI tractography data apply. We used CSD tractography, which is capable of resolving crossing fibre tracts,[79] to reconstruct structural brain networks, decreasing the number of false-negative findings.[80] However, other difficulties of the tracking algorithm, such as modelling different fibre geometries and a potential increase of false-positive streamlines, need to be considered. By having included only links for which streamlines have been generated for all participants, we again reduced the influence of false-positive streamlines on the results. However, this procedure may have excluded relevant connections for the group contrast. In addition, it should be kept in mind that by using the diffusion parameter FA as an edge weight for the connectivity matrices, no strong inferences of the state of the anatomic connection between any 2 regions of interest can be made. Fractional anisotropy is modulated by a range of microstructural factors and the indication of lower or higher FA values in regard to the degree of structural connectivity remains unclear.[81] Finally, the resolution of the data and FreeSurfer parcellation limits the interpretation; e.g., we cannot ascertain which specific subnuclei of the amygdala and structures of the brainstem are involved in the detected network.

Conclusion

This exploratory study is, to our knowledge, the first to report altered structural connectivity (i.e., FA values) in individuals with DPD compared with healthy controls. Our results support the model of frontolimbic dysbalance suggested to underlie emotional numbing in individuals with DPD, while at the same time emphasizing the role of the temporal lobes, as suggested by an early conceptualization of the disorder.[9] We conclude that dysfunctional interaction on a network level as well as abnormal fibre tract connectivity on a link-based level, may contribute to the heterogenic symptomatology observed in individuals with DPD, which might also inform a transdiagnostic perspective.

Clinical implications could potentially be drawn from our findings in the long-term. One emphasis may lie in strengthening multimodal integration and embodiment in DPD. For severe and chronic courses, an interesting consideration on doing so refers to the implementation of repetitive transcranial magnetic stimulation above temporoparietal regions. In a first clinical trial, Mantovani and colleagues[82] reported significant symptom reduction in 6 of 12 participants after 3 weeks of low-frequency repetitive transcranial magnetic stimulation on the right temporoparietal junction, with the strongest improvement observed in anomalous body experiences (71% improvement in responders[83]). However, having used an exploratory approach, our results as well as their implications ought to be verified in a confirmatory study.

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Table S1

Intercorrelations between questionnaire scores.

Questionnaire	BDI	CDS_30	CTQ sum	DES	LSAS	STAI-T	DFS func	DFS dysfunc	ERQ appraisal	ERQ suppression	KIMS	TAS-20
BDI	1	.648**	.166	.650**	.448**	.768**	.723**	-.725**	.435**	-.441**	-.719**	.638**
CDS_30	.648**	1	.303*	.878**	.490**	.616**	.530**	-.456**	.431**	-.389**	-.742**	.665**
CTQ sum	.166	.303*	1	.319*	.537**	.391**	.379*	-.159	.077	-.256	-.455**	.328*
DES	.650**	.878**	.319*	1	.547**	.665**	.544**	-.496**	.397**	-.516**	-.735**	.655**
LSAS	.448**	.490**	.537**	.547**	1	.631**	.488**	-.473**	.210	-.492**	-.674**	.680**
STAI-T	.768**	.616**	.391**	.665**	.631**	1	.853**	-.659**	.447**	-.509**	-.817**	.629**
DFS func	.723**	.530**	.379*	.544**	.488**	.853**	1	-.655**	.346*	-.365*	-.702**	.493**
DFS dysfunc	-.725**	-.456**	-.159	-.496**	-.473**	-.659**	-.655**	1	-.409**	.402**	.648**	-.513**
ERQ appraisal	.435**	.431**	.077	.397**	.210	.447**	.346*	-.409**	1	-.123	-.409**	.253
ERQ suppression	-.441**	-.389**	-.256	-.516**	-.492**	-.509**	-.365*	.402**	-.123	1	.517**	-.549**
KIMS	-.719**	-.742**	-.455**	-.735**	-.674**	-.817**	-.702**	.648**	-.409**	.517**	1	-.795**
TAS-20	.638**	.665**	.328*	.655**	.680**	.629**	.493**	-.513**	.253	-.549**	-.795**	1

BDI=Beck Depression Inventory; CDS-30=Cambridge Depersonalization Scale; CTQ=Childhood Trauma Questionnaire; DES=Dissociative Experiences Scale; DFS=Questionnaire for functional and dysfunctional self-focused attention; dysfunc=dysfunctional; ERQ=Emotion Regulation Questionnaire; func=functional; KIMS=Kentucky Inventory of Mindfulness Skills; LSAS=Liebowitz Social Anxiety Scale; PN=physical neglect score; STAI-T=State-Trait Anxiety Scale, trait version; sum=sum scores; TAS-20=Toronto Alexithymia Scale.

*p<.05 (2-tailed).

**p<.01 (2-tailed).

Table S2

Results of the partial correlation analysis between mean FA and dissociative severity when using link-based analysis (controlling for age, sex, and handedness). Mean FA of the components significantly correlated negatively with dissociative symptom severity, as measured by the CDS-30.

Components	p_{FDR}
Brain stem – – Left caudate	<.001
Right middle temporal gyrus – – Right supramarginal gyrus	<.001
Right medial OFC – – Right caudal ACC	<.001
Left temporal pole – – Left superior temporal gyrus	.002
Left medial OFC – – Left caudal ACC – – Left accumbens area	<.05

ACC=anterior cingulate cortex; CDS=Cambridge Depersonalization Scale; DPD=depersonalization/derealization disorder; FDR=false discovery rate; OFC=orbitofrontal cortex.

Table S3.

Results of the group comparison when using network-based statistics and controlling for medication effects (in addition to age, sex, and handedness). At an initial-link threshold of p_{lt}=.005, one sub-network was found comprising 8 nodes (brain regions) and 7 edges (links), for which patients with DPD displayed altered FA values compared to healthy controls (p_{FWER}=.08, on a network level).

Significant sub-network DPD ≠ HC
Left superior frontal gyrus **+ +** Right medial OFC
Right medial OFC **+ +** Right amygdala
Right amygdala **– –** Brain stem
Right medial OFC **– –** Right putamen
Right medial OFC **– –** Left lateral OFC
Right putamen **– –** Left medial OFC
Left lateral OFC **– –** Left pars triangularis

Minus signs between brain regions (**– –**) represent connections for which patients with DPD displayed lower FA values compared to healthy controls; plus signs between regions (**+ +**) represent connections for which patients displayed higher FA values compared to controls; DPD=depersonalization/derealization disorder; FA=fractional anisotropy; FWER=family wise error rate; OFC=orbitofrontal cortex.

Table S4.

Results of the group comparison when using link-based controlling procedure and controlling for medication effects (in addition to age, sex, and handedness). Eight components were found for which patients with DPD displayed significantly different FA values compared to healthy controls (all components significant at p_{FDR}<.01).

Size of component	Significant components DPD ≠ HC
2 nodes, 1 edge	Left temporal pole **– –** Left superior temporal gyrus
2 nodes, 1 edge	Right middle temporal gyrus **– –** Right supramarginal gyrus
2 nodes, 1 edge	Right amygdala **– –** Brain stem
2 nodes, 1 edge	Right precuneus **– –** Left lingual gyrus
2 nodes, 1 edge	Right lingual gyrus **– –** Left fusiform gyrus
2 nodes, 1 edge	Right lateral occipital gyrus **– –** Left pericalcarine cortex
2 nodes, 1 edge	Left lateral occipital gyrus **+ +** Left cuneus
8 nodes, 7 edges	Right superior frontal gyrus **+ +** Left medial OFC
	Left medial OFC **– –** Right putamen
	Left medial OFC **– –** Left caudal ACC
	Right putamen **– –** Right medial OFC
	Right medial OFC **– –** Left lateral OFC
	Left lateral OFC **– –** Left pars triangularis
	Left pars triangularis **– –** Left insula

Minus signs between brain regions (**– –**) represent connections for which patients with DPD displayed lower FA values compared to healthy controls; plus signs between regions (**+ +**) represent connections for which patients displayed higher FA values compared to controls; DPD=depersonalization/derealization disorder; FA=fractional anisotropy; FDR=false discovery rate; HC=healthy controls; OFC=orbitofrontal cortex.

B. Study II

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The dissociative subtype of posttraumatic stress disorder is associated with subcortical white matter alterations on a network level

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Abstract

Background: Posttraumatic stress disorder (PTSD) is characterized by intrusions, avoidance, and hyperarousal while patients of the dissociative subtype (PTSD-D) experience additional dissociative symptoms. A neurobiological model proposes hyper-inhibition of limbic structures mediated by prefrontal cortices to underlie dissociation in PTSD. Here, we tested whether functional alterations in fronto-limbic circuits are underpinned by white matter network abnormalities on a network level.

Methods: 23 women with PTSD-D and 19 women with classic PTSD participated. We employed deterministic diffusion tractography and graph theoretical analyses. Mean fractional anisotropy (FA) was chosen as a network weight and group differences assessed using network-based statistics.

Results: No significant white matter network alterations comprising both frontal and limbic structures in PTSD-D relative to classic PTSD were found. A subsequent whole brain exploratory analysis revealed relative FA alterations in PTSD-D in two subcortical networks, comprising connections between the left amygdala, hippocampus, and thalamus as well as links between the left ventral diencephalon, putamen, and pallidum, respectively. Dissociative symptom severity in the PTSD-D group correlated with FA values within both networks.

Conclusion: Our findings suggest fronto-limbic inhibition in PTSD-D may present a dynamic neural process, which is not hard-wired via white matter tracts. Our exploratory results point towards altered fiber tract communication in a limbic-thalamic circuit, which may underlie (a) an initial strong emotional reaction to trauma reminders before conscious regulatory processes are enabled and (b) deficits in early sensory processing. In addition, aberrant structural connectivity in low-level motor regions may present neural correlates for dissociation as a passive threat-response.

Keywords: Network-based statistics, Diffusion MRI, Tractography, Graph theory, PTSD, Dissociation, Trauma

1. Introduction

Posttraumatic stress disorder (PTSD) is one of the commonest trauma-related disorders with a life time prevalence of 6.8% in the general population (Kessler et al., 2005). PTSD is characterized by intrusions, avoidance, and hyperarousal, with some patients experiencing additional dissociative symptoms such as depersonalization and derealization (American Psychiatric Association, 2013). Over the past years, several empirical studies indicated that pronounced dissociative symptomatology might not be represented dimensionally in PTSD but can be attributed to a distinct subgroup of patients. The dissociative subtype of PTSD, abbreviated with "PTSD-D" in the present work, was recently included in the DSM-5 (American Psychiatric Association, 2013). In support of this novel sub-distinction, different research groups conducted latent class analyses, suggesting 12%-29.9% of patients to belong to this subtype (Armour and Hansen, 2015, Steuwe et al., 2012, Tsai et al., 2015, Waelde et al., 2005, Wolf et al., 2012) with higher prevalence rates in women (Wolf et al., 2012) and in participants having experienced childhood sexual abuse (Steuwe et al., 2012, Wolf et al., 2012), independent of gender (Yiaslas et al., 2014). Most of these studies found that patients with PTSD-D displayed higher symptom severity mediated by higher intrusive symptomatology.

It has been suggested that dissociative states in PTSD are associated with distinct physiological and neural activation patterns (Lanius et al., 2010). Psychophysiological studies are not conclusive yet but tend to indicate that non-dissociative patients display heightened heart rate during trauma-exposure (for review see Bedi and Arora, 2007), while dissociative patients display unaltered or slightly lower heart rate during acute dissociation (Griffin et al., 1997, Lanius et al., 2002). Using functional neuroimaging (fMRI), the working group around Lanius studied patients during acute dissociation and found relatively reduced blood flow in structures crucial for emotion processing (amygdala and insula; Daniels et al., 2012, Mickleborough et al., 2011) heightened blood flow in regions associated with cognitive control of affective responses (medial prefrontal cortex and rostral anterior cingulate cortex; Daniels et al., 2012, Hopper et al., 2007). The authors propose that during dissociation, prefrontal cortices overregulate limbic structures, while during intrusive re-experiencing deficient prefrontal inhibition leads to limbic hyperactivation (cf. Lanius et al., 2010, also see

Liberzon and Garfinkel, 2009). These opposing neuronal patterns of emotional over- and underregulation co-exist in patients with PTSD-D per definition, suggesting dissociation to be underpinned by dynamic neural processes. Yet, two studies have reported correlations between brain morphology and dissociative symptom severity in PTSD. Daniels et al. (2016) found increased volume of the right precentral and fusiform gyri and reduced volume in right inferior temporal gyrus in patients with PTSD-D compared to patients with classic PTSD. Dissociative symptoms severity was positively associated with grey matter volume of the right middle frontal gyrus. Nardo et al. (2013) found positive correlations between trait dissociation and grey matter volume in frontal, temporal, and inferior parietal cortices. These findings indicate that emotional overregulation in PTSD-D may be underpinned by differences in grey matter brain anatomy, which could either represent pre-morbid biological risk factors for dissociative responses or adaptations to their development. Yet, these structural aberrations only referred to locally distinct areas and no interaction with brain circuits can be inferred from these studies.

It thus remains unclear whether the observed symptomatology is further underpinned by structural alterations of the white matter in PTSD-D. A promising approach presents the investigation of white matter tract communication on a network level. Diffusion weighted imaging (DWI) allows to image the human brain connectome non-invasively (Jones and Leemans, 2011, Tournier et al., 2011), while the combined usage of tractography and graph theory enables the analysis of structural connectivity on a network level (Bullmore and Sporns, 2009, Fornito et al., 2013, Griffa et al., 2013, Zalesky et al., 2010). Here, we apply graph theoretical analyses on data of diffusion MRI tractography to identify sub-networks with distinct structural connectivity between PTSD-D patients and patients with classic PTSD. Firstly, we test whether patients with PTSD-D and classic PTSD differ with regards to their structural connectivity in fronto-limbic circuits as hypothesized based on the model limbic overregulation in the PTSD-D group as. However, to our knowledge, no study to date has analyzed structural connectivity, i.e. white matter anatomy, in PTSD-D. Therefore, we secondly carry out an exploratory whole-brain analysis aimed at theory building.

2. Methods

2.1 Participants

Diffusion imaging scans were acquired in 45 women with PTSD (mean age 40.0 ± 9.8 ys, see Table 2 for further demographics). One participant could not be clearly categorized into either the classic PTSD or the PTSD-D group (cf. section 2.3) and thus was excluded from the present analysis. Furthermore, two patients of the PTSD-D group had to be excluded due to incidental findings by a neuro-radiologist, leaving in total 23 women in the PTSD-D group and 19 women in the classic PTSD group.

Study participants were recruited via public advertisements, in collaboration with licensed psychotherapists and psychiatrists, or through mental health in- and outpatient clinics. Participants were eligible for the study if they met the following criteria: (1) between 20 and 60 years old, (2) proficient in German, (3) MRI compatible, (4) no neurological disorder, (5) no history of head injury, (6) no substance dependency, (7) no intake of benzodiazepines or anticonvulsants (subjects taking only antidepressant medication were included), and (8) PTSD as their primary disorder. If presented as the secondary diagnosis, we allowed comorbid depressive and anxiety disorders, eating disorders, borderline personality disorder, and substance abuse disorders in order to ensure ecological validity. All other Axis-I disorders were excluded, with special attention given to the exclusion of comorbid dissociative disorders to disambiguate the diagnostic status. Written informed consent was obtained from the participants prior to participation and approval of the study was granted by the ethics board at the department of medicine at the University of Magdeburg and the ethical committee of the Berlin Psychological University.

2.2 Procedure

2.2.1 Clinical diagnostics

All participants were pre-screened on the telephone regarding MRI incompatibilities, head injuries, medication, and current psychological as well as neurological disorders. Subsequently, we sent out a questionnaire package including German versions of the Essen

Trauma Inventory (Tagay et al., 2006), the Dissociative Experiences Scale (DES; Spitzer et al., 2003), and the PTSD Checklist for DSM-IV (PCL; Teegen, 1997) to screen for trauma exposure and PTSD symptoms, respectively. Eligible participants were invited for a diagnostic assessment by a licensed clinical psychologist. German versions of four standardised clinical interviews were implemented. (1) The Clinician-administered PTSD Scale (CAPS-IV; Schnyder and Moergeli, 2002) was used to establish the PTSD diagnosis, (2) the Structured Clinical Interview for DSM-IV (Wittchen et al., 1997) was implemented for the diagnosis of Axis-I disorders. To exclude subjects with dissociative disorders or primary borderline personality disorder, (3) the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D; Gast et al., 2000) and (4) the respective section of the Structured Clinical Interview for DSM-IV axis II (Fydrich et al., 1997) were employed.

2.2.2 Questionnaires and tasks

All participants completed several self-report questionnaires. To assess trait and state dissociation, German versions of the 30-item and 22-item Cambridge Depersonalization Scale (CDS-30; CDS-state; Michal et al., 2004) were implemented, respectively. Further questionnaires to characterize the dissociative experience were the Multiscale Dissociation Inventory (MDI; Brière, 2002; authorized German translation by J. Daniels [unpublished, University of Groningen, The Netherlands]), the Peritraumatic Dissociative Experiences Questionnaire (PDEQ; Marmar et al., 1994; authorized German translation by A. Maercker [unpublished, TU Dresden, Germany]), and the Somatoform Dissociation Questionnaire (SDQ-20; Mueller-Pfeiffer et al., 2010). For further sample characterization, we employed the Beck Depression Inventory (BDI-II, Hautzinger et al., 2006), the Emotion Regulation Questionnaire (ERQ; Abler and Kessler, 2009), the State-Trait Anxiety Inventory (STAI-T; Laux and Spielberger, 2001), and the Childhood Trauma Questionnaire (CTQ; Wingenfeld et al., 2010). In addition, information processing speed and executive functions were assessed using the Trail Making Test versions A and B (TMT; Stanczak et al., 1998), respectively.

2.3 Subtype allocation

The classification of participants into either the classic PTSD or the PTSD-D group was based on five diagnostic instruments: DES, CDS-30, CDS-state, CAPS, and SKID-D. Pre-defined cut-offs for each questionnaire indicated whether dissociative symptoms were prevalent or not. If patients scored above the cut-off in at least three of these five instruments, they were diagnosed with PTSD-D. Accordingly, if they scored below the cut-offs in at least three questionnaires, participants were allocated to the classic PTSD group. We specified the following cut-offs: (1) ≥ 20 in the DES, (2) ≥ 20 in the CDS-30 (only frequency; cf. Spitzer et al., 2015), (3) CDS-state ≥ 15, (4) ≥ 4 in two questions assessing depersonalization and derealization in the CAPS, (5) ≥ 4 in the two SKID-D sections measuring depersonalization and derealization, respectively.

Two participants could not be clearly classified into the PTSD or PTSD-D. One participant displayed high dissociative scores on the two self-report questionnaires but low scores regarding dissociation on the clinical interviews. We decided to exclude this participant from the analysis (cf. section 2.1), due to the strong incongruence between self- and external assessment. Another participant scored clearly below the cut-off in the CDS-30 and the SCID-D, but just above the cut-offs in all remaining three questionnaires. We decided to allocate this participant to the classic PTSD group, because of the relative congruency between self- and external assessment.

2.3 MRI Acquisition

Diffusion images and T1-weighted images were acquired on a 3T Siemens Tim Trio scanner (Siemens, Erlangen, Germany) equipped with a 12-channel head coil. Diffusion imaging was performed with a single-shot echo-planar imaging sequence using the following parameters: TR=7500ms, TE=86ms, 61 slices, voxel size=2.3x2.3x2.3mm3, slice thickness=2.3mm, FOV=220x220mm2, 64 diffusion directions, b value=1000s/mm². Structural T1-weighted images were obtained with a magnetization-prepared rapid acquisition with gradient echo sequence (TR=1.9ms, TE=2.52ms, inversion time=900ms, flip angle=9°, FoV=256x256mm2, 192 slices, 1mm isotropic voxel sizes, 50% distancing factor).

2.4 Preprocessing

The preprocessing pipeline for the structural network analysis is provided as a flow chart in Figure 1. The T1-weighted MRI scans were processed with the automated image-processing software *FreeSurfer v6.0* (https://surfer.nmr.mgh.harvard.edu/). Important processing steps include skull stripping, segmentation of subcortical white matter and deep gray matter volumetric structures, definition of the grey and white matter boundaries, and parcellation of the cerebral cortex (Fischl and Dale, 2000). We used the default settings implemented in *FreeSurfer*. Each output was visually inspected for quality control. The diffusion data was preprocessed using the default settings in *ExploreDTI*, version 4.8.6 (http://www.exploredti.com; Leemans et al., 2009). Images were corrected for subject motion using the 'Rekindle' method (Tax et al., 2015), eddy current induced geometric distortions (Leemans and Jones, 2009), and EPI distortions (Irfanoglu et al., 2012). Constrained spherical deconvolution whole brain tractography was performed (Jeurissen et al., 2011, Tax et al., 2014) for each subject. Each processing step was visually inspected for quality insurance as well as valid co-registration checked by overlaying the respective images for each subject.

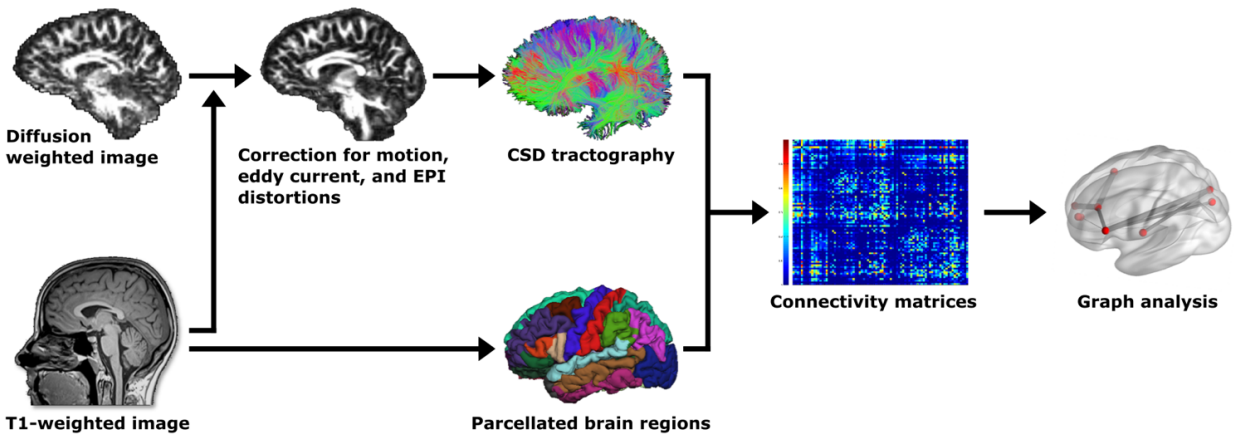

Figure 1. Flowchart of the preprocessing pipeline, which was performed using *FreeSurfer* (https://surfer.nmr.mgh.harvard.edu) and *ExploreDTI* (http://www.exploredti.com). EPI=echo-planar imaging, CSD=constrained spherical deconvolution.

2.5 Connectivity Matrices

To construct structural connectivity matrices, we used 87 predefined anatomical regions of interests (ROIs) derived from *FreeSurfer*. ROIs comprised all cortical regions from the Desikan Killiany atlas (35 areas) as well as the bilateral subcortical structures amygdala, hippocampus, caudate, putamen, pallidum, accumbens-area, thalamus, ventral diencephalon (DC), and the brain-stem. The ventral DC refers to a miscellaneous area, which comprises smaller nuclei and structures inferior to the thalamus (hypothalamus, red nuclei, medial and lateral geniculate nuclei, mammillary body, subthalamic nuclei, and substantia nigra as well as surrounding white matter). To construct structural connectivity matrices, the 87 ROI files were combined with the streamline files from *ExploreDTI*, which resulted in 87x87 connectivity matrices for each subject. Due to the deterministic tracking algorithm used, not all possible fiber tracts can be reconstructed in all subjects (Jeurissen et al., 2017, Maier-Hein et al., 2017). As this may vary between groups, we aimed to only include links in the network analyses for which fibers were tracked successfully in all participants. However, this restriction resulted in only 190 links to be entered into the analysis and we considered this procedure to be too conservative, potentially inflating false negative results. Hence, we chose to threshold the connectivity matrices by a minimum number of streamlines (maximum number of tracts in each subject * .001), which still curbs the effect of spurious streamlines (cf. Rubinov and Sporns, 2010), but allowed us to include all possible 87x87 links into the analysis.

2.6 Statistical analyses

The streamlines between each pair of ROIs were used as a mask, within which we computed mean fractional anisotropy (FA). Mean FA was used as edge weight between ROIs and served as an indicator for their structural connectivity. It is important to note that only homotopic regions are directly connected via fiber bundles, hence, not all ROI pairs entered in the present analysis are linked via direct anatomical connections, as tractography also accounts for indirect connections. The second-level network analyses, i.e. network-based statistics, and partial correlational analyses on a network level, were performed with GraphVar 1.3 (http://www.nitrc.org/projects/graphvar/; Kruschwitz et al., 2015), a toolbox run on in MATLAB R2016b (https://mathworks.com). Age was included as a covariate in all network analyses.

Group comparisons

To test for significant group differences in structural connectivity between brain regions implicated in the proposed model of fronto-limbic dysbalance, limbic and prefrontal start points were selected. In regard to limbic regions, we selected regions from the FreeSurfer parcellation (Desikan Killany atlas), which are proposed to belong to the limbic system (cf. Isaacson, 2013) and which have been reported to be undermodulated in PTSD-D (Lanius et al., 2010). Regarding frontal structures, we selected all parcellated regions within the frontal lobe. (Lanius et al., 2010). Regarding frontal structures, we selected all parcellated regions within the frontal lobe. This resulted in 8 limbic and 10 frontal ROIs, each tested bilaterally. The respective regions are listed in Table 1. Results were considered relevant if a sub-network was detected which included both at least one frontal and one limbic region.

In addition, we performed an exploratory whole-brain analysis of network-level FA differences between the PTSD-D and the classic PTSD group and thus, included all possible links (87x87 ROIs) into the analysis.

We used network-based statistics (NBS) to test for group differences between the PTSD-D and classic PTSD group. NBS is a nonparametric statistical method developed by Zalesky et al. (2010), which can be used to identify graph components within a network that are associated with an external variable, in our case group membership, while controlling the family wise error rate (FWER). Within NBS, statistical thresholding is performed in two steps: First, at every connection within a network, the hypothesis of interest is tested independently using so called initial link-thresholds. Resulting supra-threshold links may eventually form graph components. Whether any of these graph components are significant at the network level is determined by their size, which is compared to the occurrence of differently sized graph components derived from random data (i.e. by performing FWE-correction).

According to this procedure, we performed a series of t-tests to identify links between pre-defined ROIs (see above) for which the PTSD-D and classic PTSD group displayed significant differences in their structural connectivity (i.e. FA). We applied two initial link thresholds (lt) of p_{lt}=.005 and p_{lt}=.001. Following procedures in our previous paper (Sierk et al., in press), we chose more than one initial link threshold to obtain information regarding the nature of any observed group difference. Effects evident only at liberal thresholds (e.g. p_{lt}<.05) are rather subtle and topologically extended, whereas effects found at conservative thresholds (e.g.

p_{lt}<.001) are likely to disclose strong focal differences between groups (Zalesky et al., 2010). We determined the significance of identified graph component (i.e., a sub-network) by generating a corresponding null-model distribution, employing 10,000 permutations. An identified sub-network was considered statistically significant with an FWER-corrected p-value of p_{FWER}<.05. Note that multiple comparison correction is performed on a network level and thus, only the networks as a whole is considered significant and can only be interpreted as such (cf. Zalesky et al., 2010).

Table 1

Bilateral frontal and limbic structures that were entered in the first analysis, testing for group differences regarding the model of fronto-limbic dysbalance.

Limbic structures	Frontal structures
Hippocampus	Caudal middle frontal gyrus
Amygdala	Rostral middle frontal gyrus
Accumbens area	Lateral orbitofrontal cortex
Ventral diencephalon	Medial orbitofrontal cortex
Insula	Pars opercularis
Caudal anterior cingulate cortex	Pars orbitalis
Rostral anterior cingulate cortex	Pars triangularis
Posterior cingulate cortex	Parahippocampal gyrus
	Superior frontal gyrus
	Frontal pole

Correlational analyses

To test whether any identified group differences are related to dissociative symptomatology, we subjected the connectivity matrices of the PTSD-D and the classic PTSD group to a partial correlation analysis with dissociative symptom severity, as measured by the CDS-30 (controlled for age). The CDS-30 was used as it specifically assesses depersonalization and derealization and was employed to the same end in our previous study on connectivity alterations in patients with a dissociative disorder (Sierk et al., in press.). To obtain the respective sets of supra-threshold links, we employed partial correlations for mass-univariate testing in each cell of the connectivity matrix. As described in the previous section, significance of any identified graph components was tested by applying permutation testing using 10,000 random permutations of CDS-30 scores. Pearson correlations were computed across the PTSD-D and the classic PTSD group, separately.

3. Results

3.1 Demographics

Group differences regarding demographic information are listed in Table 2. Patients with PTSD-D did not differ from the classic PTSD group regarding age (*t(40)*=0.12, *p*=.908), level of education (Mann–Whitney *U*=192.00, *p*=.423), information processing speed (TMT-A; *t(40)*=0.74, *p*=.461), and executive functions (TMT-B; *t(40)*=0.57, *p*=.570). As shown in Table 2, no group differences were detected regarding depressive symptoms (i.e. BDI-II scores), trait anxiety (i.e. STAI-T scores), emotion regulation (i.e. ERQ scores), and childhood trauma experiences (i.e. CTQ scores). As expected, PTSD-D patients scored significantly higher than patients with classic PTSD on measures of trait dissociation (DES, *t(40)*=-3.21, *p*=.003), current dissociation (CDS-30, *t(37)*=-7.11, *p*<.001; MDI, *t(37)*=-4.11, *p*<.001), state dissociation (CDS-state, *t(39)*=-4.30, *p*<.001), somatoform dissociation (SDQ-20, *t(37)*=-3.42, *p*=.002), and peritraumatic dissociation (PDEQ, *t(37)*=-3.58, *p*<.001). There was a non-significant trend pointing towards higher PTSD symptom severity, as measured by the CAPS, in the PTSD-D compared to the classic PTSD group (*t(40)*=-1.80, *p*=.079). The questionnaires measuring dissociation correlated significantly with each other as well as with BDI and STAIT scores (see Appendix Table S1).

Regarding comorbidity and medication, 19 PTSD-D patients and 13 classic PTSD patients displayed comorbid disorders (cf. Table 3 for details) and two patients in the PTSD-D used antidepressant medication (Valdoxan and Escitalopram, respectively).

Table 2

Group differences regarding demographics and clinical measures.

	Classic PTSD		PTSD-D		Statistics (two-tailed t-test)		
Variable	n	Mean (SD)	n	Mean (SD)	*t* score	*df*	*p* value
Age	19	40.32 (9.44)	23	39.96 (10.38)	.12	40	.908
CDS-30	**17**	**11.82 (8.86)**	**22**	**42.23 (17.36)**	**-7.11**	**37**	**<.001**
CDS-state	**19**	**105.26 (177.93)**	**22**	**504.09 (390.37)**	**-4.30**	**39**	**<.001**
DES	**19**	**21.29 (14.35)**	**23**	**35.70 (14.60)**	**-3.21**	**40**	**.003**
MDI	**17**	**50.18 (18.12)**	**22**	**76.27 (20.79)**	**-4.11**	**37**	**<.001**
PDEQ	**17**	**17.65 (10.07)**	**22**	**27.55 (7.20)**	**-3.58**	**37**	**.001**
SDQ-20	**17**	**28.35 (8.37)**	**22**	**40.41 (12.50)**	**-3.42**	**37**	**.002**
BDI-II	17	23.06 (13.95)	23	22.52 (13.51)	.12	38	.903
CAPS	19	64.63 (11.70)	23	71.96 (14.19)	-1.80	40	.079
CTQ total	17	83.65 (12.74)	23	86.83 (12.71)	-.78	38	.440
CTQ-PA	17	11.29 (5.97)	23	11.65 (5.34)	-.20	38	.843
CTQ-PN	17	11.41 (5.20)	23	12.43 (4.87)	-.64	38	.527
CTQ-EA	17	15.71 (3.89)	23	16.43 (4.24)	-.56	38	.581
CTQ-EN	17	18.53 (4.05)	23	19.22 (5.56)	-.43	38	.668
CTQ-SA	17	13.47 (6.78)	23	15.35 (7.54)	-.81	38	.422
ERQ-R	17	24.65 (7.30)	22	24.14 (8.10)	.20	37	.840
ERQ-S	17	18.53 (6.19)	22	15.14 (4.83)	1.93	37	.062
PCL	19	36.32 (7.19)	23	40.22 (6.05)	-1.91	40	.063
STAI-T	17	54.76 (10.30)	23	58.7 (10.62)	-1.17	38	.249
TMT-A	19	26.67 (9.60)	23	24.77 (6.90)	.74	40	.461
TMT-B	19	66.52 (35.58)	23	61.31 (22.97)	.57	40	.570

BDI=Beck Depression Inventory; CAPS=Clinician-Administered PTSD Scale; CDS=Cambridge Depersonalization Scale; CTQ=Childhood Trauma Questionnaire; DES=Dissociative Experiences Scale; df=degrees of freedom; EA=emotional abuse; EN=emotional neglect; ERQ-R=Emotion Regulation Questionnaire Reappraisal; ERQ-S=Emotion Regulation Questionnaire Suppression; MDI=Multiscale Dissociation Inventory; PA=physical abuse; PDEQ=Peritraumatic Dissociative Experiences Questionnaire; PN=physical neglect; PTSD=Posttraumatic stress disorder, PTSD-D=dissociative subtype of PTSD; SA=sexual abuse; SD=standard deviation; SDQ=Somatoform Dissociation Questionnaire; STAI-T=State-Trait Anxiety Scale, trait version; TMT=Trail Making Test (Part A and B).

Table 3

Current (and where available also past) comorbid disorders among study participants, listed separately for the two groups classic PTSD (*n*=19) and PTSD-D (*n*=23). All comorbid disorders present the secondary diagnosis to PTSD.

		Classic PTSD *n* (past included)	PTSD-D *n* (past included)
Anxiety disorders	Generalized anxiety disorder	2	3
	Social anxiety disorder	7	11
	Specific phobia	3	1
	Panic disorder	3	7
	Agoraphobia without history of panic disorder	2	2
	Obsessive-compulsive disorder	0	3
	Total anxiety disorders	13	16
Mood disorders	Major depressive disorder, single episode	1 (3)	1 (1)
	Major depressive disorder	2 (6)	4 (12)
	Dysthymia	0 (0)	1 (0)
	Total mood disorders	3 (7)	5 (13)
Other	Substance use disorder	0 (4)	1 (4)
	Borderline personality disorder	2	6
	Eating disorder	0	4
	Somatoform disorder	0	1
Total comorbidity		13 (15)	19 (20)

3.2 Network-based statistics

Group comparisons

No significant group differences emerged on a network level in fronto-limbic circuits, i.e. between any of the pre-defined frontal and limbic structures (cf. Table 1), at neither initial-link threshold (p_{lt}<.005 or p_{lt}<.001).

In the exploratory whole-brain analysis, two sub-networks were identified at an initial-link threshold of p_{lt}<.005, for which patients with PTSD-D displayed altered FA compared to patients with classic PTSD (p_{FWER}=.026). The first network comprised four subcortical regions interconnected via three edges. Within this sub-network, the PTSD-D group showed relatively lower FA between the left amygdala and the left hippocampus as well as between the left hippocampus and left thalamus and higher FA values between the left thalamus and the brain stem (cf. Fig. 2A). The second network comprised three nodes and two links between the left ventral DC and the left putamen, and left pallidum, respectively (cf. Fig 2B). Within this sub-network, patients with PTSD-D displayed higher FA values compared to patients with classic PTSD. We verified that, for all participants, tracts have been reconstructed successfully for the identified links. In this exploratory analysis, no group differences were detected at an initial-link threshold of p_{lt}<.001.

Partial correlation analyses

For three patients, no questionnaire data on current dissociation severity were available, leaving 17 in the classic PTSD group and 22 in the PTSD-D group for the respective partial correlation analyses (controlled for age). Applying an initial-link threshold of p_{lt}<.005, we found significant correlations in the PTSD-D group between dissociative symptom severity (i.e. CDS-30 scores) and connectivity values in three sub-networks. A 5-node network, 3-node-network, and a 2-node network were detected, which overlapped with the sub-networks identified in the exploratory group comparison as follows: (1) Identical to the first sub-network in the group contrast, the 5-node network comprised links between the left amygdala, left hippocampus and left thalamus for which FA values correlated negatively with CDS-30 scores and a link between the left thalamus and brain stem, for which FA and dissociative symptom severity correlated positively (p_{FWER}=.027). In addition, the sub-network comprised connections between the left hippocampus and right thalamus to the brain stem

(positive correlation between FA and CDS-30 scores), i.e. it is more topologically extended than the network identified in the group comparison (cf. Fig 2C). (2) Identical to the second sub-network of the group contrast, higher FA values correlated positively with CDS-30 scores between left pallidum, left ventral DC and left putamen (p_{FWER}=.029; cf. Fig. 2D). The third sub-network did not overlap with the sub-networks found in the group contrast. It comprises the link between left and right precuneus, for which higher FA values correlated with higher symptom severity (p_{FWER}=.038).

In the classic PTSD group, two sub-networks were detected for which FA values correlated negatively with dissociative symptom severity, which refer to (a) the connection between the right caudate and right thalamus and to (b) the link between the left hippocampus and left caudate. These sub-networks did not overlap with any of the links found in the exploratory group comparison. All partial correlation results are listed in Table 4 and the respective overlap with the results of the group comparison is visualized in Figure 2C and 2D.

Post hoc analyses

Considering the high comorbidity with depressive and anxiety disorders in our sample as well as significant inter-correlations between questionnaires assessing anxiety, depression, and dissociation (cf. Table S2), further verification was warranted to confirm whether associations between FA values and CDS-30 scores in the PTSD-D group were specifically driven by dissociation severity. Thus, we performed additional partial correlation analyses (controlling for age) between anxiety (STAI-T scores), depressive symptoms (BDI-II scores) and FA values on a network level in the PTSD-D group (initial-link threshold of p_{lt}<.005). The results are provided in the Appendix in Table S2 and S3. The identified sub-networks did not overlap with any links found in the exploratory group contrast. Thus, employing these results as exclusive masks, we determined that FA values of the two subcortical networks correlated solely with dissociative symptom severity.

In addition, the present sample comprised more patients in the PTSD-D group who displayed secondary comorbid borderline personality disorder (*n*=6) in comparison to patients in the classic PTSD group (*n*=2). Therefore, we excluded patients with comorbid borderline personality disorder and reran the group analysis (see Table S4). The results only minimally diverted from the original group contrast, i.e. the four-node network comprised an additional link, i.e. between the left hippocampus and left caudate, for which PTSD-D patients displayed

lower FA compared to classic PTSD (four-node subnetwork significant at p_{FWER}=.024). The second three-node sub-network was identical, i.e. PTSD-D patients still displayed higher FA between left pallidum, left ventral DC, and left pallidum *(p_{FWER}*=.031).

Table 4

Results of the partial correlation analysis (controlled for age) between dissociative symptom severity, as measured by the CDS-30, and interregional FA displayed for the PTSD-D and classic PTSD. At an initial-link threshold of p_{lt}<.005, two subnetworks in the classic PTSD group and three sub-networks in the PTSD-D group were identified within which FA values correlated significantly with dissociative symptom severity.

Sub-networks within FA correlated negatively with CDS-30			
Classic PTSD (*n*=17)	p_{FWER}	PTSD-D (*n*=22)	p_{FWER}
(1) Le hippocampus **– –** Le caudate	.032	(1) Ri thalamus **+ +** Brain stem **+ +** Le hippocampus **+** **+** **/** **|** Le thalamus Le amygdala	.027
(2) Ri caudate **– –** Ri thalamus	.032	(2) Le putamen **+ +** Le ventral DC **+ +** Le pallidum	.029
		(3) Ri precuneus **+ +** Le precuneus	.038

CDS=Cambridge Depersonalization Scale; Le=left; Lt=initial-link threshold; FA=fractional anisotropy; FWER=family wise error rate; Ri=right; Minus signs between brain regions (**– –**) represent connections for which FA correlated negatively with CDS-30 scores; plus signs between regions (**+ +**) represent connections for which FA correlated positively with CDS-30 scores.

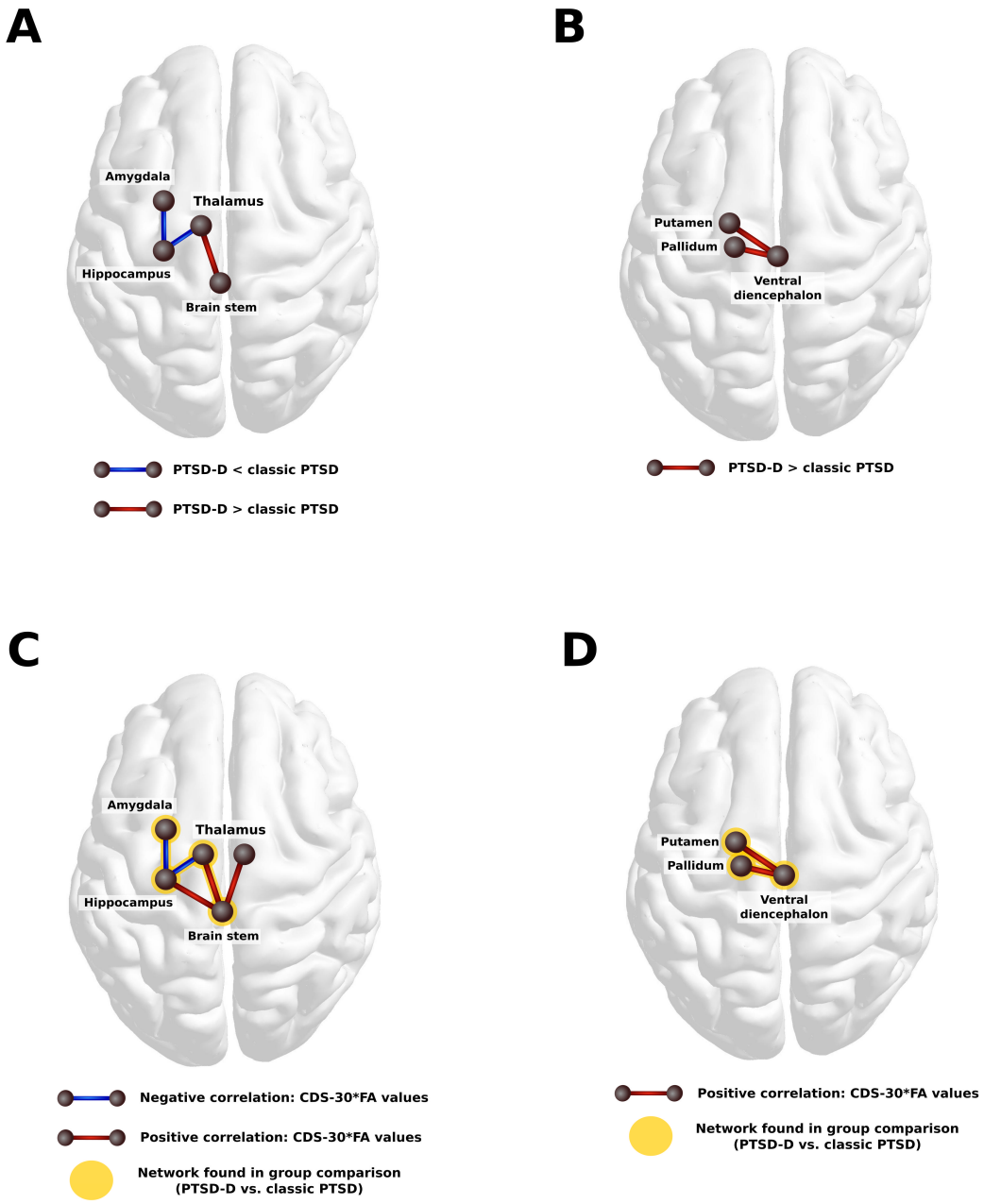

Figure 2. Visualization of the results found in the group comparison (**A** and **B**) and in the partial correlational analyses (**C** and **D**), both controlled for age. In the group comparison, two sub-networks were identified, in which patients with PTSD-D displayed altered FA values compared to patients with classic PTSD. **A:** Sub-network, in which patients with PTSD-D displayed relatively lower FA (blue connections) between the left amygdala, left hippocampus, left thalamus and higher FA (red connection) between the left thalamus and the brain stem (p_{FWER}=.026). **B:** Sub-network, in which PTSD-D Patients displayed higher FA between left pallidum, left ventral DC, and left putamen compared to the classic PTSD group (p_{FWER}=.027). **C:** Visualization of first sub-network for which FA values correlated with dissociative symptom severity (CDS-30 scores) in the PTSD-D group only (p_{FWER}=.027). **D:** Visualization of second subnetwork for which FA values correlated with dissociative symptom severity in patients with PTSD-D (p_{FWER}=.029). Blue connections indicate negative and red connections represent positive correlation between FA and CDS-30 scores. Yellow highlights underneath nodes and edges demonstrate the overlap between the two networks found in the partial correlation analysis and the networks identified in the group contrast.

4. Discussion

This is the first study to have investigated differences in structural connectivity between female patients with a history of childhood trauma suffering from the dissociative subtype of PTSD (PTSD-D) versus classic PTSD. The a priori hypothesized connectivity differences involving fronto-limbic structures were not confirmed. Subsequent exploratory analyses revealed subcortical white matter alterations in two sub-networks in patients with PTSD-D relative to patients with classic PTSD, which also showed a significant correlation with dissociation severity in patients with PTSD-D, but not classical PTSD.

The null-finding regarding group differences in structural connectivity in fronto-limbic circuits suggests either that fronto-limbic inhibition in PTSD-D presents a dynamic neural process which is not hard-wired via white matter tracts, or that frontal structures play a less central role than previously assumed. Most support for the fronto-limbic dysbalance model of PTSD-D to date has emerged from functional activation as well as functional connectivity studies (Nicholson et al., 2017, for review see Lanius et al., 2010), which both measure changes in blood flow and are methods geared to capture dynamic activity patterns in the brain. Moreover, the co-existent emotional over- and under-modulation in individuals with PTSD-D suggests dynamic response patterns that are mediated by metabolic changes and might not require underlying structural alterations. However, our null-finding also indicates that symptoms of depersonalization and derealization in PTSD might differ neurobiologically from the same symptoms in depersonalization/derealization disorders, for which we recently reported white matter network alterations in fronto-limbic as well as temporal structures (Sierk et al., in press.).

Our exploratory results may instead indicate that phenomenological differences in PTSD-D relative to classic PTSD are associated with altered white matter connectivity in subcortical circuits. Dissociative symptom severity, but not depression or trait anxiety scores, correlated with FA values within both identified sub-networks in the PTSD-D group. This further supports the assumption that these group differences are directly related to the dissociative symptomatology. In the first identified sub-network, patients with PTSD-D displayed significantly lower structural connectivity (i.e. FA values) between the left amygdala,

hippocampus, and thalamus and higher FA between the left thalamus and the brain stem compared to patients with classic PTSD. The thalamus receives afferent sensory input from the brain stem via the internal capsule, while the fornix connects amygdala and hippocampus to the anterior nuclei of the thalamus (Catani et al., 2013). In healthy individuals, alterations in this limbic-thalamo circuit have been associated with altered consciousness (Blumenfeld, 2012) and selective memory deficits (Carlesimo et al., 2011, Gilboa et al., 2006) – both phenomena observed in patients with PTSD-D. It has been suggested that during the traumatic event amygdala-mediated sensory representation of the scene is strengthened, disconnected from hippocampus-dependent contextual information, which gives rise to de-contextualized re-experiencing (Brewin et al., 2010). This modulation may be amplified if consciousness is lowered during dissociation. Congruently, peritraumatic dissociation has been identified as a strong predictor for intrusive symptomatology (Ozer et al., 2003), the severity of peritraumatic dissociation correlated with activation of brain structures subserving autobiographic memory recall (Daniels et al., 2012), and patients with PTSD-D display heightened intrusive symptom severity in some studies (Stein et al., 2013). Moreover, reduced amygdalar and hippocampal volume has been reported in women with dissociative identity disorder (DID) and comorbid PTSD, and dissociative symptom severity was found to be negatively correlated with hippocampal volume in women with PTSD due to childhood sexual abuse (Bremner et al., 2003, Stein et al., 1997). Interestingly, Felmingham et al. (2008) found heightened activity of the amygdala and parahippocampus in patients with PTSD-D only during the subliminal exposition of fearful faces. Thus, altered structural connectivity in limbic-thalamic circuits may present a pre-existing risk factor for sensory disintegration and an initial (pre-conscious) heightened limbic response to stress, leading to dissociation and exacerbation of integrative memory processes. Alternatively, the severity of trauma may modulate the emotional reaction and thus the likelihood that an individual is driven into an altered state of consciousness, regardless of the subject's biological predisposition (cf. Lanius, 2015, Putnam, 1997). When this state is frequently re-activated as seen in PTSD-D, respective changes in the white matter microstructure may evolve. Our cross-sectional design limits weighting of either explanation. Yet, in both scenarios, it is conceivable that a dissociative response to a traumatic event and subsequent reminders may be adopted as a conscious coping style over time.

Our second exploratory results indicate higher structural connectivity between the left pallidum, left ventral DC, and left putamen. Our findings compliment previous work showing patients with PTSD and comorbid DID display larger bilateral putamen and right pallidum compared to PTSD-patients without DID (Chalavi et al., 2015). Chalavi et al. (2015) also found volumetric measurements of both structures to correlate positively with dissociative symptom severity. Activation of the head of the right caudate (adjacent to the putamen) has previously been associated with dissociative analgesia in PTSD (Mickleborough et al., 2011) and activation of the caudate with specific dissociative identity states (Reinders et al., 2014). The putamen (with the caudate part of the dorsal striatum) and the pallidum belong to the basal ganglia and are responsible for inhibiting and activating movement impulses, respectively. Excitatory and inhibitory direct pathways run between the pallidum, putamen, and the substantia nigra and subthalamic nuclei, respectively – both structures included in the ventral DC. It is possible that altered structural connectivity in these low-level motor-related structures underlie passive threat response such as freezing – a state that is assumed to be the homologue of dissociation in animals (for review see Hagenaars et al., 2014).

In conjunction, our explorative findings suggest that aberrations in subcortical inter-connectivity in PTSD-D is worth pursuing further. However, the results of our exploratory analysis should purely be used for theory building and ought to be replicated with pre-registration (Szucs and Ioannidis, 2017).

Limitations

The generalization of our results is limited by the following factors: First, the findings presented here were not hypothesized a priori and thus need to be replicated in a confirmatory study. Second, to ensure ecological validity, we did not exclude patients with certain comorbidities or patients taking anti-depressants. However, only two patients took anti-depressant medication and we controlled for comorbid effects in our post-hoc analyses.

Third, our results cannot be generalized to men or women with traumatization during adulthood as our sample consisted exclusively of women with a history of childhood trauma. However, as the CTQ did not evidence a significant group difference with regard to the severity of childhood trauma, it seems unlikely that the observed group differences are related to the nature of the traumatic experience per se. Forth, the results of the dissociation assessment tools employed for allocating participants into the two PTSD subgroups indicated that their selectivity is not absolute, as several participants of the classic PTSD group also exhibited a low level of dissociative symptoms. However, group allocation resulted in highly significant mean differences for all dissociation questionnaires, while keeping the two groups comparable with respect to all other assessed domains.

Fifth, the resolution of the data and FreeSurfer parcellation limits the interpretation; e.g. we cannot ascertain which specific subnuclei of the thalamus and the ventral DC are involved in the detected circuits. Fifth, general methodological issues apply in regard to the graph theoretical analysis of diffusion MRI tractography data. By using constrained spherical deconvolution tractography to reconstruct brain networks of white matter fiber bundles, which is capable of resolving crossing fiber tracts (Jeurissen et al., 2013), the number of false negative findings was decreased (Tournier et al., 2007). However, other challenges of the tracking algorithm, e.g. modelling distinctive fiber geometries, may increase false-positive streamlines and thus present a limitation. Finally, it should be considered that weighting the connectivity matrices with the diffusion parameter FA does not allow strong inferences of the state of the anatomical connection. Because FA is modulated by a variety of microstructural factors, lower or higher FA between regions does not present an implication for the degree of structural connectivity (Jones et al., 2013).

5. Conclusion

The proposed model of over-regulation of limbic structures by prefrontal regions in PTSD-D is not underpinned by group difference white matter connectivity on a network level and thus may rather present a dynamic neural process better detectable using functional neuroimaging. Our exploratory results however yielded interesting alterations in structural connectivity between subcortical areas in PTSD-D relative to classic PTSD, which suggest distinct low-level emotional, sensory, and motor processes that might give rise to dissociative responses during and after trauma.

Our findings may hold clinical implications by potentially supporting new avenues of interventions for patients with PTSD-D, in which emotion regulation strategies are strengthened before trauma-focussed therapy is implemented to treat intrusive symptomatology (cf. Cloitre et al., 2002, Steil et al., 2011). Respective therapeutic elements have already shown to effectively reduce dissociative symptoms in women with PTSD related to childhood abuse (Cloitre et al., 2012). Future longitudinal studies should investigate whether alterations in initial sensory encoding depict a risk factor to overregulate emotions and how this may inform advances for psychotherapeutic pre- and interventions for those effected.

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Supplementary Material – Study II

Table S1

Intercorrelations between questionnaire scores.

Questionnaire	BDI	CAPS	CDS_30	CTQ sum	DES	ERQ-R	ERQ-S	MDI	PCL	PDEQ	SQR-20	STAI-T
BDI	1											
CAPS	.24	1										
CDS_30	.32*	.38*	1									
CTQ sum	.17	.07	.22	1								
DES	.12	-.07	-.09	-.13	1							
ERQ-R	.33*	.33*	.15	.01	-.21	1						
ERQ-S	-.21	-.34*	-.39*	-.07	-.10	.04	1					
MDI	.36*	.44**	.81***	.16	-.10	.22	-.25	1				
PCL	.23	.27	.57***	.27	.04	.07	-.11	.55***	1			
PDEQ	-.08	.40*	.57***	.25	-.17	.003	-.12	.48**	.51**	1		
SDQ-20	.37*	.36*	.81***	.37*	-.08	.28	-.18	.83***	.54***	.57***	1	
STAI-T	.63**	.45**	.51**	.10	-.13	.49**	-.24	.42**	.43**	.15	.40*	1

BDI=Beck Depression Inventory; CAPS=Clinician-Administered PTSD Scale; CDS=Cambridge Depersonalization Scale; CTQ=Childhood Trauma Questionnaire; DES=Dissociative Experiences Scale; ERQ-R=Emotion Regulation Questionnaire Reappraisal; ERQ-S=Emotion Regulation Questionnaire Suppression; MDI=Multiscale Dissociation Inventory; PDEQ=Peritraumatic Dissociative Experiences Questionnaire; SDQ=Somatoform Dissociation Questionnaire; STAI-T=State-Trait Anxiety Scale, trait version;

*Correlation is significant at $p<.05$ (2-tailed)

**Correlation is significant at $p<.01$ (2-tailed)

***Correlation is significant at $p<.001$ (2-tailed)

Table S2

Results of the partial correlation analysis (controlled for age) between trait anxiety, as measure by the STAI-T, and interregional FA in the PTSD-D group only. At an applied initial-link threshold of p_{lt}<.005, three sub-networks were identified within FA values correlated with STAI-T scores.

Sub-networks within FA correlated with STAI-T scores	p_{FWER}
Right rostral middle frontal gyrus **– –** Left rostral middle frontal gyrus	.040
Right ventral diencephalon **– –** Right putamen	.040
Right precuneus **+ +** Left precuneus	.040
Right caudate **+ +** Right thalamus	.040

Lt=initial-link threshold; PTSD-D=dissociative subtype of posttraumatic stress disorder; FA=fractional anisotropy; FWER=family wise error rate, STAI-T=State-Trait Anxiety Scale, trait version; Minus signs between brain regions (**– –**) represent connections for which FA correlated negatively with STAI-T scores; plus signs between regions (**+ +**) represent connections for which FA correlated positively with STAI-T scores.

Table S3

Results of the partial correlation analysis (controlled for age) between depressive symptoms, as measure by the BDI-II, and interregional FA in the PTSD-D group only. At an applied initial-link threshold of p_{lt}<.005, four sub-networks were identified within FA values correlated with BDI-II scores.

Sub-networks within FA correlated with BDI-II scores	p_{FWER}
Right rostral middle frontal gyrus **– –** Left rostral middle frontal gyrus	.042
Right ventral diencephalon **– –** Right putamen	.042
Braim stem **– –** Left caudate	.042
Right precuneus **+ +** Left precuneus	.042

Lt=initial-link threshold; PTSD-D=dissociative subtype of posttraumatic stress disorder; FA=fractional anisotropy; FWER=family wise error rate, BDI-II=Beck Depression Inventory; Minus signs between brain regions (**– –**) represent connections for which FA correlated negatively with BDI-II scores; plus signs between regions (**+ +**) represent connections for which FA correlated positively with BDI-II scores.

Table S4

Results of the group comparison (controlled for age) after excluding patients with secondary borderline personality disorder (*n*=6). At an initial-link threshold of p_{lt}<.005, two subnetworks were identified for which patients with PTSD-D displayed altered FA compared to patients with classic PTSD.

Significant subnetworks	p_{FWER}
(1) Left amygdala **––** Left hippocampus **––** Left thalamus **++** Brain stem Left caudate	.024
(2) Left putamen **++** Left ventral diencephalon **++** Left pallidum	.031

Lt=initial-link threshold; FA=fractional anisotropy; FWER=family wise error rate. Minus signs between brain regions (**––**) represent connections, for which patients with PTSD-D displayed lower FA than patients with classic PTSD; plus signs between regions (**++**) represent connections, for which the PTSD-D group displayed lower FA than the classic PTSD group.

C. Study III

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Allocentric spatial memory performance predicts intrusive memory severity in posttraumatic stress disorder

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Abstract

Background: Posttraumatic stress disorder (PTSD) is characterised by distressing trauma-related memories. According to the dual representation theory, intrusive memories arise from strengthened egocentric encoding and a poor contextual encoding, with spatial context requiring allocentric processing. Contextualization of mental imagery is proposed to be formed hierarchically through the ventral visual stream (VVS) to the hippocampal formation. Here, we tested this notion by investigating whether neuronal aberrations in structures of the VVS or in the hippocampus, as well as allocentric memory performance are associated with intrusive memory severity.

Methods: The sample comprised 33 women with PTSD due to childhood trauma. Allocentric memory performance was measured with the virtual Town Square Task and T1-weighted images acquired on a 3T Siemens Scanner. Intrusive memories were evoked by presenting an audio script describing parts of their trauma while in the scanner (script-driven imagery). Based on bivariate correlations, a planned multiple regression analysis was performed with allocentric memory performance and cortical thickness of the left lingual gyrus as predictive variables for intrusive symptom severity.

Results: The regression analysis showed that lower allocentric memory performance was significantly associated with more intrusive memory severity. Post hoc exploratory analyses revealed a negative correlation between age since index trauma and left hippocampal volume.

Limitations: Our results are based on correlational analyses, causality cannot be inferred.

Conclusion: This study supports the dual representation theory, which emphasizes the role of allocentric-spatial memory for the contextualization of mental imagery in PTSD. Clinical implications are discussed.

Keywords: Trauma, PTSD, Allocentric processing, Hippocampus, MRI

1. Introduction

The understanding and treatment of trauma-related disorders is a crucial challenge in the field of global mental health to date. One potential sequela of trauma is posttraumatic stress disorder (PTSD) with a life time prevalence of 6.8% in the general population (Kessler et al., 2005), which can rise to 69%-92% in populations affected by war and torture (Kolassa, Kolassa, Ertl, Papassotiropoulos, & De Quervain, 2010; Moisander & Edston, 2003). A core symptom of PTSD consists of recurrent involuntary memories of the traumatic event. Intrusive memories are thought to be triggered by internal or external cues and often get actively avoided due to their distressing mnemonic content (American Psychiatric Association, 2013).

For visual intrusions, the dual representation model proposed by Brewin and co-workers (Brewin, Dalgleish, & Joseph, 1996; Brewin, Gregory, Lipton, & Burgess, 2010; following Nadel & Jacobs, 1998) assumes two connected types of memory to be involved in storing and retrieving intrusive images: (1) Contextualized representations, which are responsible for storing the spatiotemporal context of a specific scene and (2) sensory bound representations, which carry the respective sensory-perceptual features. The contextual representation is thought to rely on the hippocampal formation, located in the medial temporal lobe, and is assumed to be coded within the ventral visual stream (VVS), allowing integration with other autobiographical memories (cf. Brewin, 2015). Sensory representations are hypothesised to be formed in the insula and dorsal visual stream areas, mediated by processes in the amygdala. The dorsal visual stream is associated with creating images of the environment from a viewer-dependent perspective (egocentric), while appropriate contextual encoding additionally requires allocentric processing (viewer-independent). In their revised dual representation theory, Brewin and colleagues (2010) presume an amygdala-mediated strengthening of egocentric sensory visual representations during the traumatic moment in the context of a weak hippocampus-dependent allocentric representation. According to this model, intrusive imagery reflects an imbalance between strong emotion-laden traumatic memories and weak associative and contextual representations. In PTSD, sensory cues (e.g. smell or sound) can trigger involuntary retrieval of those de-contextualised, distressing images ‘bottom-up’, whereas in healthy memory, voluntary recall of the contextualised

traumatic content is formed in the hippocampal system controlled ‘top-down’ via prefrontal cortices (cf. Bisby & Burgess, 2017).

Empirical support for the dual representation theory stems from studies in healthy individuals as well as in individuals with PTSD. In healthy cohorts, a common approach to investigate intrusive memories is the trauma film paradigm (for review see James et al., 2016), in which participants watch at least one traumatic video and report the experience of intrusive memories or thoughts in a diary over the subsequent days. Researchers have used the trauma film paradigm to manipulate trauma processing either before, during, or after encoding of the traumatic material. Relevant for the present work are findings showing a decrease of intrusive images by deploying a visuospatial task either during encoding (Bourne, Frasquilho, Roth, & Holmes, 2010; Brewin & Saunders, 2001; Holmes, Brewin, & Hennessy, 2004) or directly thereafter (Holmes, James, Coode-Bate, & Deeprose, 2009; Holmes, James, Kilford, & Deeprose, 2010), with preliminary translational evidence in survivors of a motor vehicle accident (Iyadurai et al., 2017). A possible explanation is that visuospatial tasks compete for perceptual resources, which leads to an attenuation of the sensory representation and thus to less intrusive memories (cf. Brewin, 2014; Stuart, Holmes, & Brewin, 2006).

Influential factors on intrusive memory development can also be revealed by considering individual cognitive differences. Meyer, Krans, van Ast, and Smeets (2017) tested 81 healthy individuals with a contextual cueing paradigm and found an inverse relationship between memory contextualization learning abilities and visual intrusive memories, but not verbal intrusive thoughts (Meyer et al., 2017). In line with these findings, Bisby, King, Brewin, Burgess, and Curran (2010) deployed the Town Square Task in a healthy cohort (*n*=48) to assess allocentric spatial memory and found that participants' allocentric memory performance correlated negatively with the amount of experienced intrusions in the week after watching traumatic videos. The authors tested further implications of the dual representation model by suppressing hippocampal-dependent memory during encoding of the trauma videos via the administration of alcohol (low/high dosage versus placebo). Consistent with the model, a low dosage of alcohol was linked to reduced allocentric spatial memory performance and resulted in the development of more intrusions.

Findings from analogue experiments do not translate directly to clinical populations who have experienced real-life trauma, but some parallels are evident. Reduced hippocampal volume

has been reported by numerous studies in PTSD (cf. O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015) and was recently confirmed by the largest neuroimaging study in PTSD today ((ENIGMA-PGC consortium study involving 1868 subjects, comparing 794 patients with PTSD to trauma-exposed controls; Logue et al., 2018). Building on these findings, Smith, Burgess, Brewin, and King (2015) investigated allocentric spatial processing and allocentric spatial memory ability in 29 patients with PTSD and 30 trauma-exposed controls. The authors found both hippocampus-dependent allocentric spatial processing and memory to be selectively impaired in PTSD, while egocentric spatial memory was spared. Reduced spatial processing abilities in PTSD compared to trauma-controls have also been reported in other work (Gilbertson et al., 2007; Miller, McDougall, Thomas, & Wiener, 2017; Tempesta, Mazza, Iaria, De Gennaro, & Ferrara, 2012). Interestingly, patients phenomenologically experience intrusive memories to lack context, i.e. they reflect isolated moments, disjointed from what happened before or after (Michael, Ehlers, Halligan, & Clark, 2005), which supports the view of intrusions as presenting de-contextualised egocentric representations of the traumatic scene.

In contrast, some cognitive psychologists consider intrusive memories not to be different from other autobiographical memories. They assume the mnemonic process for traumatic and ordinary events are mechanistically equal (Rubin, Berntsen, & Bohni, 2008), making the etiology of intrusive memories still a controversial issue in the study of PTSD. Moreover, evidence is scarce regarding the association between intrusions and brain morphology as most studies focus on general PTSD symptom severity instead of distinct symptom clusters (cf. Karl et al., 2006). One study has reported reduced volume in bilateral inferior temporal cortex, which is part of the VVS and involved in processing the context of visual objects and scenes, to be associated with increased re-experiencing (Kroes, Rugg, Whalley, & Brewin, 2011). Two others reported negative correlations between re-experiencing symptoms and left hippocampal volume in PTSD (Lindauer, Olff, van Meijel, Carlier, & Gersons, 2006; Villarreal et al., 2002).

In sum, good empirical evidence exists for impairments in hippocampus-based contextual memory in patients with PTSD and for an inverse relationship between allocentric spatial memory and intrusive memories in healthy cohorts. Yet, a systematic investigation of the relationship between allocentric spatial memory, brain morphology, and intrusive memories

in PTSD is outstanding. This may in part be due to the difficulty in quantifying intrusive memories in patients with PTSD. They are generally assessed retrospectively with self-report questionnaires or clinical interviews asking for their frequency in the past month(s). This approach may not be adequate as patients actively avoid exposure to trauma reminders that could trigger intrusive recall (cf. Brewin, 2015). Thus, in the present study, a symptom provocation paradigm triggering intrusive memories will be administered to address the question of whether allocentric spatial memory performance, and morphometric changes in areas of the VVS and the hippocampus, are related to intrusive memory severity in PTSD. We will employ the Town Square Task, which enables us to obtain a measure of allocentric spatial memory while controlling for egocentric spatial processing (cf. King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002). This task is particularly useful for testing implications of the dual representation model, which proposes that involuntary memory reflects the difference between strong egocentric and weak allocentric encoding. We will further control for general visuospatial ability and working memory performance as potential confounding factors affecting allocentric memory performance.

2. Methods

2.1 Participants

A total of 41 women with a history of childhood trauma were recruited via public advertisements, through mental health in- and outpatient clinics, and in collaboration with private psychotherapists and psychiatrists. Female participants were included in the study if they were diagnosed with current PTSD (see below) and in addition met the following criteria: (1) ages 20 to 60 years; (2) sufficient proficiency in German; (3) MRI compatible; (4) no history of head injury; (5) no incidental finding by the neuroradiologist (examination after the MR scan); (6) no history of substance dependency within the past 6 months; (7) no intake of benzodiazepines or anticonvulsants (8) no comorbid psychiatric disorders other than secondary depressive and anxiety disorders, borderline personality disorder, eating disorders, and substance abuse disorders, which we allowed to ensure ecological validity. For the same reason, participants taking mild antidepressant medication were included. The study protocol was approved by the ethics boards of the Faculty of Medicine, University of Magdeburg and the Berlin Psychological University. Written informed consent was obtained from all participants and they received a monetary compensation for their participation.

2.2 Procedure

2.2.1 Clinical diagnostics

Subjects interested in participating in the study received a screening questionnaire via mail. Here, self-report information on MRI incompatibilities, previous head injuries, current medication, and current psychological as well as neurological disorders was acquired and trauma exposure and PTSD symptom severity were assessed via German versions of the Essen Trauma Inventory (Tagay et al., 2006) and the PTSD Checklist for DSM-IV (PCL; Teegen, 1997), respectively. Eligible subjects were invited for a comprehensive psychological assessment by a clinical psychologist (A.M.) who administered German versions of four standardised interviews: The PTSD diagnosis and symptom severity were established using the Clinician-Administered PTSD Scale (CAPS-IV; Schnyder & Moergeli, 2002). The Structured Clinical Interview for DSM-IV (Wittchen, Zaudig, & Fydrich, 1997) was used to assess axis I disorders.

To verify that no primary diagnosis of borderline personality disorder was present, the respective section of the Structured Clinical Interview for DSM-IV Axis II (Fydrich, Renneberg, Schmitz, & Wittchen, 1997) was conducted. Finally, we employed the Structured Clinical Interview for DSM-IV Dissociative Disorders (Gast, Zündorf, & Hofmann, 2000) to exclude patients with dissociative disorders. All participants completed German versions of the following self-report questionnaires for sample characterization: the Beck Depression Inventory (BDI-II, Hautzinger, Keller, & Kühner, 2006), the Cambridge Depersonalization Scale (CDS-30; Michal et al., 2004), the Childhood Trauma Questionnaire (CTQ; Wingenfeld et al., 2010), Dissociative Experiences Scale (DES; Spitzer, Mestel, Klingelhöfer, Gänsicke, & Freyberger, 2003), and the State-Trait Anxiety Inventory (STAI-T; Laux & Spielberger, 2001).

2.2.2 Allocentric Spatial Memory – The Town Square Task

Allocentric spatial memory was assessed with the Town Square Task, presented on a 14-inch laptop screen. The task consists of a virtual environment depicting a courtyard surrounded by visually distinct buildings. 21 red-coloured placeholders distributed in the courtyard served for the presentation of the stimuli. Subjects were exposed to 32 trials, each consisting of an encoding and a recall phase. To start the trial, participants were asked to navigate along a perimeter wall (left or right) at roof top level towards a traffic cone, which on contact brought them into a standardised view overlooking the courtyard. During the encoding phase, either three or six targets were presented in a pseudo-randomized order with a boundary condition of the same list length not being presented more than four times in a row. Images of everyday objects served as targets and appeared on the placeholders one at a time for 3 s each, with a 1 s inter-stimulus interval. Participants were instructed to remember the location (i.e. the specific placeholder) of each object. During the recall phase, the location of these targets was tested either from the same viewpoint as encoding or from a shifted viewpoint (rotated by 140°, cf. Fig. 1).

The same-view condition can be processed using only egocentric strategies, while in the shifted-view condition allocentric processing is necessary in addition to egocentric processes (cf. King et al., 2002). During recall, object locations were tested in a random stimulus order within trials, using multiple choice by placing the correct image (target) on its original placeholder and three copies (foils) on other placeholders. A small, coloured square was

superimposed on each image and participants were asked to indicate the location of the target by pressing the corresponding colour-coded button on the keyboard (cf. Fig. 1). The response time was self-paced. Furthermore, task difficulty was matched between same-view and shifted-view conditions by placing the foils always within the nearest five positions to the target in the same-view condition while distributing them evenly across locations in the shifted-view condition. In a healthy cohort, this procedure successfully resulted in comparable performance across conditions (King, Trinkler, Hartley, Vargha-Khadem, & Burgess, 2004).

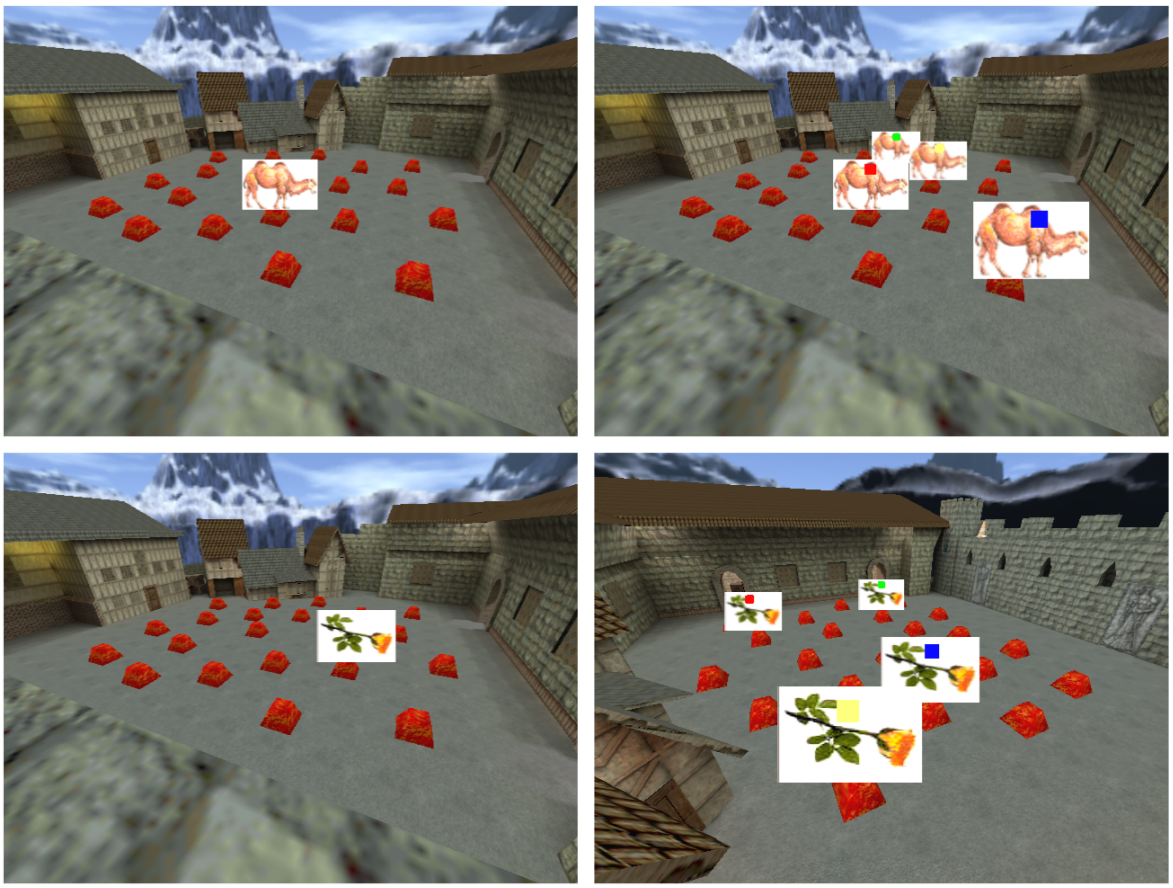

Figure 1. The Town Square Task. The left upper and lower panel display the presentation of items during the encoding phase. The upper right panel displays the location test during the recall phase in the same-view condition while the lower right panel shows the respective location test in the shifted-view condition. During recall, the correct image is placed on its original placeholder and three foils are placed on other placeholders. The superimposed coloured squares are used for participants to indicate their response.

2.2.3 Working Memory – The N-back Task

Some participants use verbal rehearsal strategies during spatial processing, which draws on working memory resources (cf. Baddeley, 2000). Thus, individual differences in retention span may influence performance on the Town Square Task and need to be controlled for. We employed the n-back paradigm, which is a neurocognitive test commonly used to measure working memory capacity (Kearney-Ramos et al., 2014; Redick & Lindsey, 2013). In this task, participants press a key whenever the current item matches the item that had been presented n items back (cf. Redick & Lindsey, 2013). We implemented four levels of difficulty, i.e. a 0-back task, 1-back task, 2-back task, and a 3-back task, using a block design. Single capital letters (font style: 'Arial'; font size: 100) were chosen as stimuli and were presented for 1 s in the centre of a 14-inch laptop screen with an inter-stimulus interval of 500 ms. In the 0-back condition, subjects were asked to hit the response key whenever the letter X appeared on the screen. In the 1-, 2-, and 3-back condition, subjects were instructed to press a marked key on the keyboard if the present letter corresponded to the letter shown 1, 2, or 3 items back, respectively. Each condition consisted of 20 stimuli including six targets and each condition was presented three times throughout the task in a pseudo-randomized order (boundary condition: no direct repetition of the same condition), resulting in 12 testing blocks overall.

2.2.4 Screening for general visuospatial ability

We implemented a brief measure (12-item) of general visuospatial ability (Raven's Advanced Progressive Matrices: RAPM, Set I; Raven, 1938). The RAPM is a standardised assessment of non-verbal abstract reasoning and visuo-spatial problem-solving abilities. Set 1 consists of 12 geometric patterns with a missing piece. Subjects were instructed to pick the correct missing piece from a pool of eight similar pieces. The first item served for practice. If participants chose the correct missing piece they were asked to complete the remaining 11 items. The task was self-paced and subjects were informed that no time limit applies. The number of correct pieces was computed as a measure of general visuospatial ability.

2.2.5 Symptom provocation – script-driven imagery

Following the behavioural assessments, we conducted the script-driven imagery paradigm in the scanner, which is a symptom provocation task commonly used in PTSD research (Daniels, Coupland, et al., 2012; Daniels et al., 2011; Daniels, Hegadoren, et al., 2012). According to the published procedure (Lanius et al., 2002), individualised scripts containing descriptions of one neutral and one traumatic event in the patient's life were created. The neutral autobiographical event served as the control condition and it was ensured that an event was chosen which neither elicited positive nor negative emotions. For the traumatic script, participants were asked to describe scenes from which reminders have triggered intrusive symptoms in the past. Both descriptions were each condensed to a 30 s audio script and recorded for presentation in the MRI environment. During exposure, participants were asked to imagine the events vividly while listening to the 30 s audio script and for 30 s thereafter (i.e. 60 s imagery period) and not to avoid symptoms if they arose. A rest period of 2-minutes was given between trials. Each script was presented three times, with all neutral runs preceding the traumatic ones to avoid carry over effects (cf. Fig. 2). Upon completion of the three trials per condition, participants first filled out the Response to Script-Driven Imagery Scale (RSDI; Hopper, Frewen, Sack, Lanius, & Van der Kolk, 2007) and then answered six questions assessing the experience of intrusive and dissociative symptoms for each trial. With regards to intrusions, participants were asked "*During Trial X, did you re-experience part of the trauma involuntarily (intrusions)?"*. The response was given on a 7-point-Likert scale from 0 (not at all) to 6 (very strong). This work was conducted within a larger study, which investigates the neurobiology of dissociation in PTSD by using a placebo-controlled, pharmacological challenge paradigm. The present study only considers reported intrusions after trauma exposition under placebo.

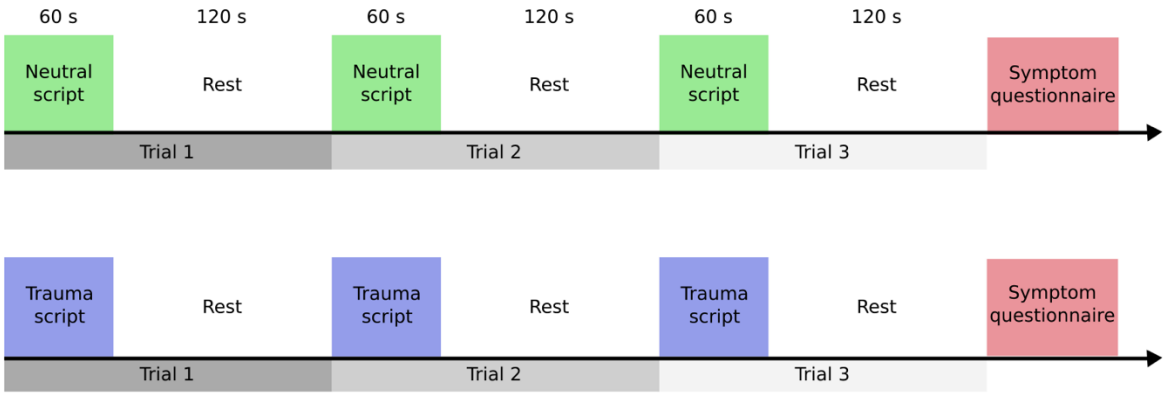

Figure 2. The script-driven imagery paradigm. First, the neutral script was presented three times. Each trial consisted of 60 s of imagining a neutral scene followed by 120 s of rest. At the end of all three trials participants received a questionnaire regarding the experience of intrusive symptoms. Subsequently, the trauma script was employed following the same procedure as the neutral script.

2.2.6 MRI acquisition and Preprocessing

Structural MR images were obtained on a 3T Siemens Tim Trio scanner equipped with a 12-channel head coil. T1-weighted images were acquired with a magnetization-prepared rapid acquisition with gradient echo sequence using the following parameters: TR=1.9ms, TE=2.52ms, inversion time=900ms, flip angle=9°, FoV=256mm, 192 slices, 1mm isovoxels, 50% distancing factor. Measurements of cortical thickness and volume of cortical and subcortical regions, respectively, were acquired using the default settings of FreeSurfer version v6.0 (https://surfer.nmr.mgh.harvard.edu/), which have been described in previous publications (Fischl & Dale, 2000). Important preprocessing steps included intensity normalization and skull stripping, segmentation of subcortical white matter and deep gray matter volumetric structures, and parcellation of the cerebral cortex. Each output was visually inspected for quality insurance. From the Desikan Killany atlas, we selected left and right hippocampus and the following eight bilateral regions of interest as part of the ventral visual stream: lateral occipital gyrus, fusiform gyrus, lingual gyrus, sulcus of the pericalcarine gyrus, middle temporal gyrus, inferior temporal gyrus, temporal pole, and parahippocampal gyrus.

2.3 Statistical analyses

Egocentric and allocentric memory score (Town Square Task)

To obtain a measure of egocentric memory performance, we computed an overall percentage correct score (number of items correct/total number of items) across trial length for the same-view condition (see Table 2). To obtain a measure of allocentric memory performance, we first calculated an overall percentage correct score for the shifted-view condition and then subtracted the egocentric memory score to isolate allocentric spatial memory performance while controlling for confounding differences in egocentric spatial processing. A log transformation was conducted on the performance scores of the Town Square Task, because their distributions were negatively skewed. After transformation the data was normally distributed as confirmed by a one-sample Kolmogorov-Smirnov test (egocentric memory performance: $D(33)=.129$, $p>.179$; allocentric memory score $D(33)=.128$, $p=.200$). The data of eight participants were excluded (two as they misinterpreted the instruction and six due to performance at chance level, i.e. <25%), reducing the original sample of $n=41$ to $n=33$ for the present analysis.

Working memory (n-back task)

Working memory performance was computed by averaging the sensitivity index d' (Macmillan & Creelman, 1990) across all four difficulty levels. Two participants did not complete the n-back task and two participants were excluded after outlier detection, that is, their d' average score exceeded three times the interquartile range. This left a sample of 31 subjects for whom both allocentric memory and working memory performance were available.

Intrusive memories (symptom provocation task)

To quantify the severity of intrusive memories during symptom provocation, the mean of the three intensity ratings that participants provided for each trial after the script-driven imagery paradigm (cf. section 2.2.5) was computed.

Structural data (MRI)

Cortical thickness of VVS areas, volumetric measures of the hippocampi, and total intracranial volume were derived from the standard statistical directory of FreeSurfer. To control for

inter-individual variability in head size, we normalised hippocampal volume by intracranial volume using the residual approach (cf. Voevodskaya et al., 2014).

Multiple linear regression analysis

We performed a planned multiple linear regression analysis. Predictors were selected based on bivariate association with intrusive memory severity. Pearson's correlations were computed between intrusive memory severity and the variables age, RAPM score, working memory, left and right hippocampal volume, cortical thickness measurements of bilateral VVS structures, and allocentric memory score. The regression model was considered significant at the statistical threshold of $p<.05$. All statistical analyses were performed in SPSS version 25 (SPSS, IBM Corp. in Armonk, NY).

3. Results

3.1. Population characteristics

Demographics and psychometric scores of the sample are presented in Table 1. Participants had a mean age of 39.7 and an average CAPS score of 68.73. Age at index trauma was on average 15.24. All participants reported childhood trauma, which they did not always specify as their index trauma. Age at first trauma was not acquired. Almost all participants (*n*=32) displayed comorbid disorders, mainly secondary anxiety disorders (*n*=30), borderline personality disorder (*n*=9), and mood disorders (*n*=7). For further details on comorbidity see the Appendix, Table A.1. Two patients used the antidepressant medication Valdoxan and Escitalopram, respectively.

3.2. Experimental results

Descriptives

Descriptive statistics of performance and intrusive memory severity are shown in Table 2. Participants reported significantly higher intrusive memory severity after listening to the trauma script than to the neutral script (paired sample t-test: $t(32)=-11.60$, $p<.001$, cf. Fig 3A). Participants performed significantly better in the same-view than in the shifted-view condition $t(32)=-5.83$, $p<.001$). The mean allocentric memory score for this sample was -.16.

Multiple linear regression analysis

Two variables correlated significantly with intrusive memory severity. First, the allocentric memory score negatively correlated with intrusive memory severity ($r=-.44$, $p=.011$). This correlation stayed significant after controlling for general visuo-spatial ability (RAPM score) and working memory performance ($r=-.474$, $p=.009$), which were available for 31 participants. Second, cortical thickness (CT) of the left lingual gyrus correlated negatively with intrusive memory severity ($r=-.37$, $p=.035$). Note that the allocentric memory score correlated positively with CT of the left lingual gyrus, while controlling for RAPM score and working memory performance ($r=.40$, $p=.032$). Intercorrelations of all variables are provided in the appendix, Table A.2. We entered the allocentric memory score and CT measurements of the

left lingual gyrus as predictors into a multiple linear regression model. The results indicated that the two variables explained a significant amount of variance in intrusive symptom severity (R^2=.19, F(2,32)=4.81, p=.015). Only a lower allocentric memory score significantly predicted higher intrusive memory severity (β=-.35, p=.048; cf. Fig. 3B) while the left lingual gyrus did not provide a unique contribution (β=-.24, p=.161).

Post hoc analyses

First, considering the high comorbidity of mood and anxiety disorders in our sample as well as the significant correlation between age and allocentric memory score (see the Appendix Table A.2), we ran post hoc partial correlational analyses between the allocentric memory score and intrusive memory severity, controlling for age, depressive symptom severity (BDI-II scores), and trait anxiety (STAI-T scores), which were available for 30 participants. The negative correlation between the allocentric memory score and intrusive memory severity stayed significant (r=-.43, p=.025).

Second, the allocentric memory score was computed by subtracting egocentric memory performance (same view condition) from the performance score in the shifted-view condition. To rule out the possibility that the association between the allocentric memory score and intrusive memory severity arose due to variability in egocentric memory processing and not allocentric processing, we subjected egocentric memory performance to partial correlational analysis with intrusive symptom severity. When controlling for age and RAPM score, there was a significant correlation between higher egocentric memory performance and higher intrusive symptom severity (r=.38, p=.030). However, this association disappeared when additionally controlling for depression and anxiety scores (r=.13, p=.505).

Finally, to test for potential effects of duration of symptoms, we performed Pearson's correlation between age since index trauma, intrusive memories, and brain morphology. No association was found between age since index trauma and intrusive memory severity or cortical thickness of VVS structures, respectively. A significant negative correlation was found between age since index trauma and left hippocampal volume (r=-.36, p=.027, uncorrected; n=41, cf. Fig. 3C).

Table 1

Sample characteristics.

Variable	*n*	*Min.*	*Max.*	*Mean*	*SD*
Age	33	23	58	39.67	10.16
Est. age at index trauma*	33	3	49	15.24	10.05
Est. years since index trauma*	33	2	48	24.21	12.84
BDI-II	30	1	53	22.07	14.16
CAPS re-experiencing subscale	33	8	30	20.18	5.75
CAPS avoidance subscale	33	12	43	27.15	8.64
CAPS hyperarousal subscale	33	12	31	22.82	4.75
CAPS total	33	41	95	68.73	15.23
CDS-30	30	0	80	28.73	21.58
CTQ	28	65	112	86.71	14.53
DES	33	3	62	28.80	16.20
PCL	33	25	50	39.12	6.49
STAI-T	30	37	75	56.70	11.10

BDI=Beck Depression Inventory; CAPS=Clinician-Administered PTSD Scale; CDS=Cambridge Depersonalization Scale; CTQ=Childhood Trauma Questionnaire; DES=Dissociative Experiences Scale; Est.=Estimated; PCL=PTSD Checklist for DSM-IV; STAI-T=State-Trait Anxiety Scale, trait version. *Note that descriptives for age at and since index trauma are estimates as some participants indicated a time range instead of a specific age; in these cases, the beginning of the reported time period was chosen as the estimated age at index trauma.

Table 2

Descriptive statistics of behavioural performance and intrusive memory severity.

Variable	*n*	*Min.*	*Max.*	*Mean*	*SD*
RAPM	33	7	12	10.61	1.44
N-back d'	31	-2.09	1.31	.14	.84
TSQ Performance total	33	.35	.87	.68	.14
TSQ Performance egocentric condition	33	.40	.93	.75	.13
TSQ Performance allocentric condition	33	.26	.83	.60	.16
Allocentric memory score	33	-.33	.03	-.16	.10
Trauma script - Intrusive memory severity Trial 1	33	0	6	3.58	1.64
Trauma script - Intrusive memory severity Trial 2	33	0	6	3.81	1.78
Trauma script - Intrusive memory severity Trial 3	33	0	6	4.36	1.85
Trauma script - Mean intrusive memory severity	33	0	6	3.92	1.56
Neutral script - Mean intrusive memory severity	33	0	4.67	.73	1.10

Allocentric memory score=difference between egocentric and allocentric spatial memory performance; RAPM=Raven's Advanced Progressive Matrices, Set I; SD=standard deviation; TSQ=Town Square Task. Participants rated the intensity of intrusive symptoms experienced during trauma exposition on a 7-point-Likert scale.

Table 3

Results of the multiple linear regression analysis (*n* = 33)

Predictor	*β*	*t*	*p*
Allocentric memory performance	-.35	-2.06	.048
Cortical thickness of left lingual gyrus	-.24	-1.44	.161
Model			
F(32)	4.81		
R^2	.43		
Adjusted R^2	.19		
Significant F change	.015		

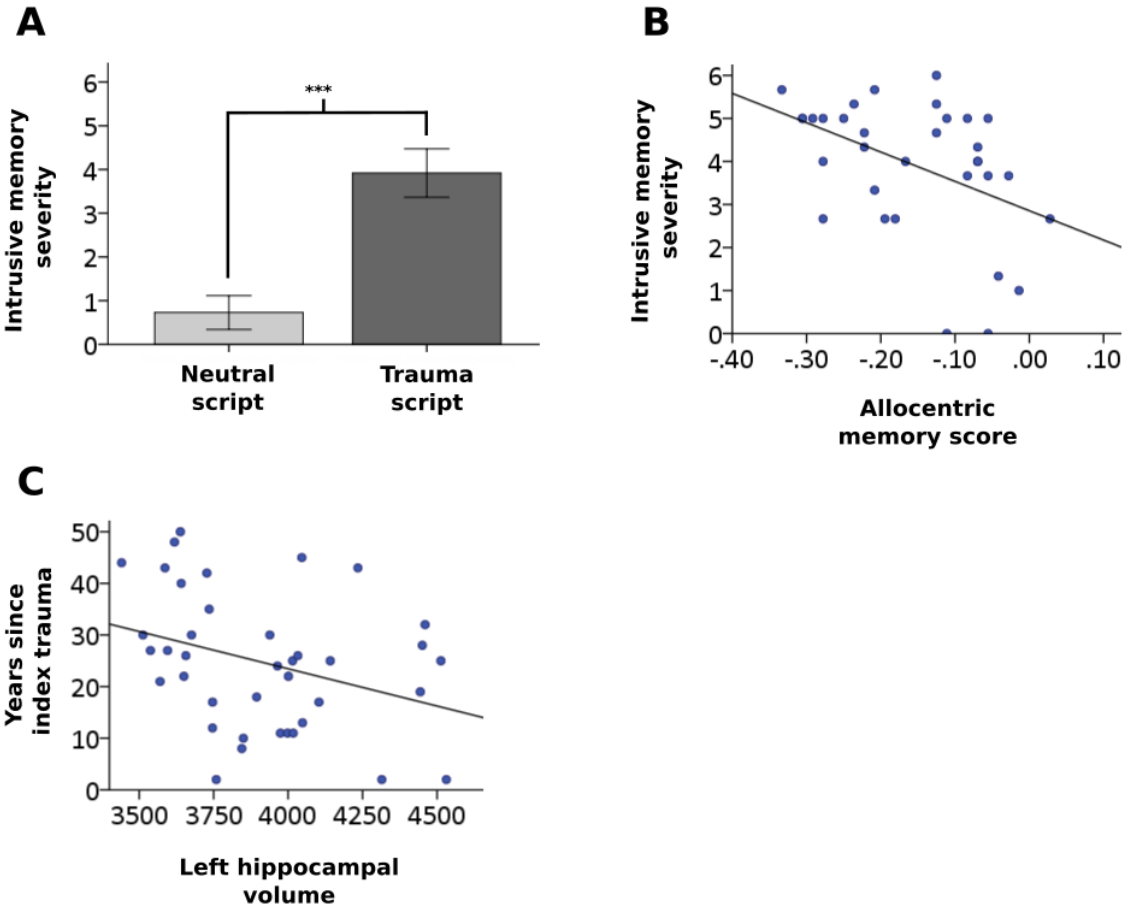

Figure 3. Results of the symptom provocation task and the multiple linear regression analysis. A: Participants reported significantly higher intrusive memory severity after imagining the traumatic scene than after imagining the neutral scene. B: The regression analysis revealed that lower allocentric memory performance significantly predicted more intrusive memory severity. The respective scatterplot is displayed. C: Post hoc analysis revealed a significant negative correlation between age since index trauma and left hippocampal volume (p=.027, uncorrected; n=41).

4. Discussion

4.1. Allocentric spatial memory, intrusive memories and brain morphology

We investigated the predictive capacity of allocentric spatial memory performance, cortical thickness of ventral visual stream (VVS) structures, and hippocampal volume for intrusive memory severity in patients with PTSD. In a planned multiple linear regression model, higher allocentric memory performance significantly predicted lower intrusive memory severity. This relationship could not be accounted for by age, general visuospatial ability, egocentric memory performance, working memory, depression or anxiety scores. Our results complement previous studies, which reported a selective impairment of allocentric spatial memory in PTSD (Gilbertson et al., 2007; Smith et al., 2015) and stronger allocentric processing to be associated with fewer intrusive memories in healthy subjects following an analogue trauma (Bisby et al., 2010).

To our knowledge, this is the first study to provide the missing link by showing an association between lower allocentric memory performance and more frequent intrusive memories in a clinical population. Previous studies, which investigated allocentric memory in PTSD have not measured or considered intrusive memory severity (Astur et al., 2006; Gilbertson et al., 2007; Smith et al., 2015). Our findings further support the dual representation model which emphasizes the role of allocentric-spatial memory for contextualizing mental imagery in PTSD. Due to our cross-sectional study design, we can only speculate whether impaired allocentric memory ability presents a risk factor for the development of posttraumatic intrusive memories or a consequence of traumatic stress. Our sample comprised women with childhood abuse, albeit not all participants reported their childhood trauma as their index trauma. Allocentric processing is assumed to be hippocampal-dependent (Hartley et al., 2007; King et al., 2002) and reduced hippocampal volume has been associated with childhood abuse (Teicher et al., 2017) as well as cumulative stress exposure (Hanson et al., 2015). Congruently, we found a negative correlation between left hippocampal volume and years since index trauma. However, no association between hippocampal volume and allocentric spatial memory performance or intrusive memory severity was detected.

We hypothesized that structures of the VVS predict intrusive memory severity. Reduced cortical thickness of the left lingual gyrus correlated significantly with intrusive memory severity, but did not remain a significant predictor of intrusive memory severity in the multiple regression model. Yet, as cortical thickness of the left lingual gyrus was also positively associated with allocentric memory performance, it might be worth considering its role in mnemonic processing of affective stimuli. It has previously been linked to visual as well as crossmodal spatial attention (Driver & Spence, 2000; Macaluso, Frith, & Driver, 2000) and has been associated with visual memory (Bogousslavsky, Miklossy, Deruaz, Assal, & Regli, 1987). Studies in women with PTSD due to childhood abuse reported reduced cortical thickness in the right lingual gyrus compared to trauma controls (Tomoda, Navalta, Polcari, Sadato, & Teicher, 2009) and increased blood flow during re-experiencing (Bremner et al., 1999). Also, altered connectivity between the bilateral lingual gyrus and the left dorsal anterior cingulate cortex has been associated with resilience to childhood maltreatment (van der Werff et al., 2013). Hence, it might be possible that traumatic experiences during sensitive times in childhood restrain the development of areas necessary for declarative memory formation and thus for the creation of a coherent spatio-temporal context for an event, which may present a vulnerability factor for the development of posttraumatic intrusive memories. However, having not obtained data on age at first trauma, we cannot substantiate these speculations, while our cross-sectional design and lack of power further restrict any causal inferences. Future studies should investigate the role of areas involved in the contextualization of mental imagery further using a longitudinal design in larger samples.

4.2. Limitations

The following limitations need to be considered: First, our sample comprised solely women who experienced childhood trauma. Our results cannot be generalized to a male clinical population or to individuals who experienced a different type of trauma. Second, our assessment of visual intrusions only related to a brief time period. Third, we instructed participants to image the event vividly and may have only assessed visual intrusive memories. Thus, we cannot draw any conclusions regarding the effect of allocentric spatial memory on intrusive thoughts or other sensory intrusions. Lastly, as our findings are based on correlational analyses, no directionality can be inferred.

4.3. Clinical implications

Our findings have relevant clinical implications for psychological intervention, specifically for trauma-focused therapy in PTSD (cf. Ehlers & Clark, 2000). Patients are typically asked to relive their trauma via imagery and update negative appraisals. According to most standard procedures, patients imagine the traumatic scene in front of their eyes, i.e. reconstructing their egocentric representation (Bisiach & Luzzatti, 1978). The dual representation theory proposes that strengthening the allocentric representation, e.g. by imagining the scene from a different perspective as done for example in screen techniques (Sachsse, 2009), facilitates the integration of contextual details and thus reduces intrusive re-experiencing. Our finding of an inverse relationship between allocentric spatial memory performance and intrusive memory severity suggests that patients with severe intrusive memories will have more difficulty creating an allocentric representation and may need specific guidance. To date there are case studies that support this approach (Kaur, Murphy, & Smith, 2016). Further trials should investigate whether such a module would be effective at reducing the frequency and intensity of intrusive memories and how strengthening an allocentric representation may be implemented effectively. Our findings may also imply that a strong premorbid allocentric memory ability could present a resilience factor for the development of posttraumatic intrusive memories, which is particularly relevant for populations who are at greater risk for traumatic exposure, such as first responders or soldiers. Further studies testing this implication are warranted.

5. Conclusion

This is the first study to report a significant association between allocentric spatial memory and intrusive memory severity in patients with PTSD. Our work accentuates the crucial role of allocentric-spatial memory for the contextualization of mental imagery in PTSD. Psychological therapies may benefit from additional elements comprising allocentric re-encoding of the traumatic scene to specifically treat intrusive memories in posttraumatic psychopathology.

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Supplementary Material – Study III

Table A.1

Current comorbid disorders among study participants (*n*=33). All comorbid disorders present the secondary diagnosis to PTSD.

	Disorders	Number of participants (past included)
Anxiety disorders	Generalized anxiety disorder	4
	Social anxiety disorder	16
	Specific phobia	1
	Panic disorder	11
	Agora phobia without history of panic disorder	3
	Obsessive–compulsive disorder	3
	Total anxiety disorders	25
Mood disorders	Major depressive disorder Present	5 (12)
	Major depressive disorder single episode	2 (4)
	Dysthymia	1 (0)
	Total mood disorders	7 (15)
Other	Borderline Personality disorder	9
	Eating disorder	4
	Substance abuse disorder	0 (5)
	Somatoform disorder	1
Total comorbidity		28 (32)

Table A.2

Intercorrelations between variables of interest. Variables were selected as predictors for the multiple linear regression analysis if they correlated significantly with intrusive memory severity.

	Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1.	Intrusive memories	1																						
2.	Allocentric memory	-.44**	1																					
3.	Age	.24	-.45**	1																				
4.	RAPM	.09	-.03	-.25	1																			
5.	Working memory	-.09	-.04	-.11	.34	1																		
6.	L-Hippocampus	.17	-.14	-.16	.24	.10	1																	
7.	R-Hippocampus	.08	-.12	.08	<.001	-.12	.75	1																
8.	L-lat occipital c	-.14	.16	.16	.10	.16	.18	.11	1															
9.	R- lat occipital c	-.26	.04	-.44**	.19	.08	-.05	-.29*	.17	1														
10.	L-lingual g	-.37*	.36*	-.23	.19	.24	.04	-.19	.38*	.24	1													
11.	R-lingual g	-.04	.17	-.44**	.21	.20	.12	-.15	.22	.29	.63***	1												
12.	L-fusiform g	-.30	.36*	-.29	.17	.32	.02	-.14	.61***	.33*	.59***	.55***	1											
13.	R-fusiform g	-.22	.29	-.11	.11	.01	.18	.16	.50**	.21	.53***	.40**	.56***	1										
14.	L- pericalcarine g	.03	.01	0.2	-.04	-.02	.29*	.06	.21	.35*	.55***	.68***	.27	.34*	1									
15.	R- pericalcarine g	.11	.06	-.25	-.01	.10	.10	-.05	.2	.23	.49**	.75***	.36*	.46**	.64***	1								
16.	L-inf temp g	.07	-.18	-.09	.08	-.03	.07	-.10	.33*	.56***	.08	.22	.21	.38*	.39*	.34*	1							
17.	R-inf temp g	-.18	.05	-.31*	-.24	-.01	.22	.14	.25	.36*	.40*	.55***	.28	.49**	.57***	.60***	.30*	1						
18.	L-middle temp g	-.21	.28	-.58	.33*	.17	.18	.07	.40**	.58***	.24	.40**	.56***	.61***	.23	.27	.43**	.36*	1					
19.	R-middle temp g	-.26	.31*	-.11	.16	-.04	.08	.05	.64***	.40*	.23	-.09	.54***	.38*	-.09	-.02	.27	.04	.53***	1				
20.	L-temp pole	.08	-.05	-.11	.21	-.03	.20	.24	.27	.21	.01	-.07	.22	.27	-.09	.13	.33*	.15	.33*	.55***	1			
21.	R-temp pole	-.03	-.06	-.07	.04	-.21	.29*	.38*	.08	.02	.04	-.26	-.16	.16	-.04	.08	.17	.09	.11	.41*	.67***	1		
22.	L-parahipp g	-.06	.30*	-.25	-.05	.24	.33*	.03	.25	.16	.45**	.33*	.25	.37*	.34*	.39*	-.04	.32*	.27	.15	-.05	-.10	1	
23.	R-parahipp g	-.15	.35*	-.50**	.15	.19	.25	.06	.33*	.32*	.50***	.43**	.40*	.44**	.29	.40*	.26	.41**	.53***	.32*	.36*	.15	.55***	1

C=cortex; inf=inferior; g=gyrus,L=Left; lat=lateral; parahipp=parahippocampal; R=right; RAPM= Raven's Advanced Progressive Matrices Set I; s=sulcus of; temp=temporal;

*Correlation is significant at $p<.05$

**Correlation is significant at $p<.01$

***Correlation is significant at p<.001

D. Lebenslauf

As pages 157-160 contain personal information (Curriculum Vitae, Publications, percentage share), they are not a constituent part of this publication.

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F. Prozentualer Eigenanteil

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G. Eidesstattliche Erklärung

Ich versichere, dass ich meine Dissertation

„Neurobiological Underpinnings of Trauma-related Psychopathology"

selbstständig, ohne unerlaubte Hilfe angefertigt und mich dabei keiner anderen als der von mir ausdrücklich bezeichneten Quellen und Hilfen bedient habe.

Die Dissertation wurde in der jetzigen oder einer ähnlichen Form noch bei keiner anderen Hochschule eingereicht und hat noch keinen sonstigen Prüfungszwecken gedient.

London (GB), Juni, 2018 Anika Sierk