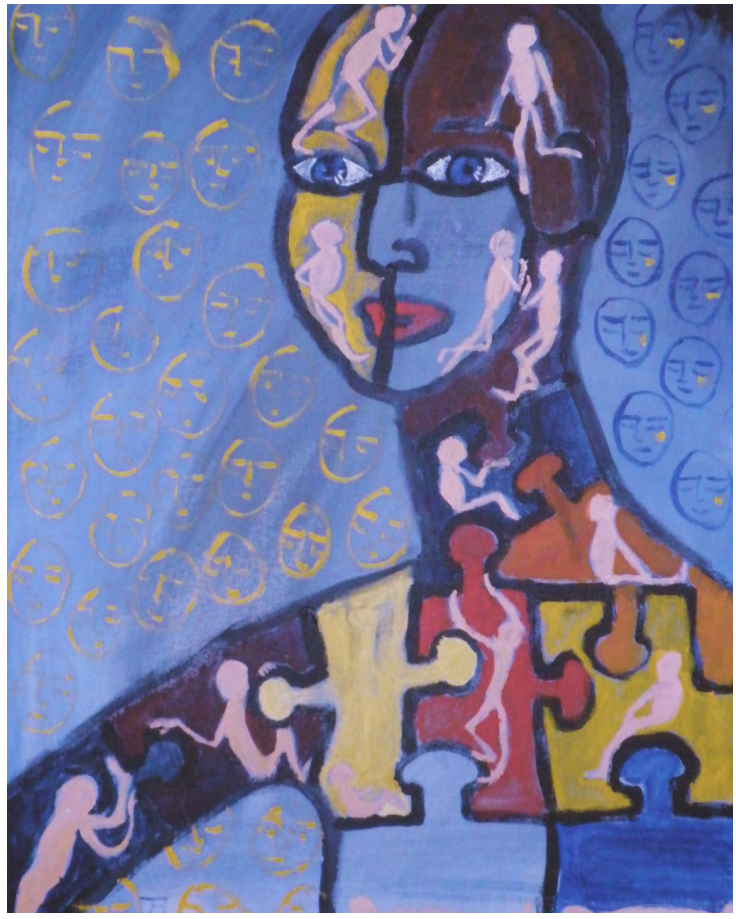

PIECES OF THE PUZZLE

Empirical studies on the diagnosis
Dissociative Identity Disorder

Eline Vissia

PIECES OF THE PUZZLE

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EMPIRICAL STUDIES ON THE DIAGNOSIS DISSOCIATIVE IDENTITY DISORDER

Eline M. Vissia

ISBN printed version: 978-90-367-8735-2
ISBN digital version: 978-90-367-8734-5

Cover illustration: Esther Veerman
Cover design: Marrit Jagers op Akkerhuis

Design: Ferdinand van Nispen tot Pannerden,
Citroenvlinder DTP&Vormgeving, *my*-thesis.nl
Marrit Jagers op Akkerhuis
Printed by: GVO Drukkers en vormgevers, Ede, The Netherlands

The printing of this thesis was supported by:

rijksuniversiteit groningen

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EMPIRICAL STUDIES ON THE DIAGNOSIS DISSOCIATIVE IDENTITY DISORDER

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

maandag 2 mei 2016 om 16:15 uur

door

Eline Margreta Vissia

geboren op 28 oktober 1986
te Heerenveen

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CHAPTER 1

GENERAL INTRODUCTION

Having multiple personality states: a participant's story[1]

"As a DID patient, I participated in the study investigating dissociative identity disorder (DID) using neuroimaging. It was exciting to get involved, because it is far from easy to "just" bring another personality part of myself to the surface. No one with DID does so easily, unless under a state of threat. I believe there is much misunderstanding about a condition as DID anyway and therefore I am very grateful that with this thesis an attempt to give clarity and insight into the brain of DID patients is made and I'm thankful that I got the opportunity to be a small link in this. On the cover you see "Puzzle", a painting I made before I was diagnosed with DID and before I knew that I consisted of multiple parts. At the time I painted this, I was hospitalized to cope with internal crisis and felt suicidal. Painting was a way to somehow stay ahead of the overwhelming emotions and in advance I did not know what I was going to make; often I was not even aware of who or what was painting. By painting, the parts in my head, which have their own life and age, communicated with the world and with the present time. When the painting was finished, and the emotion was translated to the canvas, generally it became clear what the story was about. However, sometimes it could take years for myself to understand what a painting depicted, I was not always ready to realize what an inner child wanted to make clear. Through painting, inner parts were communicating from the inside to the outside world. Sometimes it were the younger parts, inner children that tried to communicate, and sometimes other parts of the personality, such as defensive parts, or even parts that imitated perpetrators. My world inside was dark and cold, as if it were dark caves where the children were isolated, alone and withdrawn. All parts of our inner worlds were totally isolated and not in contact with each other until we began trauma therapy. We were on record as untreatable, constantly suicidal because of our defense system and we were terribly afraid to trust others.

After years of misdiagnoses and more than twenty hospitalizations, I started DID focused therapy and my fear and resistance were enormous. In the beginning I saw only an authoritarian perpetrator in my therapist. What contributed to overcome my resistance and fear was the psycho-education that helped me understand what was going on inside my head. I was so grateful that finally someone could explain my madness. It appeared that I was not crazy and

1 Translated from Dutch by the thesis' author. The original statement can be found in Dutch on page 295 in appendix A of this thesis

that somehow my defenses were logical and understandable, although most complex. And the further therapy progressed, the more insight I gained into the functioning of my own brain. Gradually a picture unfolded to me of a complex personality with different identities, which seemed to have different functions, but were also often grouped around serious traumatic experiences. The constant intrusions, severe nightmares and numerous physical reactions captured me all those years and with that, I would not have lived long anymore. Now was the time to try to enter those horrors, to meet the different identity states and change the sharp emotions to memories that would not always overwhelm me. For that purpose I also took my paintings to therapy. The paintings articulate their own language and have their unique level of communication. Sometimes just observing them is enough.

Some time ago, I brought the Foundation Art from Violence (Stichting Kunst uit Geweld) to life. The aim is to provide a platform for survivors of domestic and sexual violence for sharing their art with each other and the world. The goal is to familiarize society with the effects of such violence and to make clear what the consequences are and try wherever possible to stop it."

Esther Veerman
www.kunstuitgeweld.nl

Dissociative identity disorder

Dissociative identity disorder (DID) is considered to be at the far end of the spectrum of trauma-related psychiatric disorders (Spiegel 1984, Van der Hart, Nijenhuis & Steele 2006). According to the DSM-5 (American Psychiatric Association 2013), DID is a psychiatric disorder that is, among others, characterized by the experience of two or more distinct personality states, recurrent gaps in the recall of everyday events or important personal information, and/or traumatic events that are inconsistent with ordinary forgetting, all of which should not be an outcome of substance abuse or general medication (American Psychiatric Association 2013). In addition to DSM-IV-TR criteria (American Psychiatric Association 2000), symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Furthermore, the disturbance is not a normal part of a broadly accepted cultural or religious practice (American Psychiatric Association 2013).

Personality states

DID is characterized by the development of different types of dissociative personality states. Such states have been classified as neutral personality states (NPS) or trauma-related personality states (TPS) (Reinders et al. 2003, Reinders et al. 2006, Reinders et al. 2012). In an NPS, DID patients concentrate on functioning in daily life. To that end, NPS has full or partial amnesia for traumatic memories, thereby disabling recognition of trauma-related information. In contrast, TPS does have conscious access to the traumatic memories. Personality states have previously also been referred to as neutral identity state (NIS) and trauma-related identity state (TIS) (Reinders et al. 2006, Reinders et al. 2012). The indicators NPS and TPS are derived from the terms "apparently normal part of the personality (ANP)" and "emotional part of the personality (EP)", respectively, which are used in the Theory of Structural Dissociation of the Personality (TSDP) (Van der Hart, Nijenhuis & Steele 2006, Nijenhuis 2015). This theory defines dissociation as a division of personality into different types of subsystems, each with their own first-person perspective, that is, their own point of view as to who they are, what the world is like, and how they relate to that world (Nijenhuis 2015). Nijenhuis and Van de Hart (2011) outline a corporation metaphor, in which dissociation can be compared with a corporation that encompasses several departments and temporary projects. The corporation lacks a central management and is organized by interactions among all departments and employees. There is no hierarchically highest level dissociative part that guides lower level parts. The metaphor reflects the fact that no matter how dissociated and different parts of the personality may be, they are still linked and together they constitute a whole system (Braude 1995, Van der Hart, Nijenhuis & Steele 2006).

Nijenhuis et al. (2002, 2009) and Reinders (2008) suggested that studies in DID need to recognize and assess various dissociative personality states. To date, a handful of studies investigated personality state differences (Reinders et al. 2003, Reinders et al. 2006, Hermans et al. 2006, Reinders et al. 2012, Huntjens, Verschuere & McNally 2012, Schlumpf et al. 2013, Schlumpf et al. 2014). The emphasis in this thesis will be, among others, on acknowledging the differences between personality states and the importance to study those states in order to reach more clarity about psychological and neurobiological correlates of DID.

Dorahy et al. (2004) recommended that studies in DID need to recognize and cognitively assess various dissociative personality states when studying working memory, since working memory performance may covary with different prototypical dissociative personality states. A cognitive architecture supporting vigilance and bias for threat stimuli is increasingly suggested by studies regarding attention and working memory in DID (Dorahy et al. 2014). The nature of this architecture may vary depending on the characteristics of the dissociative personality state that is assessed (Dale et al. 2008, Dorahy, Middleton & Irwin 2005, Hermans et al. 2006).

Prevalence

Prevalence rates for DID vary widely, which can be largely explained by the choice of diagnostic instrument and cultural differences in symptom interpretation (Friedl, Draijer & de Jonge 2000). The prevalence of DID appears to be highest in emergency psychiatric settings and affects approximately 1% of the general population (Dorahy et al. 2014). The International Society for the Study of Trauma and Dissociation (ISSTD) has reported that the prevalence of DID is between 1% and 3% in the general population, and between 1% and 5% in inpatient groups in Europe and North America (International Society for the Study of Trauma and Dissociation 2011, Van der Hart, Nijenhuis 2009). Cross-cultural consistency of DID is suggested by similar reported symptom profiles in North America (Ross et al. 1990), The Netherlands (Boon, Draijer 1993b), Turkey (Sar, Yargic & Tutkun 1996, Akyuz et al. 1999) and Puerto Rico (Martinez-Taboas 1991).

DID simulation

In a review of studies comparing diagnosed DID with simulated DID (Boysen, VanBergen 2014) it was concluded that results provided more support for a sociocognitive model than for a trauma model (see below for further description of the models). Among others, inter-identity transfer of information was replicated various times using a variety of methods (Allen, Movius 2000, Kong, Allen & Glisky 2008, Huntjens et al. 2006, Huntjens, Verschuere & McNally 2012). This finding can support a skeptical view towards the accuracy of memory experiences among people diagnosed with DID (Boysen, VanBergen 2014). On the other hand, simulators and DID patients showed significant differences on some clinical measures and DID patients showed cognitive deficits in memory

and performance speed (Boysen, VanBergen 2014). Differences between both DID patients and DID simulating healthy control groups have been reported more broadly, covering several measures (Reinders et al. 2012, Schlumpf et al. 2013, Schlumpf et al. 2014, Brand et al. 2006, Welburn et al. 2003, Hopper et al. 2002). Boysen and VanBergen (2014) noted that if systematic differences in brain functioning will be found between patients diagnosed with DID and DID simulators, this might provide supporting evidence for areas of the brain previously identified as related to DID, thereby contributing to the debate regarding factors of influence in this controversial psychiatric disorder.

Posttraumatic stress disorder

The trauma model posits that DID and posttraumatic stress disorder (PTSD) are etiologically and phenomenologically related disorders (Spiegel 1984, Van der Hart, Nijenhuis & Steele 2005, Bremner 1999). The link between dissociative symptoms and PTSD has been studied in various populations whereby dissociation has been shown to be a strong predictive factor for PTSD (Koopman, Classen & Spiegel 1994, Briere, Scott & Weathers 2005, Wabnitz, Gast & Catani 2013, Shalev et al. 1996, Bremner et al. 1992). Regarding the relationship between complex dissociative disorders and PTSD, one core assumption of the TSDP is that trauma-related disorders can be arranged on a continuum ranging from simple forms of PTSD and acute stress disorders to complex PTSD and DID (Van der Hart, Nijenhuis & Steele 2005).

According to DSM-5, the diagnostic criteria for PTSD include a history of exposure to a traumatic event that meets specific qualifications and symptoms from each of four symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity (American Psychiatric Association 2013). The dissociative subtype of PTSD is new to DSM-5 (Lanius et al. 2010, Lanius et al. 2012). This subtype responds to trauma cues with a distinct pattern of neurobiological responses (Lanius et al. 2010) and may benefit differently from current treatments (Lanius et al. 2012) than PTSD patients with the more common undermodulated type, that involves a predominance of re-experiencing and hyperarousal symptoms (Lanius et al. 2010). Such important clinical implications highlight the need to further unravel the complex interplay of traumatic stress, dissociation, and related disorders.

Reinders et al. (2014) proposed an extended PTSD-based neurobiological model for emotion modulation in DID. It was found that hypo-aroused personality states activated the PFC, cingulate, posterior association areas and parahippocampal gyri, thereby overmodulating emotion regulation; hyper-aroused personality states activated the amygdala and insula as well as the dorsal striatum, thereby undermodulating emotion regulation. By including a PTSD group in studies of this thesis, and compare PTSD with DID, we are able to directly test the trauma model on both neuronal and psychological measures.

Etiology debate

Dissociative identity disorder is controversial (Gillig 2009) and probably the most disputed psychiatric diagnosis (Reinders 2008). For decades the disorder has been officially recognized in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III (American Psychiatric Association 1980) (defined as Multiple Personality Disorder), DSM-IV (American Psychiatric Association 1994), DSM-5 (American Psychiatric Association 2013)), but many patients with DID share a history of years of misdiagnosis and various hospitalizations similar to Esther's experience. Genuine DID patients present their dissociative symptoms with great reluctance. Because of the often mild phenomenology and the usually high shame threshold, symptoms have to be actively enquired after, as most patients do not report them spontaneously (Steinberg 1994). Only gradually, in a stable therapeutic environment, dissociative symptoms can be debriefed and explored, which has led skeptics to assume that DID has an iatrogenic origin. According to a survey among practitioners of patients with DID (Putnam et al. 1986), it took an average of seven years from the first contact with social workers to the time of adequate diagnosis, with nearly four prior other diagnoses. Under -and misdiagnosis may be related to unfamiliarity with the spectrum of dissociative disorders, disbelief that they exist, or lack of knowledge and appreciation of their epidemiology (Coons 1998, Brand et al. 2012). High comorbidity rates (Ellason, Ross 1997, Sar et al. 2004, Sar et al. 2006, Rodewald et al. 2011, Ross, Ferrell & Schroeder 2014, Bozkurt et al. 2014) complicate the diagnosis even further. To date, many clinicians and scientists still question the validity and even existence of DID (Merckelbach, Devilly & Rassin 2002, Piper, Merskey 2004a, Sar 2005, Coons 2005, Fraser 2005, Pope et al. 2006, Paris 2012, Lynn et al. 2014).

Trauma and fantasy models of DID

Supporters of the diametrically opposed trauma and fantasy models (Dalenberg et al. 2012) have engaged in a fierce debate regarding the etiology of DID. The fantasy model (Merckelbach, Muris 2001, Merckelbach, Devilly & Rassin 2002, Piper, Merskey 2004b, Pope et al. 2006, Piper, Merskey 2004a), also referred to as the sociocognitive/iatrogenic model (Spanos 1994, Spanos 1996, Lilienfeld et al. 1999) or non-trauma-related model (Reinders et al. 2012), regards DID as a simulation mediated by high suggestibility and/or fantasy proneness, suggestive psychotherapy and/or suggestive sociocultural influences (Giesbrecht et al. 2007, Rassin, Merckelbach & Spaan 2001, Giesbrecht, Merckelbach 2006, Giesbrecht et al. 2008, Lynn et al. 2012, Merckelbach, Rassin & Muris 2000, Merckelbach, Horselenberg & Muris 2001). The sociocognitive view includes the idea that DID can be easily created in motivated suggestible individuals and that few suggestions would suffice to generate the symptoms of DID (Spanos 1996). Although fantasy proneness and suggestibility refer to different concepts, they are highly correlated (Merckelbach, Van de Ven 2001, Braffman, Kirsch 1999, Levin, Spei 2004) and dissociative symptoms correlate with fantasy proneness, heightened suggestibility, and susceptibility to pseudomemories in student samples (Merckelbach, Muris 2001, Rauschenberger, Lynn 1995). Opponents of the trauma model also suggested that mild cognitive impairment (Giesbrecht et al. 2008) or sleep disturbances (Van Heugten-van der Kloet et al. 2014) can be alternative mediating factors.

The trauma model postulates that DID is related to a combination of factors that include chronic emotional neglect and emotional, physical, and/or sexual abuse from early childhood, insufficient integrative capacity, attachment problems, and lack of affect-regulation by caretakers (Gleaves 1996, Spiegel 2006, Spiegel et al. 2011, Putnam 1992, Van der Hart, Nijenhuis & Steele 2006, Dell, O'neil 2009). Within the trauma-related view DID is thought to be a severe form of posttraumatic stress disorder, belonging at the far end of the spectrum of trauma-related psychiatric disorders (Spiegel 1984, Van der Hart, Nijenhuis & Steele 2005, Steele, Van der Hart & Nijenhuis 2009). Holders of the trauma-related view recognize that some features of dissociative personality states can be influenced by sociocultural factors (Van der Hart, Nijenhuis & Steele 2006), that false positive cases of DID have evolved in a treatment setting, and that some psychiatric patients imitate DID (Draijer,

Boon 1999). However, they also note that there are differences between genuine and imitated DID and that there is no evidence that DID can (sub-) consciously be created by sociocultural factors (Gleaves 1996). Even if DID symptoms can be created iatrogenically or enacted (Spanos 1994) this does not demonstrate that genuine trauma-related DID does not exist (Elzinga, Van Dyck & Spinhoven 1998).

To date, the fantasy model has hardly been tested in studies involving DID patients (cf. (Van Heugten-van der Kloet et al. 2014)), and evidence that the complex phenomenology and psychobiology of DID can be created and sustained over time by these factors is lacking (Gleaves 1996, Brown, Frischholz & Schefin 1999, Xiao et al. 2006, Loewenstein 2007). The model mainly relies on studies with nonclinical samples regarding fantasy proneness, suggestibility, and memory, and cover only a small subset of the many studies on DID and traumatic dissociation (Loewenstein 2007). Despite this lack of empirical support, the fantasy model of DID is influential in contemporary psychiatry and there have been proposals to prevent the inclusion of DID in the DSM-5 (Gharaibeh, Merskey 2009). Although proponents of the model acknowledge that "most individuals with DID exhibit signs and symptoms of psychopathology and experience intense subjective distress" (Lilienfeld, Lynn 2003) (p.131), they believe these problems should be attributed to other disorders such as bipolar disorder, somatization disorder, and primarily, borderline and hysterical personality disorder (as described in Van der Hart, Nijenhuis 2009). Given these largely contradicting views, it seems to be of major importance to further study dissociative identity disorder, testing both models. In line with this, Brand et al. (2012) and, more recently Lanius (2015), specified the importance of conducting more neurobiological research.

This thesis aims to explore the etiology of DID in a design that acknowledges both the trauma and fantasy model. Moving beyond these positions, the hypothesis is tested whether DID has a unique pattern in brain structure and function when compared with control groups. Specifically, by identifying personality state differences in functional brain mechanisms as well as several psychological measures, results can further inform holders of both views about the etiology of DID and contribute to achieving consensus regarding diagnosis and treatment. In the past decades, research on the effects of trauma and mechanisms of recovery has evolved in various different directions. Despite these advances, countless individuals affected by traumatic stress still do

not receive optimal care, which is incredibly costly to the mental health care system (Coons 1998, Brand et al. 2012, Insel, Cuthbert 2015). Findings from (fundamental) research need to be better translated to clinical applications. This project has emerged from a neuroscientific interest with a translational aim and was set up in close collaboration with experts in the clinical field.

Trauma, dissociation and attachment

Trauma

In psychopathology trauma is regarded an unbearable and inescapable life-threatening experience in the face of which a person is powerless (Herman 1992, Farina, Liotti 2013, Van der Kolk 1996, Krystal 1988). It has been postulated that traumatic experiences overwhelm a person's defense ability and take over the usual fight or flight defensive responses (Schore 2009). The activation of an archaic defense system causes a disconnection between the various functional levels of the mind, prevents the integration of the traumatic event in psychological life and causes the discontinuity and fragmentation of consciousness and memory (Schore 2009, Nijenhuis et al. 1998b, Putnam 1997).

Trauma can be seen as a psychological "wound" evolved in relation to a variety of associated psychological, biological, social, and other environmental factors (Nijenhuis, Van der Hart 2011). Psychobiological factors include limitations of the exposed individual's integrative capacity as revealed in dissociative reactions, affect dysregulation, and persistent avoidance of traumatic memories. Several studies show that traumatic pathogenetic processes cause detached states and neurobiological damage, impair a person's integrative capacity and cause the fragmentation of behavioral strategies, mental activities, autobiographic and procedural memories, as well as the sense of self (Schore 2009, Farina, Liotti 2013).

Early maltreatment has enduring negative effects on brain development (Teicher et al. 2002, Teicher et al. 2003, Teicher, Tomoda & Andersen 2006). Because children have limited coping and self-regulatory capability in early stages of development they are easily overwhelmed (Putnam 1997) and abuse during this time disrupts self-regulation of emotion as well as early organization of self-perception (Putnam 1997). Emotional dysregulation and

maltreatment during developmental years often co-occur and may be the precipitant of psychiatric treatment (Putnam 1997, Brand et al. 2012, Gentile, Dillon & Gillig 2013) and the neurobiological sequelae of early stress and maltreatment may play a significant role in the emergence of psychiatric disorders during development (Teicher et al. 2003). DID has been associated with prolonged, severe and early childhood trauma (Chu et al. 1999, Boon, Draijer 1993b, Putnam et al. 1986) and the vast majority of DID patients report severe forms of abuse.

Clinical and neurobiological studies show that childhood traumatic experiences typically affect the mental functions most heavily dependent on the development and functioning of large associative networks, such as the state of consciousness and self-consciousness, or from the integration of different brain areas, such as emotional control and autobiographic memory (Chu 2010, Lanius, Vermetten & Pain 2010, Teicher et al. 2010, Tononi, Koch 2008, Farina, Liotti 2013).

Dissociation

Many divergent experiences have been described as dissociative, ranging from normal failures in attention to the breakdown of memory processes as seen in dissociative disorders. There is no consensus on the meaning of the term dissociation and the term is, in psychopathology, essentially used to define three different yet related concepts (Farina, Liotti 2013): 1) a diagnostic category, Dissociative Disorders (DD) of the ICD-10 and DSM-5; 2) a group of symptoms, dissociative in nature such as amnesia or derealization; 3) some pathogenic processes caused by traumatic experiences interfering with the integration of mental functions. Both retrospective and prospective studies and clinical observation suggest that dissociation is the central pathogenic mechanism rather than a peripheral feature of trauma related disorders (Sar 2011). Dissociative symptoms can disrupt every area of psychological functioning and are usually divided into two types (Spiegel et al. 2013): first there are unbidden intrusions into awareness and behavior, with accompanying deficits in continuity of subjective experience, labeled “positive” dissociative symptoms, and second, there is an inability to access information or to control mental functions, called “negative” dissociative symptoms (Spiegel et al. 2013).

Clinicians and researchers seem to agree that dissociation is the loss of the ability of the mind to integrate some of its higher functions (Dutra et al. 2009, Waller, Putnam & Carlson 1996, Farina, Liotti 2013). Dissociation can be broadly defined as a structured separation of mental processes that are normally integrated (Spiegel, Cardena 1991), such as memory, consciousness and identity (Liotti 2004). Dissociation in DID appears to serve as an automatic defense mechanism which reduces the impact of highly aversive or traumatic events (Van IJzendoorn, Schuengel 1996). Boon and Draijer (1993a) note that the assumption of a dissociative continuum, ranging from 'normal' forms of dissociation[2] to pathological dissociation such as found in DID (Hilgard 1977, Ludwig 1983, Bernstein, Putnam 1986, Putnam 1989), is in contrast with Janet's original ideas (Janet 1907) in which dissociative states are regarded as discrete pathological states and dissociation is defined as a lack of integration among two or more different "systems of ideas and functions that constitute personality" (p332) (Nijenhuis, Van der Hart 2011). The term dissociation was used by Janet to indicate a disorder of the integrative capacity leading to a mental fragmentation over several levels: from a deficit in the field of consciousness to an impairment of the unity of the subject's personality (Van der Hart, Nijenhuis & Steele 2006). The disconnection of the normally overlapping and integrated functional levels of the mental functions is induced by the violent emotions caused by traumatic experiences (Van der Hart, Dorahy 2006). The development of a structured clinical interview for diagnosing dissociative disorders, which examines the quality and seriousness of five dissociative symptom classes (SCID-D) (Steinberg 1993) has contributed to the phenomenological knowledge of the various forms of dissociation.

In line with Cardena (1994) and Allen (2001), Brown (2006) and Holmes (2005) proposed a different classification of dissociative phenomena. They proposed two distinct forms of dissociation, namely detachment and compartmentalization. Detachment consists of depersonalization, derealization, and related phenomena, like out of-body experiences. These experiences are typically triggered by overwhelming emotions caused by life-threatening experiences (Lanius et al. 2010). Compartmentalization, in contrast, encompasses dissociative amnesia, somatoform dissociation, surfacing of traumatic memories and distorted emotional and identity unity control (alternation of multiple personalities) (Nijenhuis, Van der Hart 2011, Holmes

2 Such as daydreaming or losing oneself in a good book

et al. 2005, Nijenhuis et al. 1998a) and stem from the compartmentalization of normally integrated functions. Compartmentalization symptoms are typically a consequence of traumatic development and seem to modify the very structure of the personality (Lanius et al. 2010, Chu 2010, Classen et al. 2006), whereas detachment symptoms are experienced by everybody in extreme situations.

Putnam (1997) proposed a trauma-related developmental pathway to complex dissociative disorders such as DID via repetitive evocation of "discrete behavioral states" in the traumatized infant or young child (Van der Hart, Nijenhuis 2009). These states are precursors to a normally cohesive personality. Recurrent traumatization of the child compromises developmental psychobiological processes and involves a lack of integration among behavioral states and, eventually, dissociative parts of the personality (Putnam 1997).

Psychodynamic views regard dissociation as a psychological defense that emerges when an individual lacks the capacity, skills, motivation, or social support to integrate extremely stressful events or resolve intrapsychic conflict (Howell 2005, Kluft 1985). Recent psychodynamic views on dissociative disorders have integrated object relations, ego and self-psychology, intersubjectivity, and affect and attachment theories to further the understanding and treatment of these complex disorders (Howell 2005, Kluft, Foote 1999).

Attachment

Attachment theory is a psychological model that attempts to describe the dynamics of long-term interpersonal relationships between individuals and is often integrated with a psychodynamic perspective. This theory relates DID to highly disturbed attachment patterns between caretakers and their children (Lyons-Ruth et al. 2006, Barach 1991). This pattern involves the caretaker's extreme emotional unavailability and unduly frightened and frightening behaviors toward the child, resulting in a disorganized attachment style (Van der Hart, Nijenhuis 2009). Fear without solution, caused by the interaction with a seriously neglectful, maltreating, dissociated or simply frightened parent, prevents children from coherently organize their normal attachment behaviors (Main, Hesse 1990, Farina, Liotti 2013). Results of a prospective

study indicate that neglect and verbal violence in childhood are the traumatic experiences most closely associated with the development of dissociative disorders and symptoms in adulthood (Dutra et al. 2009). Disorganized attachment plays a central role in trauma-related disorders. It has been suggested that the propensity to react to traumatic events with dissociation is related to disorganization of early attachment and its developmental sequelae (Liotti 2004). It is hypothesized that early disorganized attachment is the first step in many developmental pathways that lead to increased vulnerability to dissociative disorders and dissociative reactions to later traumas in the face of traumatic experiences during childhood and adolescence (Liotti 1992).

The attachment system, although more often active during infancy and childhood, is operant throughout an individual's life and powerfully activated during and after any experience of fear and of physical or psychological pain (Liotti 2004). A need to cope with a traumatic stressor activates the attachment system. Disorganization of attachment closely mimics the collapse of the integrative functions of consciousness that characterize any dissociative experience, and may be the first instance of dissociative reactions during life (Liotti 2004). Treatment of dissociative patients with developmental trauma disorders is complex and must be based on a multi-phase program, where the first goal is to overcome relational and arousal modulation difficulties (Cloitre et al. 2011, Courtois, Ford 2009).

Closely related concepts

Traumatic experiences, attachment dynamics and dissociative reactions seem to be intertwined, like three threads woven into a single strand (Liotti 2004). This strand may extend into developmental pathways leading, in the presence of later traumas, to complex forms of posttraumatic stress disorder, dissociative disorders and borderline personality disorder. Early childhood trauma-related consequences and to neglect or attachment related problems often co-exist (Draijer 2003, Courtois, Ford 2009). Traumatic experiences in children are often inflicted by people they depend on and who should protect them. Not only do children develop posttraumatic stress symptoms accordingly, also severe problems in affect regulation and social relationships might emerge (Draijer, Langeland 2009). It has been indicated that dissociation, although trauma-related, is neglect-related as well (Draijer, Langeland 1999). In particular, maternal dysfunction was found to be related to

the level of dissociation (Draijer, Langeland 1999). This implies the importance of object relations and attachment in the diagnosis and treatment of patients with dissociative disorders. Secure attachment rests on the basis of emotion regulation and insecure, especially disorganized, attachment, together with trauma, may profoundly disturb affect regulation.

DSM-5 did not include dissociative disorders (DD) under the Trauma- and Stressor-Related Disorders, as the diagnostic criteria for dissociative disorders do not include a stressor criterion (Criterion A), although the DDs in DSM-5 were deliberately placed just after the Trauma- and Stressor-Related Disorders group to indicate that most DD are associated with traumatic experiences (Reinders et al. 2014, Spiegel et al. 2013).

Since 2009, attempts to introduce the diagnosis of complex posttraumatic stress disorder for adults in the DSM-5 have been made, defined as Developmental Trauma Disorder among the disorders with onset in childhood and adolescence (Sar 2011). Complex PTSD presents with clinical features of full or partial PTSD together with symptoms from three additional clusters, namely problems in emotional regulation, negative self-concept, and problems in interpersonal relations (Marinova, Maercker 2015). Complex PTSD is proposed as a new diagnostic entity in ICD-11 and typically occurs after prolonged and complex trauma.

Effects on the brain

Carlson et al. (2010) regard learning as the process by which experiences change the nervous system and behavior accordingly. Learning is crucial to human survival. If we could not form memories as infants, we could not learn to do anything or benefit from experience. Early stress signals the nascent brain to develop along an alternative pathway adapting itself to survive and reproduce in a malevolent stress-filled world (Teicher, Tomoda & Andersen 2006). In psychotrauma, protection against the overwhelming exposure of threatening stimuli may be realized by inhibiting information processing. The DSM-5 definition (Spiegel et al. 2013, American Psychiatric Association 2013) of dissociation along with the general clinical assumption (Van der Hart, Nijenhuis & Steele 2006) suggest that individuals who experience high levels of dissociation, will show information processing dysfunction, such as disturbances in attention and memory, provoked by the implied defensive

function of dissociation (Spiegel, Cardena 1991, Van der Kolk, Fisler 1995, Van der Hart et al. 2004).

Stress has effects on brain areas that play a critical role in learning and memory, including the hippocampus and prefrontal cortex (PFC) (Bremner et al. 2004, McEwen, Nasca & Gray 2015). It has been well documented that stress hormones may damage the brain when secretion is excessive or unnecessarily prolonged (McEwen 2002). The hippocampus, in particular, is a major target for stress hormones due to the abundant presence of receptors for glucocorticoids. Early-life chronic exposure to stress and glucocorticoids could result in the suppression of neurogenesis, a reduction in dendritic branching or neuronal atrophy or neural loss in the hippocampus (McEwen 1999, Sapolsky 1993), which is involved in memory processes. Childhood maltreatment is considered to be a severe life stressor and specific effects of maltreatment may depend on the age at the time of the maltreatment, and severity, frequency and duration of the maltreatment and the identity of the abuser (Andersen et al. 2008). Studies examining the neuroanatomical correlates of childhood maltreatment in adults found decreased gray matter volume in the hippocampus (Vythilingam et al. 2002, Kitayama et al. 2005) and changes in the PFC (Teicher et al. 2003, Van Harmelen et al. 2010).

Brain structure

Structural magnetic resonance imaging (sMRI) studies found in general a smaller volume of the hippocampus in PTSD patients and childhood-maltreated individuals as compared with traumatized and healthy controls (Karl et al. 2006, Kuhn, Gallinat 2013). For DID, some studies reported smaller volume of the hippocampus (Ehling, Nijenhuis & Krikke 2008, Irle et al. 2009, Tsai et al. 1999, Vermetten et al. 2006) as compared with healthy controls. As hippocampal volume loss has been linked to elevated levels of glucocorticoids secretion during stress, these results suggest a trauma-related nature of DID (McEwen 1999, Sapolsky 1993). To date, no studies have compared hippocampus morphology in DID with a trauma-related disorder such as PTSD to test for similarities of these disorders. In order to directly test the trauma model's hypothesis, we will include both PTSD and healthy controls as control groups for DID and compare hippocampus shape and volume. As the prefrontal cortex matures, response to stress becomes more restrictive (Lyss et al. 1999) due to the inhibitory influence of the prefrontal

cortex on other regions (Brake et al. 2000). It has been hypothesized however that early stress activates the developing PFC, altering its development and producing precocious maturation but stunted final capacity (Teicher et al. 1996, Teicher et al. 2003).

Working memory

Memory, and especially working memory is vulnerable to stress (Arnsten 1998), which appears to impair performance during tasks that require prefrontal cortex (PFC) operations (Arnsten 2009). Working memory (WM) has been defined as a limited capacity system that provides temporary maintenance and manipulation of information necessary to execute complex tasks (Baddeley 1996, Baddeley 2003). One of these tasks can be the exclusion of unwanted or irrelevant material from consciousness (Brewin, Smart 2005). Meta-analyses (Owen et al. 2005, Rottschy et al. 2012) have shown the involvement of the prefrontal-parietal network (PPN) during working memory processes in healthy participants. Cole et al (2014) suggest a critical role for the frontoparietal control system in promoting and maintaining mental health. They proposed that this system implements feedback control to regulate symptoms and named it the "immune system of the mind". They noted the frontoparietal control system as an important target for future research. Okon-Singer et al. (2015) described research that demonstrates that stress, anxiety, and other kinds of emotion can profoundly influence key elements of cognition, including selective attention, working memory, and cognitive control. Circuits involved in attention, executive control, and working memory contribute, in turn, to the regulation of emotion.

There is compelling evidence that brain regions and psychological processes commonly associated with cognition, such as the dorsolateral prefrontal cortex and working memory, play a central role in emotion (Okon-Singer et al. 2015). In a recent meta-analysis (Scott et al. 2015) it was suggested that PTSD patients show hypoactivation of regions involved in attention and working memory. In PTSD, several brain imaging studies have demonstrated working memory deficits associated with altered prefrontal activation (Galletly et al. 2001, Clark et al. 2003, Elzinga et al. 2007, Moores et al. 2008, Weber et al. 2005). Patel et al., (2012) described lower activation in dlPFC and lateral parietal cortex in PTSD patients coupled with higher precuneus activation. These authors proposed that the loss of top-down inhibition is one of the

main components underlying impaired extinction or under-modulation of affect. A review (Aupperle et al. 2012) reported subtle impairments in response inhibition and attention regulation in PTSD that may be exacerbated within emotional or trauma-related contexts, and may relate to dorsal prefrontal dysfunction. Rolls (2013) reviews evidence suggesting that the maintenance of a regulatory goal in emotion regulation highly depends on working memory (Okon-Singer et al. 2015). Research examining working memory and attentional mechanisms has attempted to build a cognitive profile of several other psychiatric conditions (Nigg 2000), but results regarding the relation between dissociation and working memory have been ambiguous. Inconsistent results regarding dissociation and working memory require clarification (Giesbrecht et al. 2008).

One multi-subject functional magnetic resonance imaging (fMRI) study has been conducted in dissociative disorders (Elzinga et al. 2007). This study assessed working memory performance in patients with dissociative disorders (DID and DD-NOS) as compared with healthy controls. Dissociative patients showed enhanced working memory performance together with greater activation in the left anterior PFC, dorsolateral PFC and parietal cortex compared with controls. Unfortunately, it remains unclear which type of personality state (NPS or TPS) was tested. Since it is known from previous studies that different types of personality states display distinct patterns of neural activation (for example (Reinders et al. 2003, Reinders et al. 2006)), personality state differences (NPS/TPS) need to be examined for working memory functioning as compared with multiple control groups, testing both the trauma and fantasy model.

Neuroimaging DID

Over the past few decades a variety of methods have been developed to study the brain (Matthews, Jezzard 2004). Neuroimaging includes the use of various techniques to either directly or indirectly image the structure, pharmacology or function of the brain. Structural MRI is a neuroimaging technique for performing volumetric measurements of the brain tissue classes, with a spatial resolution on a millimeter scale. Tissue classes include white matter, gray matter and cerebrospinal fluid. Pathological conditions related to trauma may affect the gray and white matter of the brain (Bremner et al. 1997, Carrion

et al. 2001) and by the use of sMRI, potential neuroanatomical abnormalities in DID and PTSD patients can be studied.

Functional magnetic resonance imaging (fMRI) is a procedure that measures brain activity by detecting associated changes in blood flow. This technique relies on the fact that cerebral blood flow and neuronal activation are coupled (that is, when an area of the brain is in use, blood flow to that region also increases). Blood oxygenation level dependent (BOLD) fMRI is a powerful approach to define activity in the human brain (Matthews, Jezzard 2004).

Despite the fact that imaging neuroscience has been around for more than 20 years and is by now the predominant technique in behavior and cognitive neuroscience (Friston 2009), few neuroimaging studies have been conducted in patients with DID (Dorahy et al. 2014, Dalenberg et al. 2012, Reinders 2008). In contrast, numerous functional neuroimaging studies have studied the neural mechanism underlying PTSD. Although imaging studies have elucidated neurophysiological markers of the dissociative response in patients with a range of DD and PTSD, studies performed specifically in DID patients are more limited (Dorahy et al. 2014), even though prevalence estimates are similar to for example schizophrenia, a disorder that many neuroimaging studies were devoted to. Dorahy et al. (2014) reviewed psychobiological findings and suggested a unique neurophysiological profile in DID.

Switching processes in DID are characterized by activation and inhibition of various brain areas and the exact patterning of these may be related to the psychobiological characteristics of the dissociative personality states involved (Dorahy et al. 2014). During a personality state switch, Tsai et al. (1999) observed brain activity in hippocampal areas, as well as the parahippocampus, medial temporal structures, substantia nigra, and global pallidus, as well as right hippocampal activation when the participant was returning to her original identity (Dorahy et al. 2014). Savoy et al. (2012) demonstrated involvement of the dorsolateral prefrontal cortex, the anterior prefrontal cortex, and orbitofrontal cortex, as well as bilateral activation in the nucleus accumbens during switching in a DID patient.

Reinders et al. (2003) conducted a PET study in DID and found two distinct states of self-awareness, each with its own access to autobiographical trauma-related memory with involvement of the medial prefrontal cortex

and the posterior associative cortices in the representation of these different states of consciousness. In another study (Reinders et al. 2006), the different personality states were associated with different brain activation patterns when confronted with trauma-related cues. The cortical multimodal posterior association areas (PAA), the subcortical amygdala and subparts of the dorsal striatum were described to be involved in the psychopathology of DID. Their findings were unrelated to fantasy proneness (Reinders et al. 2012), since neither high nor low fantasy prone mentally healthy simulating controls were able to enact the psychophysiological and neural activation patterns of the authentic dissociative personality states.

In response to subliminally presented neutral and angry faces, Schlumpf et al. (2013) found abnormal reaction times for EP (equivalent of TPS), but not for ANP (equivalent of NPS), and EP activated different brain areas including in the parahippocampal gyrus, the brainstem, face-sensitive regions, and motor-related areas. Furthermore, Schlumpf et al. (2014) compared ANP and EP on resting state measures and found that ANP showed elevated perfusion in bilateral thalamus. Compared with ANP, EP had increased perfusion in the dorsomedial prefrontal cortex, primary somatosensory cortex, and motor-related areas. In both studies, patterns could not be mimicked by ANP and EP simulating healthy controls. Others (Mathew, Jack & West 1985) found hyperperfusion in the right temporal cortex in a single case study in a DID patient. Two uncontrolled resting state studies also found the involvement of the temporal lobe of the brain in DID (Saxe et al. 1992, Sheehan, Thurber & Sewall 2006) and two controlled studies, that included the largest sample of 21 DID patients in studies into DID using brain imaging techniques to date (Sar et al. 2001, Sar, Unal & Ozturk 2007) found bilateral frontal perfusion differences between patients and controls. The latter results are consistent with a neurodevelopmental model for DID proposed by Forrest (2001), underlining deficient functionality of the orbitofrontal region in the brain. The orbitofrontal lobe has been hypothesized to be affected by early trauma (Dorahy et al. 2014).

Findings from the majority of the above described studies have indicated the involvement of the frontal, parietal and temporal cortices and the hippocampus and striatum in the neuropsychopathology of DID.

Thesis outline

As described in previous paragraphs, neuroimaging studies in DID are limited and the disorder remains controversial. In order to add insight to the etiology debate regarding DID, further research is needed to elucidate the neural and psychological substrates of this disorder.

The aim of this thesis is to provide more knowledge about DID. A group of DID simulating healthy controls was included in studies of this thesis to investigate the degree to which DID can be simulated on both neural and psychological measures, allowing a direct test of the fantasy model. A global overview of thesis related topics is provided above in the general introduction. Chapter 2 discusses a range of psychological measures in DID and several control groups, covering both the trauma and fantasy model. Chapter 3 focuses on investigating differences in morphology of the hippocampus between DID, PTSD and HC in relation to childhood maltreatment. Chapter 4 and 5 focus on working memory functioning and test the trauma and fantasy model respectively, including both PTSD and DID simulating healthy controls as control groups. Finally, a general discussion follows, with a reference to implications for clinical practice and suggestions for future research. In sum, this thesis focuses on the etiology discussion of dissociative identity disorder in a broad sense and more specifically the importance of assessing personality state differences.

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CHAPTER 3

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ABNORMAL HIPPOCAMPAL MORPHOLOGY IN DISSOCIATIVE IDENTITY DISORDER AND POSTTRAUMATIC STRESS DISORDER CORRELATES WITH CHILDHOOD TRAUMA AND DISSOCIATIVE SYMPTOMS

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Published in Human Brain Mapping, 2015

ABSTRACT

Background: Smaller hippocampal volume has been reported in individuals with posttraumatic stress disorder (PTSD) and dissociative identity disorder (DID), but the regional specificity of hippocampal volume reductions and the association with severity of dissociative symptoms and/or childhood traumatization are still unclear.

Methods: Brain structural MRI scans were analyzed for 33 outpatients (17 with DID and 16 with PTSD only) and 28 healthy controls (HC), all matched for age, sex, and education. DID patients met criteria for PTSD (PTSD-DID). Hippocampal global and subfield volumes and shape measurements were extracted.

Results: We found that global hippocampal volume was significantly smaller in all 33 patients (left: 6.75%; right: 8.33%) compared with HC. PTSD-DID (left: 10.19%; right: 11.37%) and PTSD-only with a history of childhood traumatization (left: 7.11%; right: 7.31%) had significantly smaller global hippocampal volume relative to HC. PTSD-DID had abnormal shape and significantly smaller volume in the CA2-3, CA4-DG and (pre)subiculum compared with HC.

Conclusion: In the patient groups, smaller global and subfield hippocampal volumes significantly correlated with higher severity of childhood traumatization and dissociative symptoms. These findings support a childhood trauma-related etiology for abnormal hippocampal morphology in both PTSD and DID and can further the understanding of neurobiological mechanisms involved in these disorders.

INTRODUCTION

Recent epidemiological and neurobiological research in trauma-related disorders has focused on the relationship between childhood and chronic trauma and dissociation. This has led to the recent nosological inclusion of a dissociative subtype of Posttraumatic Stress Disorder (PTSD) (Lanius et al. 2010) in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013). The dissociative disorders category has also recently been placed next to the trauma- and stress-related disorders category "to indicate the close relationship between them"(Spiegel et al. 2013). However, neurobiological evidence for a close relationship between PTSD and dissociative disorders is sparse. Furthermore, to date, the link between neuroanatomical abnormalities and childhood traumatization and/ or dissociative symptoms in PTSD and dissociative disorders remains unclear.

A smaller hippocampal volume is the most consistently reported neuroanatomical finding in individuals with a history of childhood adversity, with or without psychiatric disorders (Andersen et al. 2008, Bremner et al. 2003, Dannlowski et al. 2012, Samplin et al. 2013, Stein et al. 1997, Thomaes et al. 2010). Relevant to our study, a meta-analysis of structural brain imaging studies in childhood-related PTSD has revealed significantly smaller hippocampal volume in adults, but not children, with PTSD compared with healthy controls (HC) (Woon, Hedges 2008). However, none of these PTSD studies has investigated hippocampal shape or the regional specificity of hippocampal volume reductions in this disorder. The relation between hippocampal morphology and childhood adversity also remains unknown. Furthermore, evidence relating hippocampal structural abnormality to the severity of dissociative symptoms in PTSD is mixed. While some PTSD studies have reported a negative correlation between global hippocampal volume and severity of dissociative symptoms (Bremner et al. 2003, Stein et al. 1997), others reported no significant association (Bremner et al. 1995, Nardo et al. 2013). Therefore, the relationship between hippocampal morphology, childhood maltreatment and dissociative symptoms in a sufficiently large sample of PTSD patients is still open to test.

So far, only few structural imaging studies have investigated hippocampal volume in dissociative disorders (Ehling, Nijenhuis & Krikke 2008, Irle et al. 2009, Stein et al. 1997, Tsai et al. 1999, Vermetten et al. 2006, Weniger et al.

2008). Studies in patients with dissociative disorders and co-morbid PTSD (Ehling, Nijenhuis & Krikke 2008, Irle et al. 2009, Stein et al. 1997, Tsai et al. 1999, Vermetten et al. 2006) have found smaller hippocampal volume in these individuals relative to HC, and one study (Ehling, Nijenhuis & Krikke 2008) reported a negative correlation between hippocampal volume and severity of life-time traumatizing experience and dissociative symptoms in individuals with Dissociative Identity Disorder (DID). DID is the most severe dissociative disorder, and has been conceptualized as a severe childhood-onset PTSD (Van der Hart, Nijenhuis & Steele 2006). Interestingly, hippocampal volume has been reported as preserved in patients with dissociative disorders without co-morbid PTSD (Weniger et al. 2008). Unfortunately, these studies suffered from several limitations: small sample sizes; inclusion of patients with mixed diagnoses of dissociative disorders without differentiating these groups within the analyses (DID, dissociative amnesia, dissociative disorder-not otherwise specified); and age differences between patients and controls (Ehling, Nijenhuis & Krikke 2008, Irle et al. 2009, Stein et al. 1997, Tsai et al. 1999, Vermetten et al. 2006, Weniger et al. 2008).

Most studies on the effects of early stress on the hippocampus, including those on PTSD or DID, have only examined differences in global hippocampal volume. However, the hippocampus consists of several histologically distinct subfields, each with distinct structural and functional connections with the cortex, specialized functional properties, and different developmental trajectories (Wang et al. 2010). In individuals from the general community, childhood traumatization (assessed using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 1994) is specifically associated with relatively small volume within the CA2-3 (CA: cornu ammonis), CA4-DG (DG: dentate gyrus), subiculum, and to a lesser extent with smaller volume of the CA1 hippocampal subfields, revealing a relationship between childhood adversity maltreatment and small hippocampal subfield volumes (Teicher, Anderson & Polcari 2012). So far, only two studies evaluated hippocampal subfield volumes in PTSD patients (Bonne et al. 2008, Wang et al. 2010). These studies found smaller volume of the CA3/DG and posterior regions in PTSD patients compared with controls. However, these studies did not investigate the association with childhood traumatization or dissociative symptoms. Indeed, regional hippocampal volume and shape abnormalities have never been investigated in dissociative disorders.

The current study is the first to investigate hippocampal morphological correlates of childhood traumatization and dissociative symptoms in both DID and PTSD patients. To this end, we obtained structural MRI scans from HC and patients with DID and/or PTSD. All participants were carefully matched for age, sex, and education. We investigated global hippocampal volume, subfield volumes, as well as hippocampal regional shape deformations. In the patient samples, we examined the association between hippocampal volume and severity of self-reported early childhood traumatization, that is physical maltreatment, sexual and emotional abuse, and emotional neglect, and severity of dissociative symptoms. We tested three *a priori* hypotheses: 1) both DID and PTSD patients, as compared with HC, would have smaller global hippocampal volume, regional volumetric abnormalities, and shape deformations in various hippocampal subfields; 2) global hippocampal volume, as well as, regional volume in the CA4-DG, CA2-3 and subiculum subfields would be negatively associated with the severity of childhood traumatization; and 3) global hippocampal and regional volumes would be negatively associated with dissociative symptoms.

METHODS

Subjects

Sixty-five women (only female patients with DID volunteered to participate in this study) underwent magnetic resonance imaging (MRI): 17 with a diagnosis of DID, 16 with a diagnosis of PTSD and 32 HC. Four HC were excluded from the demographic and morphological analyses due to the presence of artifacts in the MRI scans. Participants were matched for sex, age, years of education (Table 3.1) and Western European ancestry. PTSD patients with a history of interpersonal traumatizing events and DID patients were recruited via mental healthcare institutions and internet advertisements.

The diagnosis of DID was confirmed by one of two DID experts (E.N. or N.D.) using the Structural Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) (Boon, Draijer 1993b, Steinberg 1993), during which PTSD co-morbidity was assessed as well. The evaluation revealed that all DID patients met criteria for either current co-morbid PTSD (82.35%) or PTSD in remission (17.65%). Therefore, we refer to this sample as "PTSD-DID". The personal

therapists of the patients with PTSD-DID reported the following co-morbid disorders based on DSM-IV classification (American Psychiatric Association 1994): somatoform disorder (n=2), recurrent major depression (n=4), dysthymic disorder (n=1), trauma-related specific phobias (n=2), personality disorder-not otherwise specified (n=2), mixed personality disorders (n=2), borderline personality disorder symptoms (n=3), dependent personality disorder symptoms (n=1), histrionic personality disorder symptoms (n=1), eating disorder (n=2), sleeping disorder (n=2), and catalepsy (n=1).

Severity of psychoform and somatoform dissociative symptoms were evaluated using the Dissociative Experiences Scale (DES) (Bernstein, Putnam 1986) and Somatoform Dissociation Questionnaire (SDQ-20) (Nijenhuis et al. 1996), respectively. The 5-item SDQ-5 was derived from the SDQ-20. These five items as a group discriminate best between patients with and without a dissociative disorder (Nijenhuis et al. 1997, Nijenhuis et al. 1998). The cut-off scores that we used for the DES and SDQ-5 were 25 and 7, respectively (Boon, Draijer 1993a, Nijenhuis et al. 1997). Severity of lifetime traumatizing events were assessed with the Traumatic Experiences Checklist (TEC) (Nijenhuis, Van der Hart & Kruger 2002). PTSD-DID patients completed these questionnaires in their predominant identity state and all of them reported experiencing severe traumatizing events starting from their childhood and extended into their adult life including severe emotional neglect and abuse, physical maltreatment or extreme physical punishments, and sexual abuse. Childhood maltreatment was retrospectively assessed using the CTQ (Bernstein et al. 1994). The CTQ is a retrospective 28-item self-report inventory that measures the severity of five different types of childhood traumatization (i.e. emotional abuse and neglect, physical abuse and neglect and sexual abuse) with scores ranging from 5 to 25 for each trauma type. Total childhood traumatization is calculated as the sum of all the five subscores. In PTSD-DID, CTQ scores were obtained from a trauma-conscious state.

In the sixteen PTSD patients, symptom severity was assessed using the Clinician Administered PTSD Scale (CAPS) interview (Blake et al. 1995) conducted by researchers E.V. and M.G.. Eleven of the PTSD patients reported multiple types of interpersonal traumatizing events during childhood (n=6) or starting from childhood and continuing into adult life (n=5). The remaining 5 PTSD patients reported traumatizing events only during adult life. Two PTSD patients scored high on the DES/SDQ-20 and therefore underwent a SCID-D

interview and DID was excluded. Hence, we refer to this patient group as "PTSD-only". As both PTSD-DID and PTSD-only groups shared the diagnosis of PTSD, we further merged them into one larger group, referred to as "All-PTSD", in order to investigate the common morphological features of PTSD.

HC were recruited through advertisements in local newspapers. Additional exclusion criteria for HC were: a high score of (psychoform/somatoform) dissociative symptoms (evaluated with the DES and SDQ-20, respectively), psychiatric disorder in the past or at present, or a high score on the TEC. All HC were free of present and past psychiatric medication. Exclusion criteria for all participants were: age outside the range of 18-65, pregnancy, systemic or neurological illness, claustrophobia, presence of metal implants in the body and alcohol/drug abuse. Details of psychotropic medications usage are provided in Table 3.1.

After complete description of the study to the subjects, written informed consent was obtained according to procedures approved by the Medical Ethical Committee (METc) of the University Medical Center Groningen (UMCG) and of the Amsterdam Medical Center (AMC).

Image acquisition

T1-weighted anatomical MR scans (MPRAGE, TR=9.95ms, TE=5.6ms, flip-angle=8°, 1x1x1mm voxels, number of slices=160, total scan-time=10m 14s) were acquired on two (UMCG and AMC) 3T MR scanners (Philips Medical Systems, Best, NL) in The Netherlands after a reproducibility study determined one optimized structural MRI protocol for the two centers (Chalavi et al. 2012). All-PTSD patients and their matched HC were scanned interleaved within a short time interval and the samples were balanced over the two centers: twenty All-PTSD patients (ten PTSD-DID, ten PTSD-only) and nineteen HC were scanned at UMCG (see supplementary material S3.1 for more details).

Image analysis

Manual measures of global volume and shape analysis of the hippocampus

After preprocessing the MR images the hippocampi were manually traced using MultiTracer by a single rater (SC), who was blind to all demographical variables and was trained by an expert (JHC) according to an established protocol (Thompson et al. 2004) (details in supplementary material S3.1). Hippocampal global volumes obtained from these tracings were statistically analyzed. To assess the shape deformations of different hippocampal subfields, an anatomical surface mesh modeling method was applied according to standard procedures (Thompson et al. 2004). In brief: Localized gray matter contractions and expansions of the hippocampal surface were established corresponding to the CA1, CA2-3 and subiculum. In each individual, the medial core, a central 3D curve threading down the long axis of the structure, was computed and from each point on the hippocampal surface, a radial distance measure was derived to the medial core. Statistical comparisons were made at each hippocampal surface point between the groups to index contrasts on a local scale. Probability values from these statistical comparisons were mapped onto an average hippocampal shape for the entire sample to generate a 3D representation of the structural differences between the groups. The approximate overlay of the hippocampal subfields was defined based on the Duvernoy atlas (Duvernoy 1988) (Figure 3.1a).

Automated extraction of hippocampal global and subfield volumes

We used FreeSurfer v5.1 (http://surfer.nmr.mgh.harvard.edu) to segment all images into tissue classes and to extract estimates of hippocampal subfield volumes (CA1, CA2-CA3, CA4-DG, subiculum, presubiculum and fimbria) (Van Leemput et al. 2009). An estimate of parenchymal volume (total gray matter (GM) + total white matter (WM)) was also obtained using FreeSurfer and was used in subsequent statistical analyses to correct for whole-brain size.

Statistical analysis

The effect of PTSD diagnosis was first investigated on the global hippocampal and subfield volumes by comparing volumetric measurements between All-PTSD and HC. To this end, a repeated-measures analysis of covariance (ANCOVA) was used with hemisphere (left or right) as the repeated measure and age and parenchymal volume as covariates. The analysis was then followed by pairwise *t*-tests to compare left and right hippocampal volumes separately between: 1) PTSD-DID vs. HC, 2) PTSD-DID vs. PTSD-only, and 3) PTSD-only vs. HC. Furthermore, in order to ascertain that our findings are not due to the differences in the medication usage between the groups, these analyses were repeated after excluding the patients with a history of using different types of psychiatric medications (see supplementary material S3.2: Tables S3.1-S3.3).

To assess regional hippocampal shape deformations, statistical regression analyses, with age and parenchymal volume as covariates, were conducted at each hippocampal surface point to map the associations between group and radial distance, a measure of local hippocampal shape. The resulting statistical maps (*P*-map) of group differences (uncorrected) were displayed on the hippocampal surface template, which was created by averaging hippocampal shapes from the entire sample. Furthermore, permutation tests with 10,000 iterations and a threshold of $p<0.05$ were run to obtain an omnibus corrected *p*-value for each *P*-map.

In the All-PTSD group, we tested the association of severity of childhood traumatizing events with global hippocampal and subfield volumes using partial correlations while controlling for age and parenchymal volume. Furthermore, a possible link between global and subfield hippocampal volumes and severity of dissociative symptoms was tested using partial correlations while adjusting for age and parenchymal volume.

Table 3.1 Demographic and clinical characteristics of the participants

	All-PTSD to HC comparison			Different group comparisons				
	Mean (SD)		t-test: *P* Value	Mean (SD)		t-test: *P* Value		
	All-PTSD (n=33)	HC (n=28)	All-PTSD vs. HC	PTSD-DID (n=17)	PTSD-only (n=16)	PTSD-DID vs. HC	PTSD-DID vs. PTSD-only	PTSD-only vs. HC
All-PTSD to HC comparison				Different group comparisons				
Mean (SD)			t-test: *P* Value	Mean (SD)		t-test: *P* Value		
All-PTSD (n=33)	HC (n=28)	All-PTSD vs. HC	PTSD-DID (n=17)	PTSD-only (n=16)	PTSD-DID vs. HC	PTSD-DID vs. PTSD-only	PTSD-only vs. HC	
Demographics								
Age, years	42.33 (10.91)	41.75 (12.29)	0.85	43.82 (9.85)	40.75 (12.05)	0.56	0.45	0.78
Education, years	14.91 (0.91)	15.04 (1.20)	0.64	14.88 (0.99)	14.94 (0.85)	0.64	0.88	0.77
Handedness, n (%right)	29 (90.63%)	27 (96.43%)	0.37	14 (87.50%)	15 (93.75%)	0.54	0.99	0.99
Medication history								
Antipsychotics: n(typical,atypical)	past:2(1,1) current:8(2,6)[1]	past: 0 current: 0	-	past:2(1,1) current:8(2,6)[1]	past: 0 current: 0	-	-	-
Anti-epileptics: n	past:1 current:3	past: 0 current: 0	-	past:1 current:3	past: 0 current: 0	-	-	-
Antidepressant: n	past: 2 current:12	past: 0 current: 0	-	past: 2 current:10	past: 0 current: 2	-	-	-

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	Mean (SD)		t-test: *P* Value	Mean (SD)		t-test: *P* Value		
	All-PTSD (n=33)	HC (n=28)	All-PTSD vs. HC	PTSD-DID (n=17)	PTSD-only (n=16)	PTSD-DID vs. HC	PTSD-DID vs. PTSD-only	PTSD-only vs. HC
Clinical measures								
Dissociative symptoms								
Psychoform (DES)	38.79 (22.09)	5.02 (3.10)	<0.001*	54.41 (16.18)	22.18 (13.83)	<0.001*	<0.001*	<0.001*
Somatoform (SDQ-20)	45.24 (19.65)	22.04 (2.21)	<0.001*	57.06 (17.26)	32.69 (13.43)	<0.001*	<0.001*	<0.001*
Traumatic experience checklist (TEC)								
Total lifetime trauma	14.40 (5.16)	1.96 (1.93)	<0.001*	17.53 (4.08)	11.06 (4.01)	<0.001*	<0.001*	<0.001*
Childhood Trauma Questionnaire (CTQ)[2]								
emotional neglect	19.90 (5.69)	10.36(4.14)	<0.001*	23.40 (2.26)	16.63 (6.02)	<0.001*	<0.001*	<0.001*
physical neglect	13.87 (5.22)	7.42 (2.28)	<0.001*	17.47 (3.87)	10.50 (3.93)	<0.001*	<0.001*	0.020*
emotional abuse	18.48 (6.56)	7.50 (2.56)	<0.001*	22.80 (3.30)	14.44 (6.31)	<0.001*	<0.001*	<0.001*
physical abuse	12.35 (5.94)	5.43 (1.34)	<0.001*	15.60 (5.37)	9.31 (4.84)	<0.001*	<0.001*	0.018*
sexual abuse	13.84 (7.69)	5.29 (0.73)	<0.001*	17.87 (7.32)	10.06 (6.06)	<0.001*	<0.001*	0.024*
Total trauma	78.45 (26.92)	36.00 (8.00)	<0.001*	97.13 (16.63)	60.94 (22.70)	<0.001*	<0.001*	<0.001*

Abbreviations:
PTSD-only= patients with only posttraumatic stress disorder; PTSD-DID= patients with PTSD and dissociative identity disorder; All-PTSD= includes both PTSD-only and PTSD-DID patient groups. HC= healthy controls; [1] one PTSD-DID patient used typical antipsychotics in the past but stopped and was using atypical antipsychotics at the time of the MRI scan. Another PTSD-DID patient was using atypical antipsychotics in the past but was not using any antipsychotics at the time of the MRI scan.
*[2] CTQ data was available for 15 PTSD-DID, 16 PTSD-only and 14 HC; * P-value<=0.05*

RESULTS

Hippocampal global and subfield volumes

We found a significant main effect of PTSD on global hippocampal volumes ($F(2,54)=6.65$, $p=0.003$) which was independent of hemisphere (group x side) (Wilks' Lambda=0.97, $F(1,57)=1.69$, $p=0.20$). We also found a significant main effect of PTSD diagnosis on hippocampal subfield volumes ($F(12,44)=3.19$, $p=0.002$), also independent of hemisphere (group x side: Wilks' Lambda=0.99, $F(1,55)=0.052$, $p=0.82$).

Bilateral global hippocampal volumes were significantly smaller (left: 6.75%; right 8.33%) in All-PTSD compared with HC (Table 3.2). Further pairwise *t*-tests (Table 3.2) showed that PTSD-DID had significantly smaller bilateral hippocampal volumes as compared with PTSD-only (left: 7.25%; right: 6.58%) and to HC groups (left: 10.19%; right: 11.37%). We also found a trend for a smaller right hippocampal volume in PTSD-only as compared with HC (right: 5.13%; $p=0.067$). *Post hoc* analyses (see supplementary material S3.3) revealed that bilateral hippocampal volumes were only significantly smaller in those PTSD-only patients with childhood onset traumatizing events (left: 7.11%; right: 7.31%) (see Figure 3.2).

Compared with HC, the All-PTSD group had significantly smaller volume in the bilateral CA2-3, right CA4-DG, and left presubiculum, and, at trend level, also in the right CA1, left CA4-DG and bilateral subiculum. Pairwise *t*-tests revealed that PTSD-DID patients had significantly smaller right CA1, bilateral CA2-3, CA4-DG and subiculum, and left presubiculum volumes than HC. Furthermore, the PTSD-DID group showed significantly smaller left CA4-DG and subiculum volumes than the PTSD-only group. In contrast, hippocampal subfield volumes of the PTSD-only group were not different from those of HC.

Table 3.2 Statistical analyses of parenchymal (cm^3), hippocampal global (mm^3) and subfields (0.5 mm^3) volumes

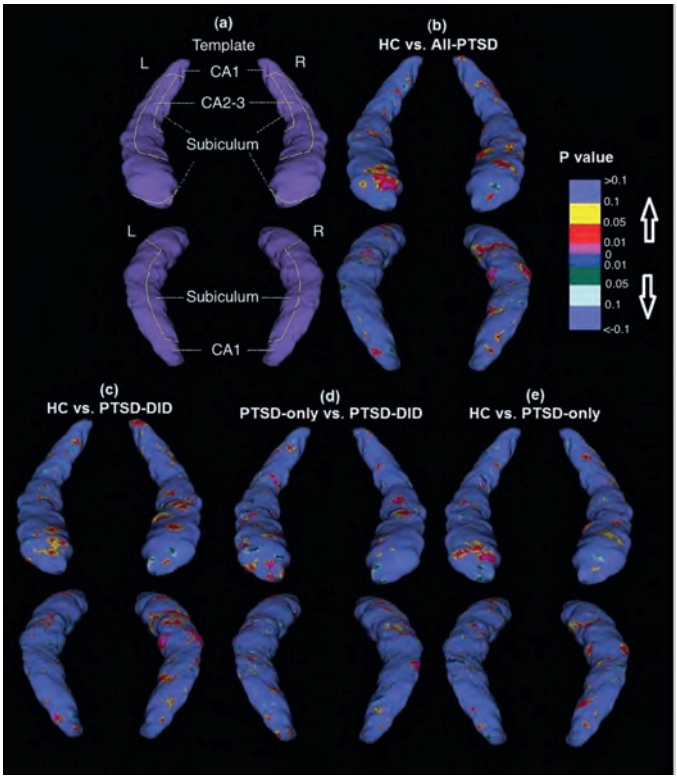
Measurement	All-PTSD to HC comparison			Different group comparisons				
	Mean (SD)		t-test: *P* Value (change%)	Mean (SD)		t-test: *P* Value (change%)		
	All-PTSD (n=33)	HC (n=28)	All-PTSD vs. HC	PTSD-DID (n=17)	PTSD-only (n=16)	PTSD-DID vs. HC	PTSD-DID vs. PTSD-only	PTSD-only vs. HC
Parenchymal	1072 (779)	1084 (599)	0.69 (-1.11)	1068 (819)	1075 (759)	0.48 (-1.48)	0.78 (-0.65)	0.70 (-0.83)
Global volume								
Left hippocampus	2086 (229)	2237 (196)	**0.012*** (-6.75)	2009 (208)	2166 (228)	**0.001*** (-10.19)	**0.046*** (-7.25)	0.30 (-3.17)
Right hippocampus	2145 (204)	2340 (205)	**0.001*** (-8.33)	2074 (185)	2220 (202)	**<0.001*** (-11.37)	**0.047*** (-6.58)	0.067^ (-5.13)
Subfield volumes								
Left CA1	2436 (321)	2421 (304)	0.56 (0.62)	2366 (330)	2511 (302)	0.78 (-2.28)	0.16 (-5.77)	0.20 (3.70)
Right CA1	2425 (300)	2551 (265)	0.090^ (-4.94)	2382 (258)	2471 (341)	**0.024*** (-6.62)	0.12 (-3.61)	0.60 (-3.12)
Left CA2-3	6789 (857)	7284 (832)	**0.031*** (-6.80)	6578 (995)	7012 (640)	**0.009*** (-9.70)	0.12 (-6.19)	0.38 (-3.73)
Right CA2-3	7303 (930)	7778 (851)	**0.043*** (-6.11)	7074 (838)	7547 (986)	**0.006*** (-9.06)	0.052^ (-6.26)	0.57 (-2.98)
Left CA4-DG	3836 (506)	4094 (462)	0.053^ (-6.30)	3680 (580)	4003 (361)	**0.007*** (-10.12)	**0.046*** (-8.07)	0.66 (-2.22)
Right CA4-DG	4032 (464)	4361 (468)	**0.009*** (-7.54)	3942 (455)	4128 (470)	**0.003*** (-9.61)	0.13 (-4.50)	0.19 (-5.34)
Left presubiculum	3521 (361)	3721 (364)	**0.027*** (-5.37)	3413 (361)	3635 (336)	**0.007*** (-8.28)	0.11 (-6.09)	0.35 (-2.32)
Right presubiculum	3413 (350)	3591 (377)	0.12 (-4.96)	3430 (344)	3396 (368)	0.30 (-4.48)	0.64 (1.00)	0.13 (-5.43)
Left subiculum	4680 (561)	4919 (439)	0.082^ (-4.86)	4476 (567)	4896 (482)	**0.007*** (-9.00)	**0.022*** (-8.57)	0.89 (-0.46)
Right subiculum	4694 (435)	4905 (442)	0.085^ (-4.30)	4613 (412)	4780 (455)	**0.020*** (-5.95)	0.10^ (-3.49)	0.63 (-2.54)
Left fimbria	498 (104)	498 (164)	0.90 (0.00)	491 (115)	507 (95)	0.83 (-1.58)	0.85 (-3.20)	0.99 (1.67)
Right fimbria	503 (90)	471(158)	0.25 (6.79)	521 (92)	485 (87)	0.11 (10.59)	0.24 (7.48)	0.80 (2.89)

Abbreviations:
*PTSD-only = patients with only posttraumatic stress disorder; PTSD-DID= patients with PTSD and dissociative identity disorder; All-PTSD= includes both PTSD-only and PTSD-DID patient groups. HC= healthy controls; * P-value ≤ 0.05; ^ 0.05 < P-value ≤ 0.1 (a trend)*

Hippocampal shape analysis

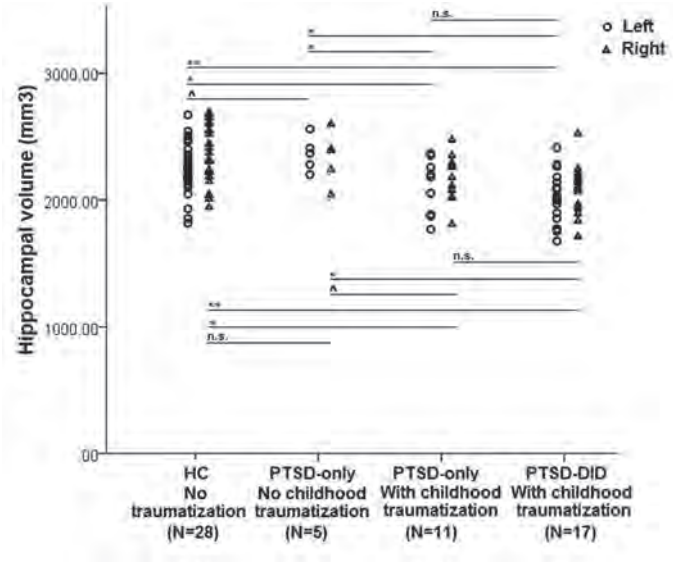
As compared with HC, All-PTSD (Figure 3.1b) as well as both PTSD-DID (Figure 3.1c) and PTSD-only (Figure 3.1e) showed deformations in the CA1, CA2-3 and subiculum. Direct comparison of shape measures between PTSD-DID and PTSD-only showed relative contractions in the CA1, CA2-3 and subiculum in PTSD-DID (Figure 3.1d). The results of these shape analyses did not survive multiple comparison correction with permutations. Uncorrected shape deformation results are presented for exploratory purposes because they support and inform on the significant volumetric results.

Figure 3.1 a) A schematic representation of the hippocampal subfields mapped onto a representative hippocampal surface obtained by averaging the surface from all the participants. In addition, 3D maps of regional hippocampal shape differences (uncorrected) are shown comparing (b) All-PTSD vs. HC, (c) PTSD-DID vs. HC, (d) PTSD-DID vs. PTSD-only and (e) PTSD-only vs. HC. Upper rows represent anterior view and lower rows represent posterior view.



Abbreviations:
PTSD-only = patients with only posttraumatic stress disorder; PTSD-DID= patients with PTSD and dissociative identity disorder; All-PTSD= includes both PTSD-only and PTSD-DID patient groups; HC= healthy controls.

Figure 3.2 Left and right hippocampal volumes in different diagnosis groups



Abbreviations:
*PTSD-only = patients with only posttraumatic stress disorder; PTSD-DID= patients with PTSD and dissociative identity disorder; HC= healthy controls; ** P-value<=0.001; * P-value ≤ 0.05; ^ 0.05 < P-value ≤ 0.1; n.s.: not significant*

Hippocampal volume and severity of childhood traumatization

Bilateral global hippocampal volumes were significantly, or at a trend level, negatively correlated with severity of childhood emotional neglect, physical neglect, emotional abuse, sexual abuse and total traumatization (Table 3.3 and Figure 3.3). Subfield volumes of the left CA1, CA2-3, CA4-DG and (pre) subiculum, also showed correlations with severity of childhood traumatizing events. The strongest correlations were observed between left presubiculum volume and total childhood trauma (r=-0.64, p<0.001).

Hippocampal volume and dissociative symptoms

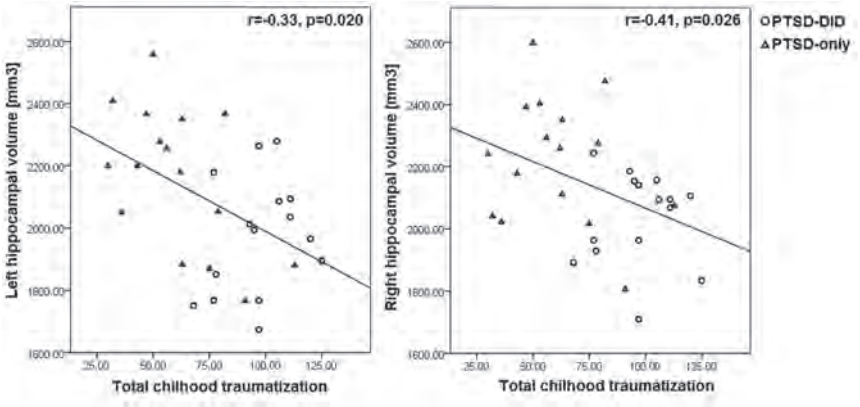
Significant negative correlations were found between severity of dissociative symptoms and the volumes of the left subiculum and presubiculum (Table 3.3). That is, the higher the severity of the psychoform and somatoform dissociative symptoms, the smaller the volume of the left subiculum and presubiculum.

Table 3.3 Correlations between hippocampal global and subfield volumes and severity of dissociative symptoms or childhood traumatizing events in the patients

	Partial correlation r(P-value)[1]							
	DES	SDQ-20	Childhood trauma questionnaire (CTQ)					
			emotional neglect	physical neglect	emotional abuse	physical abuse	sexual abuse	Total trauma
Global volume								
Left hippocampus	-0.11 (0.57)	-0.20 (0.29)	-0.49 (**0.006***)	-0.38 (**0.039***)	-0.32 (0.094^)	-0.24 (0.22)	-0.43 (**0.020***)	-0.33 (**0.020***)
Right hippocampus	-0.20 (0.29)	-0.22 (0.23)	-0.39 (**0.038***)	-0.37 (0.051^)	-0. 32 (0.093^)	-0.27 (0.16)	-0.44 (**0.018***)	-0.41 (**0.026***)
Subfield volumes								
Left CA1	-0.26 (0.15)	-0.15 (0.42)	-0.30 (0.11)	-0.13 (0.49)	-0.25 (0.19)	-0.22 (0.24)	-0.41 (**0.029***)	-0.32 (0.094^)
Right CA1	-0.15 (0.43)	0.001 (0.99)	-0.25 (0.18)	-0.25 (0.19)	-0.12 (0.54)	-0.05 (0.79)	-0.25 (0.19)	-0.21 (0.27)
Left CA2-3	-0.21 (0.25)	-0.20 (0.28)	-0.35 (0.064^)	-0.19 (0.32)	-0.36 (0.057^)	-0.24 (0.20)	-0.44 (**0.018***)	-0.38 (**0.044***)
Right CA2-3	-0.14 (0.44)	0.05 (0.79)	-0.34 (0.069^)	-0.30 (0.11)	-0.27 (0.15)	-0.15 (0.45)	-0.35 (0.059^)	-0.33 (0.081^)
Left CA4-DG	-0.25 (0.17)	-0.25 (0.17)	-0.37 (0.051^)	-0.26 (0.16)	-0.38 (**0.044***)	-0.31 (0.10^)	-0.42 (**0.022***)	-0.41 (**0.027***)
Right CA4-DG	-0.09 (0.63)	-0.05 (0.77)	-0.29 (0.12)	-0.27 (0.15)	-0.25 (0.18)	-0.13 (0.50)	-0.30 (0.12)	-0.29 (0.13)
Left presubiculum	-0.39 (**0.031***)	-0.49 (**0.005***)	-0.46 (**0.012***)	-0.60 (**0.001***)	-0.56 (**0.002***)	-0.59 (**0.001***)	-0.54 (**0.003***)	-0.64 (**<0.001***)
Right presubiculum	0.02 (0.90)	-0.21 (0.25)	-0.13 (0.51)	-0.17 (0.37)	-0.27 (0.15)	-0.26 (0.18)	-0.14 (0.45)	-0.22 (0.24)
Left subiculum	-0.37 (**0.040***)	-0.31 (0.086^)	-0.46 (**0.013***)	-0.38 (**0.041***)	-0.45 (**0.013***)	-0.46 (**0.013***)	-0.56 (**0.001***)	-0.54 (**0.002***)
Right subiculum	-0.17 (0.35)	-0.19 (0.31)	-0.33 (0.081^)	-0.31 (0.11)	-0.21 (0.26)	-0.12 (0.52)	-0.35 (0.060^)	-0.31 (0.10^)
Left fimbria	-0.03 (0.87)	0.20 (0.28)	-0.06 (0.72)	0.006 (0.98)	0.02 (0.90)	0.01 (0.95)	0.004 (0.98)	-0.002 (0.99)
Right fimbria	0.20 (0.27)	0.19 (0.31)	0.10 (0.96)	0.17 (0.37)	0.08 (0.69)	0.09 (0.63)	0.14 (0.45)	0.12 (0.54)

Abbreviations:
*CTQ= childhood trauma questionnaire; DES= dissociative experience scale; SDQ= somatoform dissociative questionnaire; PTSD= posttraumatic stress disorder; [1] Controlled for age and parenchymal volume; * P-value ≤ 0.05; ^ 0.05 < P-value ≤ 0.1 (a trend)*

Figure 3.3 Scatter plots of the bilateral global hippocampal volumes from PTSD-DID and PTSD-only groups in relation to total childhood traumatization (as assessed using CTQ)



Abbreviations:
PTSD-only = patients with only posttraumatic stress disorder; PTSD-DID= patients with PTSD and dissociative identity disorder; CTQ: Childhood Trauma Questionnaire.

DISCUSSION

This study is the first to investigate clinical correlates of global and regional morphological abnormalities of the hippocampus in DID and PTSD patients. As hypothesized, we found that in all patients with PTSD and patients with DID, relative to healthy controls, global hippocampal volume is smaller and regional volumetric abnormalities are localized in the subfields CA2-3, CA4-DG and subiculum. Furthermore, these findings are supported by evidence of hippocampal surface contractions in the subfields CA1, CA2-3 and subiculum. Another important finding is that within our patient sample, the severity of childhood traumatizing events, in particular emotional neglect and sexual abuse, was negatively correlated with global and subfield hippocampal volumes. However, severity of dissociative symptoms (psychoform or somatoform) was negatively associated with the volumes of the left presubiculum and subiculum only. These findings support a link between hippocampal morphological abnormalities and childhood traumatization in both DID and PTSD patients.

The subgroup with DID, who all had co-morbid PTSD (PTSD-DID), had significantly smaller global volumes as compared with HC (left: 10.19%; right:

11.37%) as well as compared with PTSD patients without DID (PTSD-only) (left: 7.25%; right: 6.58%). The PTSD-only group showed a trend level difference in the right global hippocampal volume when compared with HC (right: 5.13%; p=0.067), and *post hoc* analyses (see supplementary material S3.3) revealed that bilateral hippocampi were significantly smaller in those PTSD-only patients with a history of childhood onset traumatizing events (left: 7.11%; right: 7.31%), suggesting again that childhood traumatization is an important factor in the hippocampal abnormalities. These findings concur with prior neuroimaging studies in adult victims of childhood adversity, with or without PTSD (Andersen et al. 2008, Bremner et al. 2003) and in DID patients (Ehling, Nijenhuis & Krikke 2008, Irle et al. 2009, Stein et al. 1997, Tsai et al. 1999, Vermetten et al. 2006). Also, our findings support and advance a previous report of smaller hippocampal volume in DID patients with co-morbid PTSD (Vermetten et al. 2006) which was limited by the unmatched characteristics of their control group (Vermetten 2006), an issue we did not have in this study.

Smaller hippocampal volumes were particularly located in the subfields CA1, CA2-3, CA4-DG, and (pre)subiculum, a finding also supported by shape analysis results. The subiculum has specifically been associated with memory retrieval, whereas regions corresponding to CA2-3 are involved in the encoding of episodic information (Eldridge et al. 2005). The role of CA1 in encoding and retrieval of contextual memory has been reported in animal studies (Daumas et al. 2005). Therefore, abnormalities of any of these subfields could result in memory abnormalities and the localized deformations and gray matter loss in different hippocampal subfields observed in PTSD-DID and PTSD-only patients could underlie memory alterations reported in DID patients (Dorahy 2001) and the impaired (non-)declarative memory often reported in PTSD patients (for review see (Samuelson 2011)). Our study opens avenues to investigate the cognitive correlates of hippocampal abnormalities and we suggest that future research investigate the relationship between memory performance and hippocampal abnormalities in DID and PTSD with childhood traumatizing events.

Our findings of smaller volume and deformed shape of the hippocampal subfields in PTSD patients with childhood adversity and in DID patients are consistent with evidence of a relationship between stress and/or elevated level of glucocorticoids (the main stress-related hormones) and morphological alteration of the hippocampal CA1, CA2-3, CA4-DG and (pre)subiculum subfields

(Teicher, Anderson & Polcari 2012, Wang et al. 2010). Elevated levels of stress hormones can result in reduced branching of dendrites, reduced synaptic plasticity, neuronal loss or suppression of neurogenesis (Sapolsky 1993). The CA2-3 and subiculum subfields have the highest density of glucocorticoid receptors (Sarrieau et al. 1986) and hence are the most susceptible subfields to the adverse effect of stress. The CA1 neurons in the anterior hippocampus in humans project to the medial prefrontal cortex (Small et al. 2011). The morphological abnormalities of this subfield could perhaps indicate a potential disturbance in the prefrontal-limbic system, including in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis during stress (Herman et al. 2005). Therefore, they could possibly be, at least in part, related to the HPA axis dysfunction reported in the patients with PTSD (for a review see de Kloet et al. (2006)) or with a dissociative disorder (Simeon et al. 2007). The dentate gyrus is involved in neurogenesis and it has been suggested that childhood traumatization can suppress neurogenesis and hence result in smaller CA4-dentate gyrus subfield (Teicher, Anderson & Polcari 2012). This is of course conjecture and the direct relationship between hippocampal morphometric abnormalities and these stress hormone pathways and neuronal properties would need to be confirmed experimentally.

Our finding of a relationship between abnormalities of global and subfield hippocampal volume and severity of childhood traumatizing events in DID, provides a first neuroanatomical support for the hypothesis that the pathophysiology of DID is related to childhood traumatization (Van der Hart, Nijenhuis & Steele 2006, Reinders et al. 2003, Reinders et al. 2006, Reinders et al. 2012). Although, the present findings need to be confirmed by other neuroanatomical studies, they are in line with the negative correlations previously reported between severity of childhood traumatizing events and hippocampal global (Andersen et al. 2008, Dannlowski et al. 2012, Samplin et al. 2013) and subfield (Teicher, Anderson & Polcari 2012) volumes in adults from the general community with a history of early-life adversity. However, as the current study is a cross-sectional study we could not examine direct or indirect links between these measures and hence longitudinal studies are needed to further explore these.

In the two patient groups, severity of dissociative symptom was negatively correlated with the volume of presubiculum and the subiculum, but not with global hippocampal volumes. So far, limited studies have investigated this

relationship in traumatized individuals and some studies reported a negative relationship consistent with our results (Bremner et al. 2003, Ehling, Nijenhuis & Krikke 2008, Stein et al. 1997), but other studies did not find any significant association (Bremner et al. 1995, Nardo et al. 2013). While it is possible that the hippocampal morphological abnormalities in our patient samples were at least, in part, involved in the dissociative symptoms, it can be speculated that the associations between morphological measures and dissociative symptoms are actually mediated by childhood traumatization. Future studies can explore this relationship by including individuals with dissociative symptoms but without childhood traumatization.

It has been reported that some psychiatric medications including typical antipsychotics (Chakos et al. 2005), anti-epileptics (Watanabe et al. 1992) and antidepressants (Vermetten et al. 2003) can change the hippocampal morphology. Therefore, it might be argued that our findings of smaller hippocampal global and subfield volumes in PTSD-DID, and to a lesser extent in PTSD-only, are due to the higher level of medications in these patients. However, when patients with a history of using typical antipsychotics (supplementary Table S3.1) or anti-epileptics were excluded (supplementary Table S3.2), the majority of our results remained preserved. Nevertheless, when patients with a history of using antidepressants (i.e., 10 PTSD-DID and 2 PTSD-only) were excluded the group differences in the hippocampal global volume remained significant but the group differences in the subfield volumes became less or non-significant (see supplementary Tables S3.3). The latter finding can be as a result of the insufficient statistical power to detect the subtle changes due to the exclusion of a large portion of the patients. Altogether, the results of these *posthoc* analyses may indicate that the smaller hippocampal global and subfield volume in PTSD-DID and PTSD-only as compared with HC are robust findings and are not due to the history of medication usage.

Some strengths and limitations: although our sample size of 17 PTSD-DID and 16 PTSD-only patients can be considered as modest, it is in fact the largest sample of individuals with DID in which hippocampal morphology has been studied. PTSD severity was evaluated differently across the two patient groups limiting us to investigate the morphological correlates of PTSD severity. Our findings of more pronounced morphological abnormalities in DID might be due to an interaction between (co-morbid) PTSD severity and childhood traumatization (Van Voorhees et al. 2012). Medication effects

were tested (see supplementary material S3.2) and showed that the smaller hippocampal volume in PTSD-DID as compared with HC is a robust finding. However, the shape analyses did not survive multiple comparison correction, which is likely due to insufficient statistical power for conducting multiple tests across the hippocampal surface. Nevertheless, permutation testing can be considered too conservative in this context, as all the tests are treated independently, when in fact many of the surface points are highly related.

In conclusion, we provide novel evidence that smaller hippocampal global and subfield volumes and contractions of hippocampal surface in PTSD patients, with or without DID, are related to the severity of childhood traumatizing events and dissociative symptoms. Our findings are in line with the clinical observation that DID is related to chronic childhood abuse and neglect. These findings can help to understand the neurobiological mechanisms involved in PTSD and DID.

Acknowledgements

S. Chalavi is supported by a David Caul graduate research grant from the International Society for the Study of Trauma and Dissociation (ISSTD) (http://www.isst-d.org/about/awards.htm). A.A.T.S. Reinders received support from the Netherlands Organization for Scientific Research (www.nwo.nl), NWO-VENI grant no. 451-07-009. This work was supported by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. P. Dazzan's research is supported partially by a King's College London Translational Research Grant and the Psychiatry Research Trust and NARSAD. AW Toga acknowledges grant P41EB015922.

The authors would like to thank all the participants and their therapists. We also would like to thank J.A. den Boer, R. Renken, A. Nederveen, A.J. Sibeijn-Kuiper, J. Streurman and R. van Luijk-Snoeks, S. van den Berg-Faay for their assistance with data acquisition, M. Jongsma and J. Reisel for their assistance with patient inclusion and H. Hofstetter for her help with the initial phases of the project.

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SUPPLEMENTARY MATERIAL

FOR CHAPTER 3 ENTITLED

—

ABNORMAL HIPPOCAMPAL MORPHOLOGY IN DISSOCIATIVE IDENTITY DISORDER AND POSTTRAUMATIC STRESS DISORDER CORRELATES WITH CHILDHOOD TRAUMA AND DISSOCIATIVE SYMPTOMS

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S3.1 Detailed image acquisition and analysis methods

Image acquisition

Identifying individuals with posttraumatic stress disorder (PTSD), with or without dissociative identity disorder (DID), willing and able to participate in a neuroimaging study is known to provide a great challenge. As minimizing travel time increases the likelihood of participation, participants were scanned in the closest of two (University Medical Center Groningen (UMCG) and of the Amsterdam Medical Center (AMC)) 3T MR scanners (Philips Medical Systems, Best, NL) in The Netherlands. Prior to starting, a reproducibility study was conducted that resulted in an optimized structural MRI protocol with a high contrast-to-noise ratio (important for manual and automated segmentation procedures) and a high reproducibility between the two centers (Chalavi et al. 2012). At both centers T1-weighted anatomical MR scans were acquired (MPRAGE, TR=9.95ms, TE=5.6ms, flip-angle=8°, 1x1x1mm voxels, number of slices=160, total scan-time=10m14s). All-PTSD patients and their matched HC were scanned interleaved within a short time interval to avoid an interaction between group and time dependent scanner fluctuations. The samples were balanced over the two centers: twenty All-PTSD patients (ten PTSD-DID, ten PTSD-only) and nineteen HC were scanned at UMCG. Two structural MRI scans were collected from each subject whenever possible (fifteen PTSD-DID patients and fourteen HC). Where both scans were artifact-free, the first scan was used. Four HC subjects were excluded due to the presence of (motion) artifacts in the MRI scan. A total of 17 PTSD-DID, 16 PTSD-only and 28 HC subjects were included in the demographic and morphological analyses.

Image analysis

Manual measures of global volume and shape analysis of the hippocampus

Non-cortical tissue was removed from the MR images using the Brain Extraction Tool (BET) (Smith 2002) and head alignment was standardized by rigidly aligning the individual MR images with the average brain template (ICBM452) using FSL-FLIRT. The hippocampi were manually traced using MultiTracer (Woods 2003) by a single rater (SC), who was blind to all demographical and clinical variables and was trained by an expert (JHC) in this field and obtained

good inter- and intra-rater reliabilities according to the established protocol (Thompson et al. 2004). The intraclass correlation coefficients for this rater were 0.94 and 0.97 for the left and right hippocampus, respectively, which are comparable to those in previously published studies (Cole et al. 2010). The outline of each hippocampus was traced in contiguous coronal brain sections while the digitized surface contours were displayed simultaneously in all three viewing planes to facilitate the accurate identification of boundaries (Thompson et al. 2004). Hippocampal global volumes obtained from these tracings were statistically analyzed.

To assess the shape deformations of different hippocampal subfields an anatomical surface mesh modeling method (Thompson et al. 2004) matched equivalent hippocampal surface points across subjects following manual tracing of the hippocampal boundaries. In brief: localized gray matter contractions and expansions of the hippocampal surface were established corresponding to the CA1, CA2-3 and subiculum (Figure 3.1a). In each individual the medial core, a central 3D curve threading down the long axis of the structure, was computed. From each point on the hippocampal surface a radial distance measure was derived to the medial core. As the same surface grid was imposed on all subjects' hippocampi in the same coordinate space, statistical comparisons were made at each hippocampal surface point between the groups to index contrasts on a local scale. Probability values from these statistical comparisons were mapped onto an average hippocampal shape for the entire sample to generate a 3D representation of the structural differences between the groups. The approximate overlay of the hippocampal subfields was defined based on the Duvernoy atlas (Duvernoy 1988).

S3.2 Effect of medication

It has been reported that some psychiatric medications including typical antipsychotics (Chakos et al. 2005), anti-epileptics (Watanabe et al. 1992) and antidepressants (Vermetten et al. 2003) change the hippocampal morphology. In this study in order to ascertain genuine findings we repeated the analyses after excluding posttraumatic stress disorder patients with (PTSD-DID) or without (PTSD-only) dissociative identity disorder (DID) and a history of different types of psychiatric medications.

The volumetric analyses were repeated three times while excluding the patients with a history of using (i) typical antipsychotics (3 PTSD-DID) (supplementary Table S3.1), (ii) anti-epileptics (4 PTSD-DID) (supplementary Table S3.2), and (iii) antidepressants (10 PTSD-DID and 2 PTSD-only) (supplementary Table S3.3). To test the effect of PTSD diagnosis, first volumetric measurements were compared between All-PTSD vs. HC (HC: healthy controls) using analysis of covariance (ANCOVA), with group and MRI center as independent factors and age and parenchymal volume as covariates. The analysis was followed by two-sample t-tests to compare left and right hippocampal volumes separately between: 1) PTSD-DID vs. HC, 2) PTSD-DID vs. PTSD-only, and 3) PTSD-only vs. HC.

When PTSD-DID patients with a history of using typical antipsychotics were excluded (supplementary Table S3.1), the majority of the findings remained significant and only the difference in the right hippocampal global volume in PTSD-DID vs. PTSD-only comparison and right CA1 in the PTSD-DID vs. HC comparison changed from significant to trend levels ($p=0.073$ and $p=0.059$, respectively).

After excluding PTSD-DID patients with a history of using anti-epileptics (supplementary Table S3.2), we found that the effect size of group differences for PTSD-DID vs. HC as well as PTSD-DID vs. PTSD-only became larger for right and especially left hippocampal global volumes and the differences between the PTSD-DID and PTSD-only became significant in the bilateral hippocampal global volume and volume of the left CA1, right CA2-3, bilateral CA4-DG, bilateral subiculum. This may indicate that PTSD-DID patients with a history of using anti-epileptic drugs had *larger* hippocampal volumes compared with those of PTSD-DID patients without a history of using anti-epileptic drugs and therefore resulted in an underestimation of the hippocampal reductions in the PTSD-DID group.

When PTSD-DID and PTSD-only patients with a history of using antidepressants were excluded from the volumetric analyses (supplementary Table S3.3) the results of smaller left and right hippocampal volume in PTSD-DID relative to HC became less significant, which is most likely caused by insufficient statistical power. However, the pattern of differences remained the same.

In sum: The results of these *post hoc* tests show that smaller hippocampal volume in PTSD-DID compared with HC (Table 3.2 main manuscript) was a robust finding and was not due to the history of medication.

S3.3 PTSD with childhood onset traumatization

Experienced inter-personal trauma as reported by PTSD-only patients during the Clinician Administered PTSD Scale (CAPS) interview included: emotional neglect (n=4), physical and sexual abuse/violence (n=13), attack with a weapon (n=3) and witnessing drowning of a family member (n=1). Eleven of the PTSD-only patients reported experiencing multiple types of interpersonal traumas during their childhood (n=6) or trauma starting from childhood and continuing into their adult life (n=5). The remaining 5 PTSD-only patients reported experiencing trauma only in their adult life. This is while all the PTSD-DID patients reported childhood traumatic experiences on the Trauma Experience Checklist (TEC) (Nijenhuis, Van der Hart & Kruger 2002). To investigate the childhood trauma-related nature of smaller hippocampal (global and subfield) volumes in PTSD-only and PTSD-DID patients, we repeated the pairwise comparisons between groups by removing those five PTSD-only patients with only adult trauma. Results of this *post hoc* test revealed that after excluding PTSD-only patients with only adult trauma, bilateral hippocampal global volumes in the PTSD-only became significantly smaller compared with HC. Left and right global hippocampal volumes of the PTSD-only group became significantly smaller and the volume differences changed from 3.17 % and 5.13% in the original analysis to 7.11% and 7.31% in the *post hoc* analysis. Interestingly, bilateral hippocampal global volumes did not differ significantly between the PTSD-DID and PTSD-only groups anymore. With regard to the hippocampal subfield volumes, the *post hoc* analysis revealed that in addition to the findings of the main analysis, as compared with HC, All-PTSD patients had smaller volumes of the left CA4-DG and bilateral subiculum. PTSD-only group had smaller right presubiculum and trends for smaller right CA4-DG ($p=0.059$) and left presubiculum ($p=0.074$) as compared with HC. Furthermore, when the shape analysis was repeated for the second *post hoc* test, we found a trend ($p=0.090$) for a significant pattern of deformations for All-PTSD vs. HC comparison. The results revealed that after excluding PTSD-only patients with only adult trauma, the results became more significant for both hippocampal volume and shape.

Table S3.1 Statistical analyses of hippocampal global (mm^3) and subfield (0.5 mm^3) volumes after excluding patients with a history of using typical antipsychotics

Measurement	All-PTSD to HC comparison			Different group comparisons				
	Mean (SD)		t-test: P Value (change%)	Mean (SD)		t-test: P Value (change%)		
	All-PTSD (n=30)	HC (n=28)	All-PTSD vs. HC	PTSD-DID (n=14)	PTSD-only (n=16)	PTSD-DID vs. HC	PTSD-DID vs. PTSD-only	PTSD-only vs. HC
Global volume								
Left hippocampus	2079 (238)	2237 (196)	0.018* (-7.06)	1980 (216)	2166 (228)	0.001* (-11.49)	0.036* (-8.59)	0.31 (-3.17)
Right hippocampus	2149 (214)	2340 (205)	0.002* (-8.16)	2067 (204)	2220 (202)	<0.001* (-11.67)	0.073^ (-6.89)	0.076^ (-5.13)
Subfield volumes								
Left CA1	2421 (325)	2421 (304)	0.58 (-0.01)	2318 (330)	2511 (302)	0.61 (-4.26)	0.13 (-7.68)	0.20 (3.70)
Right CA1	2437 (306)	2551 (265)	0.18 (-4.47)	2397 (268)	2471 (341)	0.059^ (-6.01)	0.20 (-2.99)	0.61 (-3.12)
Left CA2-3	3747 (869)	7284 (832)	0.030* (-7.38)	6443 (1014)	7012 (640)	0.004* (-11.55)	0.059^ (-8.12)	0.38 (-3.73)
Right CA2-3	7320 (957)	7778 (851)	0.076^ (-5.89)	7062 (888)	7547 (986)	0.009* (-9.21)	0.055^ (-6.43)	0.57 (-2.98)
Left CA4-DG	3812 (515)	4094 (462)	0.045* (-6.90)	3593 (587)	4003 (361)	0.002* (-12.23)	0.014* (-10.23)	0.66 (-2.22)
Right CA4-DG	4030 (476)	4361 (468)	0.014* (-7.59)	3918 (475)	4128 (470)	0.002* (-10.16)	0.087^ (-5.09)	0.19 (-5.34)
Left presubiculum	3515 (366)	3721 (364)	0.031* (-5.55)	3378 (362)	3635 (336)	0.006* (-9.23)	0.085^ (-7.06)	0.35 (-2.32)
Right presubiculum	3389 (328)	3591 (377)	0.052^ (-5.61)	3382 (291)	3396 (368)	0.11 (-5.82)	0.91 (-0.41)	0.12 (-5.43)
Left subiculum	4670 (588)	4919 (439)	0.11 (-5.06)	4411 (607)	4896 (482)	0.006* (-10.32)	0.018* (-9.90)	0.90 (-0.46)
Right subiculum	4706 (450)	4905 (442)	0.14 (-4.06)	4620 (446)	4780 (455)	0.029* (-5.80)	0.11 (-3.34)	0.64 (-2.54)
Left fimbria	495 (108)	498 (164)	0.79 (-0.71)	481 (124)	507 (95)	0.63 (-3.42)	0.66 (-5.01)	0.99 (1.67)
Right fimbria	496 (90)	471 (158)	0.37 (5.20)	508 (95)	485 (87)	0.21 (7.83)	0.37 (4.80)	0.79 (2.89)

Abbreviations:
*PTSD= posttraumatic stress disorder; PTSD-DID= dissociative identity disorder; All-PTSD= includes patients with PTSD-only and patients with DID and co-morbid PTSD; HC= healthy controls; * P-value ≤ 0.05; ^ 0.05 < P-value ≤ 0.1 (a trend)*

Table S3.2 Statistical analyses of hippocampal global (mm^3) and subfield (0.5 mm^3) volumes after excluding patients with a history of using anti-epileptics

Measurement	All-PTSD to HC comparison			Different group comparisons				
	Mean (SD)		t-test: P Value (change%)	Mean (SD)		t-test: P Value (change%)		
	All-PTSD (n=29)	HC (n=28)	All-PTSD vs. HC	PTSD-DID (n=13)	PTSD-only (n=16)	PTSD-DID vs. HC	PTSD-DID vs. PTSD-only	PTSD-only vs. HC
Global volume								
Left hippocampus	2061 (230)	2237 (196)	0.006* (-7.87)	1932 (160)	2166 (228)	<0.001* (-13.63)	0.003* (-10.80)	0.29 (-3.17)
Right hippocampus	2134 (206)	2340 (205)	0.001* (-8.80)	2027 (160)	2220 (202)	<0.001* (-13.38)	0.011* (-8.60)	0.066^ (-5.13)
Subfield volumes								
Left CA1	2429 (291)	2421 (304)	0.68 (0.31)	2328 (252)	2511 (302)	0.37 (-3.86)	0.046* (-7.30)	0.15 (3.70)
Right CA1	2414 (291)	2551 (265)	0.071^ (-5.34)	2345 (209)	2471 (341)	0.015* (-8.06)	0.077^ (-5.10)	0.60 (-3.12)
Left CA2-3	6803 (688)	7284 (832)	0.019* (-6.61)	6545 (679)	7012 (640)	0.003* (-10.15)	0.057^ (-6.67)	0.33 (-3.73)
Right CA2-3	7259 (895)	7778 (851)	0.031* (-6.67)	6906 (639)	7547 (986)	0.002* (-11.22)	0.020* (-8.49)	0.57 (-2.98)
Left CA4-DG	3843 (420)	4094 (462)	0.035* (-6.14)	3645 (416)	4003 (361)	0.002* (-10.96)	0.014* (-8.93)	0.64 (-2.22)
Right CA4-DG	4005 (448)	4361 (468)	0.005* (-8.16)	3854 (386)	4128 (470)	0.001* (-11.63)	0.049* (-6.64)	0.18 (-5.34)
Left presubiculum	3535 (325)	3721 (364)	0.033* (-5.00)	3413 (274)	3635 (336)	0.008* (-8.28)	0.11 (-6.10)	0.32 (-2.32)
Right presubiculum	3388 (337)	3591 (377)	0.065^ (-5.66)	3377 (310)	3396 (368)	0.14 (-5.94)	0.98 (-0.54)	0.13 (-5.43)
Left subiculum	4688 (473)	4919 (439)	0.058^ (-4.70)	4432 (322)	4896 (482)	0.001* (-9.90)	0.004* (-9.48)	0.91 (-0.46)
Right subiculum	4672 (432)	4905 (442)	0.058^ (-4.76)	4538 (375)	4780 (455)	0.007* (-7.48)	0.041* (-5.07)	0.64 (-2.54)
Left fimbria	500 (109)	498 (164)	0.93 (0.26)	491 (127)	507 (95)	0.90 (-1.46)	0.91 (-3.08)	0.99 (1.67)
Right fimbria	500 (91)	471 (158)	0.32 (6.06)	518 (97)	485 (87)	0.18 (9.97)	0.32 (6.88)	0.79 (2.89)

Abbreviations:
*PTSD= posttraumatic stress disorder; PTSD-DID= dissociative identity disorder; All-PTSD= includes patients with PTSD-only and patients with DID and co-morbid PTSD; HC= healthy controls; * P-value ≤ 0.05; ^ 0.05 < P-value ≤ 0.1 (a trend)*

Table S3.3 Statistical analyses of hippocampal global (mm^3) and subfield (0.5 mm^3) volumes after excluding patients with a history of using antidepressants

Measurement	All-PTSD to HC comparison			Different group comparisons				
	Mean (SD)		t-test: P Value (change%)	Mean (SD)		t-test: P Value (change%)		
	All-PTSD (n=21)	HC (n=28)	All-PTSD vs. HC	PTSD-DID (n=7)	PTSD-only (n=14)	PTSD-DID vs. HC	PTSD-DID vs. PTSD-only	PTSD-only vs. HC
Global volume								
Left hippocampus	2127 (237)	2237 (196)	0.10^ (-4.92)	2024 (231)	2179 (230)	0.022* (-9.52)	0.096^ (-7.11)	0.52 (-2.59)
Right hippocampus	2182 (223)	2340 (205)	0.016* (-6.75)	2114 (252)	2215 (209)	0.014* (-9.66)	0.27 (-4.56)	0.093^ (-5.34)
Subfield volumes								
Left CA1	2525 (321)	2421 (304)	0.22 (4.26)	2497 (357)	2538 (314)	0.70 (3.12)	0.39 (-1.64)	0.094^ (4.54)
Right CA1	2483 (286)	2551 (265)	0.34 (-2.65)	2408 (213)	2520 (317)	0.12 (-5.57)	0.16 (-4.44)	0.99 (-1.18)
Left CA2-3	7003 (805)	7284 (832)	0.19 (-3.87)	6897 (1134)	7055 (629)	0.20 (-5.32)	0.47 (-2.24)	0.53 (-3.15)
Right CA2-3	7531 (1003)	7778 (851)	0.31 (-3.18)	7246 (1158)	7673 (929)	0.12 (-6.84)	0.17 (-5.56)	0.99 (-1.35)
Left CA4-DG	3977 (486)	4094 (462)	0.35 (-2.87)	3852 (698)	4039 (354)	0.18 (-5.92)	0.24 (-4.63)	0.95 (-1.35)
Right CA4-DG	4125 (506)	4361 (468)	0.079^ (-5.43)	4017 (630)	4178 (448)	0.058^ (-7.89)	0.25 (-3.86)	0.39 (-4.20)
Left presubiculum	3603 (334)	3721 (364)	0.24 (-3.18)	3583 (322)	3613 (351)	0.34 (-3.72)	0.77 (-0.84)	0.41 (-2.90)
Right presubiculum	3426 (373)	3591 (377)	0.19 (-4.60)	3568 (397)	3354 (354)	0.98 (-0.64)	0.27 (6.36)	0.11 (-6.58)
Left subiculum	4852 (516)	4919 (439)	0.53 (-1.37)	4719 (560)	4918 (501)	0.26 (-4.06)	0.26 (-4.04)	0.87 (-0.02)
Right subiculum	4737 (428)	4905 (442)	0.19 (-3.43)	4649 (379)	4781 (458)	0.098^ (-5.22)	0.21 (-2.76)	0.71 (-2.54)
Left fimbria	483 (116)	498 (164)	0.67 (-3.00)	437 (141)	507 (100)	0.34 (-12.27)	0.39 (-13.67)	0.99 (1.63)
Right fimbria	485 (72)	471 (158)	0.61 (2.88)	505 (32)	474 (85)	0.52 (7.22)	0.63 (6.46)	0.89 (0.71)

Abbreviations:
*PTSD= posttraumatic stress disorder; PTSD-DID= dissociative identity disorder; All-PTSD= includes patients with PTSD-only and patients with DID and co-morbid PTSD; HC= healthy controls; * P-value ≤ 0.05; ^ 0.05 < P-value ≤ 0.1 (a trend)*

This shows that hippocampal size differs between PTSD-only with childhood onset and PTSD-only with adult onset trauma and suggests that future research in PTSD needs to carefully assess the presence of childhood trauma to limit heterogeneity.

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CHAPTER 6

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SUMMARY AND GENERAL DISCUSSION

Purposes of the thesis

Dissociative identity disorder (DID) is characterized by the experience of two or more distinct personality states, recurrent gaps in the recall of everyday events or important personal information, and/or traumatic events that are inconsistent with ordinary forgetting, all of which should not be an outcome of substance abuse or general medication (American Psychiatric Association 2013). DID is distinguished by two types of prototypical dissociative personality states 1) a trauma-related personality state (TPS), in which traumatic memories are recognized as first-hand autobiographical memories, and which shows emotional and somatic responses to trauma cues; and 2) a neutral personality state (NPS) characterized by partial or complete dissociative amnesia for traumatic memories, which lacks a first-hand sense of personal autobiographical experience.

Although DID is officially recognized in the Diagnostic and Statistical Manual of Mental Disorders for decades (American Psychiatric Association 1980), it is surrounded with controversy (Gillig 2009, Dalenberg et al. 2012, Lynn et al. 2014) and probably is the most disputed of psychiatric diagnoses (Reinders 2008, Reinders et al. 2012). Unfamiliarity with the spectrum of dissociative disorders, disbelief that they exist, or lack of knowledge and appreciation of the epidemiology could lead to under- and misdiagnosis by clinicians (Coons 1998, Brand et al. 2012a). Many scientists and clinicians still question the validity of DID as a psychiatric disorder (Merckelbach, Devilly & Rassin 2002, Piper, Merskey 2004a, Sar 2005, Coons 2005, Fraser 2005, Pope et al. 2006, Paris 2012, Lynn et al. 2014) and debates regarding the etiology of DID between proponents of the *fantasy model* (Merckelbach, Muris 2001, Merckelbach, Devilly & Rassin 2002, Piper, Merskey 2004a, Piper, Merskey 2004b, Pope et al. 2006) and *trauma model* (Putnam 1992, Gleaves 1996, Spiegel 2006, Van der Hart, Nijenhuis & Steele 2006, Dell, O'neil 2009, Spiegel et al. 2011) of dissociation respectively, are ongoing.

The *fantasy model* regards DID as a simulation mediated by high suggestibility and/or fantasy proneness, suggestive psychotherapy and other suggestive sociocultural influences (Merckelbach, Rassin & Muris 2000, Merckelbach, Horselenberg & Muris 2001, Rassin, Merckelbach & Spaan 2001, Giesbrecht, Merckelbach 2006, Giesbrecht et al. 2007, Giesbrecht et al. 2008, Lynn et al. 2012). It also suggests that mild cognitive impairment (Giesbrecht et al.

2008) or sleep disturbances (Van Heugten-van der Kloet et al. 2014) can be factors of influence in DID. The fantasy model has been rarely tested in studies involving DID patients (Loewenstein 2007, Van der Hart, Nijenhuis 2009, Reinders et al. 2012) and evidence that the complex phenomenology and psychobiology of DID can be created and sustained over time by these factors is lacking (Gleaves 1996, Brown, Frischholz & Schefin 1999, Xiao et al. 2006, Loewenstein 2007).

The *trauma model* considers DID to be related to a combination of factors that includes chronic emotional neglect and emotional, physical, and/or sexual abuse from early childhood, insufficient integrative capacity, attachment problems, and lack of affect-regulation by caretakers (Putnam 1992, Gleaves 1996, Spiegel 2006, Van der Hart, Nijenhuis & Steele 2006, Dell, O'neil 2009, Spiegel et al. 2011). Within the trauma-related view DID is thought to be a severe form of posttraumatic stress disorder (PTSD), belonging to the far end of the spectrum of trauma-related psychiatric disorders (Spiegel 1984, Van der Hart, Nijenhuis & Steele 2005, Van der Hart, Nijenhuis & Steele 2006).

Dalenberg et al. (2012) reviewed the evidence for both the trauma- and fantasy model and concluded that pathological dissociation is predictive of a trauma history, even when controlling for fantasy proneness. Little support was found for the idea that the relationship between trauma and dissociation is due to suggestibility or confabulated traumatic memories. Proponents of the fantasy model (Lynn et al. 2014) suggested in response that Dalenberg et al. did not adequately consider the lack of corroboration of abuse in many studies and offered a series of critiques. In reply, Dalenberg et al. (2014) addressed these critiques and demonstrated among others a pattern of antecedent trauma to dissociation and positive response to trauma psychotherapy of dissociative patients. Although it would seem a promising step towards increased understanding of DID pathology, no neurobiological, or other, studies directly compared diagnosed genuine DID patients with PTSD, DID simulating healthy controls (DID-S) and/or HC.

Understanding the (neuro)biological consequences of childhood trauma could be crucial for identifying which individuals go on to develop physical or psychiatric disorders following traumatic experiences, whereas others remain resilient in the face of similar traumatic exposure (Baumeister et al. 2015). Objective neuroscientific information, such as structural and functional

neuroimaging data, as well as validated psychological measures could aid in understanding the correlates of DID. Studies incorporating tests for both the trauma and fantasy model of DID could help to further elucidate the etiological mechanisms for this controversial psychiatric disorder. Several studies indicated a relationship between traumatization and structural brain differences (Vythilingam et al. 2002, Bremner et al. 2003, Karl et al. 2006, Van Harmelen et al. 2010, Dannlowski et al. 2012, Kuhn, Gallinat 2013). Recently, a structural neuroimaging study, described in chapter 3, showed evidence that smaller hippocampal volume is related to the severity of childhood traumatization and dissociative symptoms in both PTSD and DID patients (Chalavi et al. 2014), which supports the trauma model of DID.

Traumatic experiences and stress have also been associated with influences on working memory functioning. Stress has been associated with detrimental effects on working memory functioning (Arnsten 1998) and it negatively affect prefrontal cortex (PFC) operations (Arnsten 2009). Successful cognitive regulation relies on intact executive functioning and engagement of the prefrontal cortex, both of which are rapidly impaired by the deleterious effects of stress (Raio et al. 2013). Concerning neuropsychological processes such as working memory, the trauma model postulates that the biology of dissociation will fit with a theory of a brain-based regulatory response to fear or other extreme emotion (Lanius et al. 2010) and that the experience of trauma and high levels of stress are related to cognitive deficits (Vasterling et al. 2002). The fantasy model hypothesizes trauma to be less important for cognitive deficits as exhibited by dissociative individuals. Cognitive deficiencies inherent to dissociation are considered as a primary source of the trauma reported (Merckelbach, Horselenberg & Schmidt 2002) and mild executive functioning disorder in dissociative individuals is thought to be present in the presence and absence of trauma stimuli (Dalenberg et al. 2012). In PTSD, neuroimaging studies have demonstrated working memory deficits associated with reduced prefrontal activation (Clark et al. 2003, Falconer et al. 2008, Moores et al. 2008, Aupperle et al. 2012, Patel et al. 2012, Scott et al. 2015). Taken together the effect of stress on WM performance and the role of cognitive deficiencies on dissociation, and the fact that traumatic experiences, stress and dissociative processes have all been associated with influences on working memory functioning it is of interest to study the neural correlates of working memory in DID and directly compare these results with PTSD. This will also inform on the validity of the trauma model as it regards DID as a severe form of PTSD.

Aims of the thesis

This thesis aimed to increase our understanding of the etiopathogenesis of DID. To this end empirical studies from three research domains were included in this thesis: first a psychological study was conducted in which symptom measures from both the trauma and fantasy perspective were included and administered to DID, PTSD, HC and DID-S. For part of the measures personality-state differences were investigated as well, because the degree to which these states could be simulated by motivated role-playing might be personality-state dependent. Similarities between DID and DID-simulating controls would provide evidence in favor of the fantasy model, whereas comparability of findings between DID and PTSD would be more in agreement with the trauma model of dissociation. A second study using brain imaging measures examined neuroanatomical abnormalities in DID compared with PTSD and HC. Whereas similarities between DID and PTSD could be indicative of a trauma model, differences may point to disorder specific abnormalities. The third and fourth study obtained functional brain imaging measures to investigate working memory functioning and its neural correlates in DID, PTSD and HC in order to test the trauma model, and in DID and DID-simulating mentally healthy controls in order to test the fantasy model, respectively.

Summary of findings

Psychological: the trauma and fantasy model tested for symptom measures

In chapter 2 we aimed to determine which etiological model receives the most support in a direct comparison by including the above matched groups and testing both the trauma and fantasy model using well-validated measures from both perspectives. We found consistently more evidence for a trauma model than for a fantasy model of DID. In general, a clear pattern was found for the trauma-related measures, in which DID patients showed the most severe symptoms. This is supportive for the trauma model's hypothesis. A continuum across groups, where DID patients showed the highest rates of trauma-related symptoms, followed by PTSD, and then the healthy control groups, can be seen as consistent with the idea that DID is a severe form of PTSD (Spiegel 1984, Van der Hart, Nijenhuis & Steele 2006).

The hypothesized relationship between dissociation and suggestibility is perhaps the most crucial point of distinction between the two models (Dalenberg et al. 2014). In conclusion of a debate between proponents of both models (Dalenberg et al. 2012, Lynn et al. 2014, Dalenberg et al. 2014), it was agreed that meta-analysis of available literature provides no support that dissociative individuals are suggestible (Dalenberg et al. 2014). It was proposed that it would be helpful for studies on dissociation, suggestibility, and fantasy proneness to include controls for comorbid pathological conditions (Dalenberg et al. 2014). With regard to fantasy measures, DID patients were not more fantasy prone than patients with PTSD or healthy actresses, which contradicts the fantasy model's hypotheses. Furthermore, DID patients did not prove to be more suggestible or prone to false memories, which is also in disagreement with the fantasy model's main ideas. On the other hand, DID patients showed elevations on a malingering test on scales including amnesia, affective, psychotic, and neurological symptoms, which is more in line with the fantasy model.

Neurostuctural: hippocampal morphology and childhood trauma

In chapter 3 we studied hippocampal morphology differences between DID, PTSD and HC in relation to childhood maltreatment. Both volumetric changes and regional shape deformations were investigated, which both benefited from an earlier MR sequence calibration and optimization study from our group (Chalavi et al. 2012) providing MR images with a high gray-white matter contrast. Results revealed that DID patients had smaller left and right hippocampal volume as compared with PTSD and HC. PTSD patients showed a trend significant smaller right hippocampal volume compared with HC. These findings are in correspondence with previous structural imaging studies in DID (Tsai et al. 1999, Vermetten et al. 2006, Ehling, Nijenhuis & Krikke 2008, Irle et al. 2009), PTSD (Gurvits et al. 1996, Kitayama et al. 2005) and victims of childhood maltreatment (Dannlowski et al. 2012). In addition, hippocampal regional shape contractions were found in different hippocampal subfields, i.e. the CA1, CA2-3 and subiculum, for DID and PTSD as compared with HC. These deformations were more widespread in the DID group. As results from shape analysis did not survive multiple comparison correction, they should be interpreted with caution. Nonetheless, they provide relevant suggestions for future investigation. Another important finding in chapter 3 is the association between smaller hippocampal volume and contractions of

hippocampal surface on one hand, and the severity of childhood traumatizing events and dissociative symptoms in PTSD and DID patients on the other hand. These findings are in line with previous studies (Andersen et al. 2008, Teicher, Anderson & Polcari 2012, Dannlowski et al. 2012) and provide empirical support for the clinical observation that DID is related to chronic childhood abuse and neglect. Chapter 3 conclusions can aid in understanding the neurobiological mechanisms involved in PTSD and DID, which is congruent with the trauma model's hypotheses.

Functional imaging: neural correlates of working memory functioning in DID

In chapter 4 we have investigated personality-state-dependent brain activation for working memory in DID in comparison to PTSD and HC. Whereas NPS of DID, HC and PTSD showed similar activation in areas of the prefrontal parietal network, TPS of DID showed limited activation in this network. In NPS, DID patients showed performance during an n-back working memory task comparable to healthy controls. However, the DID patients additionally activated left superior temporal gyrus and ventrolateral prefrontal cortex (VLPFC), which might be essential in reaching this level of performance. In contrast, TPS of DID performed worse and showed difficulty activating the prefrontal parietal network accordingly. This might be due to TPS' hyperaroused and continuous focus on trauma-related memory because TPS is the personality-state with access to traumatic memories and working memory might be flooded with these memories. Findings in TPS are similar to previous studies in PTSD (Patel et al. 2012, Hayes, Hayes & Mikedis 2012, Aupperle et al. 2012, Scott et al. 2015) reporting hypoactivation of regions involved in working memory. Results showed the importance of carefully documenting and controlling for different personality states in DID research.

In chapter 5 we tested the fantasy model. Since it could not be ruled out that DID simulating mentally healthy controls would be able to mimic the personality-state-dependent results from chapter 4, we compared the diagnosed genuine DID patients (DID-G) with a group of DID simulating mentally healthy controls (DID-S). We found consistent differences in working memory functioning between DID-G and DID-S both on a behavioral and a neural level. It can be argued these differences reflect a trauma or dissociation component in DID-G, since both trauma and dissociation have been associated with worse

working memory and executive functioning (Amrhein et al. 2008, Guralnik et al. 2007, Rivera-Velez et al. 2014, DePrince, Weinzierl & Combs 2009, Scott et al. 2015). These findings fit the trauma model's hypothesis. Personality state differences within DID-G were, however less consistent and interaction effects were not as pronounced as expected and do not fully support the trauma model. The n-back task may lack sensitivity compared with paradigms using trauma-specific stimuli (Reinders et al. 2003, Reinders et al. 2006, Reinders et al. 2012, Reinders et al. 2014, Schlumpf et al. 2013) and further research is needed. Importantly, DID-S was unable to simulate the severity of dissociation that was found in both NPS and TPS of DID-G. Dissociation was measured with the CADSS (Bremner et al. 1998), that in addition to a self-report section, has an observer part as well, which can be regarded as contributing to its reliability.

Examination of findings

Trauma versus Fantasy

The etiology of DID has been a topic of debate between proponents of the opposed trauma and fantasy models. This thesis aimed to provide empirical (neurobiological) data, which in the end informs holders of both models. Hence, the studies described in this thesis provide "pieces of the puzzle" for the etiopathogenesis of DID.

Trauma continuum, fantasy proneness and suggestibility

The fantasy model posited that DID is a simulation mediated by, among others, high suggestibility and/or fantasy proneness (Merckelbach, Rassin & Muris 2000, Merckelbach, Horselenberg & Muris 2001, Rassin, Merckelbach & Spaan 2001, Giesbrecht, Merckelbach 2006, Giesbrecht et al. 2007, Giesbrecht et al. 2008, Lynn et al. 2012). This would indicate that DID patients display higher scores on measures of these phenomena. In contrast to the fantasy model's hypotheses, DID patients were not more fantasy prone or suggestible than the participants from the other groups, nor did they generate more false memories. In contrast, DID patients showed elevations on a malingering test (SIMS), which is more congruent with the fantasy model. Studies have shown that high scores on varying types of pathology, particularly severe pathology, correlate with SIMS scores (Edens, Otto & Dwyer 1999, Merckelbach, Smith 2003, Peters et al. 2013) thus, one can both have serious psychopathology

and exaggerate (Dalenberg et al. 2014). It can be argued that the symptoms measured by the SIMS may be rare in some patient groups but are common true psychiatric symptoms among DID patients (Coons 1984, Putnam et al. 1986, Boon, Draijer 1993b, Bozkurt et al. 2014, Brand, Chasson 2015).

Indications for a continuum of trauma-related psychiatric disorders (Spiegel 1984, Van der Hart, Nijenhuis & Steele 2005) would be in favor of the trauma model. For trauma-related measures, DID patients had the highest scores, followed by PTSD, and then HC, which was indeed suggestive of a continuum of trauma-related disorders. This is in line with results from a study by Wabnitz et al. (2013) that were described as congruent with a typological model of dissociation in which severe forms of dissociation are specific to dissociative disorders and are accompanied by higher levels of trauma-specific avoidance in DD patients. These findings support the view that PTSD and dissociative disorders are related. Our findings are also in line with findings from Rodewald et al. (2011) that confirmed the hypothesis that PTSD and DID are phenomenologically related syndromes. Evidence on various symptom measures in chapter 2 consistently supported the trauma model of DID and challenged the core hypothesis of the fantasy model.

The hippocampus and childhood trauma

Studies investigating effects of childhood maltreatment on brain maturation have proposed that early stress results in a cascade of neurobiological changes, at both functional and structural levels (Teicher et al. 2003). Results of a recent review (Blanco et al. 2015) showed that a history of childhood sexual abuse was associated with irregularities in both cortical and subcortical regions of the brain. If DID is a childhood trauma-related disorder structural and functional changes should be similar to those reported in traumatized individuals. In chapter 3 we found that bilateral hippocampal volume was smaller in DID patients as compared with HC and that the right hippocampal volume was trend-wise smaller in PTSD patients. Both DID and PTSD showed contractions in several hippocampal subfields compared with HC. Additional analyses in DID and PTSD showed that smaller hippocampal volume was correlated with reported childhood trauma scores and dissociative symptoms. Chapter 3 results indicate that DID is related to childhood trauma-related experiences. If the hypothesis of the fantasy model would hold and the memories of childhood maltreatment are made up, it was unlikely to find an association between a measure of childhood maltreatment and hippocampal

volume. Smaller hippocampal volume has been found in previous studies investigating neuroanatomical differences between traumatized individuals, with or without psychiatric disorders, and healthy controls (Bremner et al. 2003, Andersen et al. 2008) and the association between childhood maltreatment and smaller hippocampal volume has been demonstrated (Teicher, Anderson & Polcari 2012). Previous studies investigating the effects of (childhood) trauma on hippocampal subfield morphology showed similar results in both humans and animals (Gould et al. 1997, Kadar et al. 1998, McEwen 1999, Andersen, Teicher 2004, Wang et al. 2010, Teicher, Anderson & Polcari 2012). Recently, Morey et al. (2015) showed that PTSD symptoms were inversely correlated with right and left hippocampal volume. Ross and colleagues showed, on the other hand, no differences between traumatized patients and controls on left or right hippocampal volumes (Ross, Goode & Schroeder 2015). Based on this finding, they suggested that dissociation might have a neuroprotective function and that reduced hippocampal volume would be most evident in individuals with high trauma exposure but low levels of dissociation. Although the authors did not test this hypotheses, they encouraged others to consider it in future studies. Chapter 3 investigated the relation between dissociation and hippocampal volume and results appeared not to be in line with Ross et al.'s hypothesis. In sum, chapter 3 provides evidence that is predominantly in line with the trauma model's hypotheses.

Dissociative-personality-state-dependent working memory

Previous research has indicated that cognitive areas play an important role in processing of trauma-related memory in NPS (Reinders et al. 2006). However, personality-state-dependent differences for cognitive processes, such as working memory were not yet systematically studied. Robust personality-state differences in response to trauma-related memory and other trauma-related cues have been reported (Reinders et al. 2003, Reinders et al. 2006, Schlumpf et al. 2013) and in chapter 4, although less robust, we found evidence that neutral and trauma-related personality states can be differentiated at a neural level during working memory. TPS activated the prefrontal parietal network to a limited extent compared with NPS. Furthermore, several brain imaging studies have demonstrated working memory deficits in PTSD associated with altered prefrontal cortex activation (Hayes, Vanelzakker & Shin 2012, Patel et al. 2012, Scott et al. 2015). If DID has a trauma-related origin, similarities between DID and PTSD would be expected for working memory performance and related brain activation patterns. Even though we did not find the

hypothesized altered brain activation in PTSD, chapter 4 described similarities between TPS and previous studies in PTSD (Patel et al. 2012, Hayes, Hayes & Mikedis 2012, Aupperle et al. 2012, Scott et al. 2015), in which hypoactivation of regions involved in working memory were reported. Together, results from chapter 4 are fairly consistent with previous personality-state differences and match the PTSD profile to some degree, suggesting a trauma-relation in DID.

DID simulation for working memory processes

Boysen and VanBergen (2014) noted that if systematic differences in brain functioning would be found between patients diagnosed with DID and DID simulators, this might offer means for improving the quality of differential diagnosis and understanding basic phenomena associated with the disorder. In chapter 5 we included a DID-S group and similarities between this group and DID patients would be more indicative for the fantasy model. Overall differences in brain activation between DID patients and simulating controls were found during a WM task, along with better performance in the DID-S group, which is in line with the trauma model. However, no specific personality-state-dependent differences in neural activation patterns were found between patients and simulating controls. The group differences are in line with previous studies that showed neural activation patterns in DID-G that could not be simulated by mentally healthy actresses (Reinders et al. 2012, Schlumpf et al. 2013, Reinders et al. 2014, Schlumpf et al. 2014). However, these previous studies also specifically found personality state differences within DID-G, and these differences were not as profound as expected in chapter 5. Furthermore, with increasing task load, in both DID-G and DID-S NPS showed more activation than TPS, which is more in line with the fantasy model. The additional recruitment of brain areas in DID-S could be related to simulation-processes. Schlumpf et al. (2014) reported differences in brain activation between controls simulating equivalents of NPS and TPS. This increased activation in simulated NPS was found in visual areas compared with simulated TPS and authors suggested that as NPS, simulators particularly engaged in visual imagery. It could be argued that areas of the prefrontal parietal network are involved in acting processes as well, since it requires both maintenance and manipulation of information necessary to execute a complex task (Baddeley 1996, Baddeley 2003). Our finding that the level of reported and observed dissociation could not be mimicked, is in favor of the trauma model. Boysen and VanBergen indicated that, despite overlap between DID and DID simulating controls and methodological flaws

which characterize many studies, differences between groups in previous studies showed that DID may not be as simple as enacting a social role (Boysen, VanBergen 2014). Our results from chapter 5 are in line with this notion, however evidence for both the trauma and fantasy model is mixed at best. The question remains whether the differences we have found can be regarded systematic and replication of results is needed in order to be less inconclusive.

Functional inaccessibility

It has been reported that amnesia is not a hallmark of DID, since inter-identity memory transfer has been shown (Huntjens et al. 2006, Kong, Allen & Glisky 2008, Huntjens, Verschuere & McNally 2012). Amnesia can be regarded as a functional mechanism, preventing memories with a high traumatic nature from entering other states of consciousness. In extension to this notion, we could argue that only TPS shows functional difficulties with working memory processes and NPS responds relatively normal. This is against the idea of a total inability in DID to adequately respond to a working memory task and activate the prefrontal parietal network accordingly. Kopelman (2000) speculated that the effect of stress on memory is mainly caused by dysfunctional frontal systems, which disrupts retrieval of autobiographical knowledge. In the case of extreme stress, this could lead to disturbance of the so-called 'personal sematic belief system' with a temporary loss of identity. It seems that in DID, there are personality-state-dependent differences at a functional level instead of absolute deficiencies. NPS can be seen as having a functional inaccessibility to trauma memories (Reinders et al. 2003, Reinders et al. 2006) and it might be that TPS has a functional difficulty to adequately use the working memory system. This would leave TPS stuck in a lower, less mature, level of functioning, therewith unable to recruit more developed PFC functions.

Subtypes within DID and PTSD

Lanius described a dissociative subtype of PTSD that responds to trauma cues with a decreased or unchanged autonomic activity (Lanius et al. 2010). PTSD patients with the more common undermodulated type show predominance of re-experiencing and hyperarousal symptoms (Lanius et al. 2010). Reinders et al. (2014) proposed an extended PTSD-based neurobiological model for

emotion modulation in DID. It was found that the hypo-aroused personality state (that is, NPS) activated the PFC, cingulate, posterior association areas and parahippocampal gyri, thereby overmodulating emotion regulation. In contrast, the hyper-aroused personality state (i.e., TPS) activated the amygdala and insula as well as the dorsal striatum, thereby undermodulating emotion regulation. In the Theory of Structural Dissociation of the Personality (TSDP), PTSD has been conceptualized as a fundamentally dissociative process (Van der Hart, Nijenhuis & Steele 2005, Van der Hart, Nijenhuis & Steele 2006, Nijenhuis, Den Boer 2009). The neurobiological similarity between DID personality states, and the PTSD subtypes raises the question whether dissociative PTSD is a specific form of PTSD or whether all forms of PTSD are fundamentally dissociative (Van der Hart, Nijenhuis & Steele 2006, Nijenhuis, Den Boer 2009, Nijenhuis 2014). Based on this notion it can be argued that in our 'relatively simple' PTSD group, the apparently normal personality states (or NPS) were those primarily participating in our study, which is corroborated by low dissociation scores in PTSD as measured with CADSS, and might help explain why we could not replicate previous results of working memory difficulty in PTSD. TPS in simple PTSD will not be triggered by the n-back task and were most likely not activated in the present study. Results would according to the TSDP be different had the PTSD patients operated as TPS rather than as NPS. To get TPS activated in PTSD, sufficiently powerful conditioned stimuli are needed. This is analogous to the assumption that more trauma-sensitive measures are needed to distinguish personality states in DID and show robust between group differences. The TSDP can offer an explanation as to why so many conflicting results are found in DID and PTSD research, when different subsystems of the personality are present. In DID we carefully documented and controlled for personality states under research, however in PTSD we did not address this issue. For future research in PTSD it is recommended to control for these states, as more specific information can be obtained regarding different profiles.

Methodological considerations

Specificity and sensitivity of a working memory task

Working memory tasks proved to be sensitive measures before as studies on dissociative symptoms (de Ruiter et al. 2004, Veltman et al. 2005, de Ruiter, Elzinga & Phaf 2006) and dissociative disorders (Elzinga et al. 2007) showed

preserved or enhanced working memory ability in comparison with healthy controls (de Ruiter et al. 2004, de Ruiter, Elzinga & Phaf 2006). Previous research examining the neural correlates of working memory function found increased responses within the dorsolateral prefrontal cortex in individuals with high trait dissociation (Veltman et al. 2005) and DD (Elzinga et al. 2007). Furthermore, the n-back task appeared to be a valid way of working memory assessment. Previous studies regarding dissociation and working memory (Veltman et al. 2005, Elzinga et al. 2007) used this type of task and a recent validation study showed that the task adequately probes the network-level neural correlates of working memory processing (Kearney-Ramos et al. 2014). In this thesis, it was shown that TPS activated prefrontal parietal regions to a limited extent associated with worse performance. The main effects (see Figures 4.2 and 5.1) showed that especially prefrontal activation is lacking in TPS, which fits the previously proposed neurobiological model of DID. Results are furthermore in line with findings from Dorahy et al. (2005, 2006), that showed weakened cognitive inhibitory functioning in DID patients, however these findings were only present in anxiety provoking situations, thereby dependent on emotional context. Working memory is shown to be affected in TPS in particular, and higher levels of anxiety and dissociation were reported, making up the profile as suggested by Dorahy et al. (2006).

Figures depicting 'glass brains' for main effects related to working memory functioning indicate larger differences than those found in direct comparisons (Figures 4.2 and 5.1), which could be related to our sample size. In direct comparisons, differences were primarily found in additional post-hoc analyses, which could be interpreted, besides an effect of sample size, as a relative insensitivity of a working memory task to differentiate between personality states in DID and compared with other groups. Speculations from Reinders et al. (2012), that personal trauma-related information is expected to have higher sensitivity for differentiation within DID and between DID and other groups, and higher likelihood of the emergence of a proposed neurobiological model, are confirmed by the current results. Reinders et al. (2003) conducted a PET study in DID and found two distinct states of self-awareness, each with its own access to autobiographical trauma-related memory with involvement of the medial PFC and the posterior associative cortices in the representation of these different states of consciousness. In another study (Reinders et al. 2006), the different personality states were associated with different brain activation patterns when confronted with trauma-related cues. Schlumpf

et al. (2013) found, in response to subliminally presented neutral and angry faces, abnormal reaction times for TPS, but not for NPS, and TPS activated different brain areas including in the parahippocampal gyrus, the brainstem, face-sensitive regions, and motor-related areas. It is recommended that future research comparing within DID personality states to controls groups use tasks with a trauma-related, disorder specific nature.

Participants

Sample size

The sample sizes we used in this thesis could be considered as modest. Since for the larger part of the measures it was required that DID patients were able to switch to, and remain in, different prototypical dissociative personality states, we were only able to include a limited number of participants in the DID group and matched control groups accordingly. In the n-back functional neuroimaging studies, the sample size might have been too small to detect robust differences between groups at a corrected threshold, since using less stringent thresholds, differences did emerge that were in line with the neurobiological model for DID (Reinders et al. 2014). In a general sense the numbers might be limited, but in this area of very complex and ill patients larger N's are exceptional. FMRI studies preferably should include circa 20 subjects (Thirion et al. 2007), although actual sample sizes in studies with dissociative disorder patients are often lower, e.g. Elzinga et al. (2007) included 16 patients and Schlumpf et al. (2013) analyzed the neuroimaging data of 11 patients.

Gender

Only female patients and controls were studied, which can be considered both as a strength and a weakness. Studies concerning a single gender sample have the advantage of excluding gender differences known to be present for brain activity during working memory (Speck et al. 2000, Goldstein et al. 2005, Bell et al. 2006). On the other hand, including only female participants limits generalization of our findings to the DID population in general. Most known patients with DID are however female (Putnam 1985) and no major differences in the clinical phenomenology of female and male patients were reported in previous studies (Bliss 1984, Ross, Norton 1989, Loewenstein, Putnam 1990).

Diagnostics

Apart from SCID-D and CAPS, we did not conduct other standardized interview to assess presence of axis-I disorders in our sample. Co-morbidity in DID is generally high (Galbraith, Neubauer 2000, Bozkurt et al. 2014), therefore future studies need to explore if the abnormalities in these patients can be due to other mental disorders or are specific to DID.

Medication

Groups in this thesis were unmatched on psychotropic medication use and it can be speculated that group differences in the functional imaging studies are influenced by medication use. Results of additional analyses in chapter 3, however indicate that the smaller volume of the hippocampus and its subfields in DID and PTSD as compared with HC are robust findings and not due to medication usage history. We furthermore believe that the within DID group personality-state differences will be less affected. Although remarkable dissociative-part dependent reactions to medication have been reported (Miller, Triggiano 1992, Moleman et al. 1994), to the best of our knowledge, no systematic studies addressed this issue.

DID group characteristics

Because of the previously mentioned requirement that DID patients achieved stability of control over switching among personality states, sufficient to participate in both NPS and TPS, we mainly studied participants in further stages, that is phase II (Steele, Van der Hart & Nijenhuis 2005), of therapy (see also Reinders et al. (2006)). One of the characteristics of phase II is that the two personality states are aware of each other's existence and may sometimes have some degree of co-consciousness. This makes it likely that in an untreated DID population symptom severity is worse and our results here are an underestimation of the true effects. Based on this consideration, our results may not be generalizable to patients who do not yet have a certain level of control over their personality states.

PTSD group characteristics

Even though agreement exists that PTSD is a trauma-related disorder, differences between 'simple' and 'complex' PTSD (Lanius, Bluhm & Frewen 2011, Ford 2015, Marinova, Maercker 2015) have been described. More recently, after the present study was initiated, a distinction in subtypes has been proposed (Lanius et al. 2010, Lanius et al. 2012). Therefore, it seems of

importance to affirm the type of PTSD included. We matched PTSD to the DID group on inter-personal trauma history, however variance within the PTSD group was present for the age of onset and CAPS scores. We recommend that future studies differentiate between PTSD subtypes and aim at a more homogeneous PTSD study group, which is likely to reduce within group variance.

Methods

Design

It can be argued that a 1x4 ANOVA design in analyses of the neuroimaging data underestimates the within DID group differences between NPS and TPS, since these are actually two measures within the same individual. Minor differences have been found between chapter 4 and 5 for within DID group personality-state comparisons. This could be related to the inclusion of different control groups (chapter 4 PTSD and HC, chapter 5 DID-S), suggesting to some degree of dependence between groups. In addition, the use of a different design could explain the variation within DID-G personality state differences between both chapters. In chapter 4 a 1x4 ANOVA design was used, since PTSD and HC could not be considered as two states of the same group, and in chapter 5 a flexible factorial design was chosen, since a 2 groups (DID-G and DID-G) by 2 states (NPS and TPS) design was the most elegant one. Also, the smoothness of residuals differs between chapter 4 and 5 as does the within and between group variance. More participants were included in chapter 4 (DID=14, PTSD=16, HC=16) than in chapter 5 (DID-G=14, DID-S=16), which is associated with differences in degrees of freedom and possibly relates to statistical power issues. The average statistical power of studies in neuroscience is low and the consequences of this include overestimation of effect size and low reproducibility of results (Button et al. 2013). Studies with low statistical power have a reduced chance of detecting a true effect, but also reduce the likelihood that a statistically significant result reflects a true effect (Button et al. 2013). It would therefore be interesting to analyze all the working memory data in one large statistical model.

Measures

Indications about childhood trauma and neglect were assessed retrospectively and could thus be prone to distortions. Trauma narratives of dissociative disorder patients are in general not very reliable because of

amnesia. Personal histories are subjective in nature and reliability is difficult to assess. This caveat does not only apply to studies in this thesis, but to all studies in the trauma field that do not provide evidence of trauma other than subjective reports. Even though many studies found evidence for a trauma-dissociation relationship, most are based on retrospective assessments. For example, a meta-analysis (Van IJzendoorn, Schuengel 1996) across more than 2000 participants revealed a rather large combined effect size for the relation between dissociation and abuse. Critics argued that the step from correlation to causation is made too easily (Kihlstrom 2005, Lynn et al. 2014) and evidence for causal links to dissociation should derive from prospective studies (Kihlstrom 2005). Ogawa et al. (1997) and Dutra et al. (2009) showed in prospective longitudinal studies that the quality of the early caregiving relationship is an important predictor for the development of dissociation. More research is however needed, which can be particularly challenging in early trauma related disorders such as DID.

The proper use of the full scale and subscales of the DES has generated considerable discussion within and across the trauma and fantasy model literature (Bernstein, Putnam 1986). Critics of the DES tend to focus on three issues: the reliability and meaning, the inclusion of absorption in the domain of dissociation, and the more general issue of giving a unitary label (dissociation) to a wide range of phenomena (Bernstein et al. 2001, Watson 2003, Giesbrecht et al. 2008). For future studies, it can be recommended to focus on items that are known as most discriminating between patients with a dissociative disorder and other psychiatric diagnoses[6] (Boon, Draijer 1993a) and without any psychiatric disorder[7] (Waller, Putnam & Carlson 1996) respectively. Furthermore, the TSDP posits that dissociative parts manifest in negative and positive dissociative symptoms that should be distinguished from alterations of consciousness (Van der Hart et al. 2004, Van der Hart, Nijenhuis & Steele 2005). Negative dissociative symptoms refer to apparent losses, for example, of memory, motor control, skills and somatosensory awareness, whereas positive dissociative symptoms represent dissociative intrusions (Van der Hart et al. 2004). Future research studying these distinct categories of symptoms could contribute to clarity about dissociative phenomenology.

6 Items: 7, 9, 13, 19, 24, 25 and 27

7 Items: 3, 5, 7, 8, 12 and 13

Clinical implications

In the past decades, research on the effects of trauma and processes of recovery has developed in many different directions. Despite considerable advances, the majority of individuals affected by traumatic experiences do not yet receive optimal care. Unfortunately, limited interdisciplinary communication is still the status quo; neuroscientists and clinicians barely work together (Holmes, Craske & Graybiel 2014). Improved transfer of scientific knowledge to clinical practice is required for better understanding and treatment of trauma-related disorders. We believe it is crucial that clinicians consider the existence of genuine cases of DID as these patients are at risk to spend several years of unsuccessful therapy (Ross, Norton & Wozney 1989, Arbour 1998). The case report that was presented in chapter 1 serves as an example for many DID patients who share a history of years of misdiagnosis and various hospitalizations. If such DID patients were diagnosed correctly earlier on, they could have benefited from phase-orientated treatment specific to DID on a younger age (Ellason, Ross 1997, Brand et al. 2012b) which is likely to improve quality of life. The sections below describe how the results presented in this thesis can translate to clinical practice.

Trauma treatment

This thesis showed a trauma-related association with hippocampal morphology and various group comparisons revealed support for the trauma model of dissociation. Findings suggest that in diagnostic procedures and psychotherapy, DID should be considered as a valid psychiatric disorder and that DID treatment according to guidelines is warranted. In addition, personality-state differences in symptom measures as well as for working memory functioning and its neural correlates were found, indicating the importance of distinguishing between prototypical dissociative personality states in research, but also to recognize and work with these personality states in clinical practice.

Working memory and emotion regulation

Inhibiting irrelevant or disturbing information is regulated by the working memory system and better working memory capacity is associated with more effective suppression of negative, personally-relevant thoughts in

suppression tasks (Bomyea, Amir 2011). Our finding of dissociative personality state differences in WM has potential clinical implications as, in TPS, patients are prone to relive traumatic memories. In DID treatment, clinicians aim to generate a wider field of consciousness in TPS and promote WM functioning. TPS could be assisted by either using Eye Movement Desensitization and Reprocessing (EMDR) (Shapiro 1996) or exposure techniques to decrease the emotionality and vividness of the traumatic memories.

Poor inhibitory control has been associated with intrusive thoughts (Bomyea, Amir 2011) and improvement of working memory is believed to relate to enhanced emotion regulation (Engen, Kanske 2013, Bomyea, Lang 2016). It has been suggested that acquisition of adaptive emotion regulation strategies is a plausible mechanism of change in psychotherapy (Moyal et al. 2015). Differences in vulnerability to unwanted intrusive cognitions have been found before and suggest that a higher working memory capacity is related to having fewer intrusive thoughts (Rosen, Engle 1998, Brewin, Smart 2005). A superior ability of individuals using repression to avoid intrusive thoughts can be explained largely by their higher working memory capacity (Geraerts et al. 2007). Schweizer et al. (2013) showed that training emotional working memory successfully enhanced the efficiency of the prefrontal parietal network, highlighting the potential of emotional working memory training for clinical groups with impoverished affective cognitive control. A recent pilot study (Saunders et al. 2015) investigated the feasibility of treating people suffering from PTSD and poor working memory by employing working memory training and transcranial direct current stimulation (tDCS). After treatment, the four participants in the study showed clinically significant improvements on a range of cognitive and emotional performance measures. Also, findings from another recent study (Bogdanov, Schwabe 2016) point to tDCS as a promising tool to reduce cognitive deficits related to working memory in, among others, post-traumatic stress disorder. It has been stated that effective interventions for youth with PTSD should target improved function of frontolimbic networks (Carrion, Wong 2012). Treatment outcome research using these potential markers can help develop more focused interventions that target the impaired learning of vulnerable youth experiencing traumatic stress. Diminished ability to control proactive interference may contribute to re-experiencing symptoms and has been proposed as a novel intervention target in PTSD (Bomyea, Stein & Lang 2015). PTSD re-experiencing symptoms and interference control performance improved significantly more for individuals in the interference

control training group relative to those in the control group. The avenues above highlight the potential of emotional working memory training for clinical groups with impoverished affective cognitive control and might be a promising way for further investigation in DID, possibly promoting emotion regulation and gaining control over distressing thoughts and feelings.

Attachment

Importance of object relations and attachment in the diagnosis and treatment of patients with dissociative disorders has been described (Draijer, Langeland 1999, Liotti 2004, Liotti 2006, Draijer, Langeland 2009). In therapy, recovery from trauma is related to reconnecting, in which the therapist has an important regulatory function. In the context of early childhood traumatization, feelings of being totally unprotected are present and phobias of attachment exist that need to be addressed in treatment (Steele, Van der Hart & Nijenhuis 2004). In psychotherapy, there is an attachment figure, that is the therapist, who can reduce the severity of early experiences. A variety of emotions and experiences can be explored, yet only in the context of a safe therapeutic alliance. Joining the experiential world of patient instead of fighting it, is essential for treatment progress (Nijenhuis 2015). Both the loss of connection related to traumatization as the reconnection are in essence social, attachment related, processes. The affective window-of-tolerance should be enhanced in DID treatment. In the therapeutic alliance, attachment can serve as a protection against overwhelming experiences. Secure attachment is positively related to emotion-regulating capacities, i.e. it is the foundation.
It is highly challenging to capture these interpersonal processes of trauma-therapy in research designs and it might illusory to find neurobiological substrates for the psychological processes. A promising direction are the attempts to (neuro)scientifically objectify for example transference mechanisms (Andersen, Baum 1994, Andersen, Chen 2002, Gerber, Peterson 2006), which offer roads for further understanding of these essential psychological processes.

Phase-oriented treatment for DID

Phase-oriented treatment (Horowitz 1973, Steele, Van der Hart & Nijenhuis 2005) helps DID patients gradually develop adaptive mental and behavioral actions, thus overcoming their phobias and structural dissociation. In phase 1,

the symptom reduction and stabilization phase, is geared toward overcoming phobias of mental contents, dissociative parts, and attachment and attachment loss with the therapist. Stabilization entails improvement of affect-regulation. Since affect-regulation and working memory seem to be related (Engen, Kanske 2013, Okon-Singer et al. 2015) and our functional imaging studies showed impaired working memory functioning in TPS, improvement of affect-regulation can be recommended. In phase 2, the treatment of traumatic memories, overcoming the phobia of traumatic memories, and phobias related to insecure attachment to the perpetrator(s), particularly in TPS is focused on. By overcoming the phobia of traumatic memories, intrusions are likely to weaken. Since fewer intrusive thoughts were shown to relate to higher working memory capacity, it can be speculated that in phase 2 working memory functioning could gradually improve (Rosen, Engle 1998, Brewin, Smart 2005). Finally, in phase 3, the integration and rehabilitation phase, treatment is focused on overcoming phobias of normal life, healthy risk-taking and change, and intimacy.

Future research

In order to further enhance knowledge regarding the mechanisms underlying DID, additional research is warranted.

Diagnostic

With fascination for the diagnosis of DID in the media, and among clinicians and patients, it has been noted that some patients are imitating the disorder (Draijer, Boon 1999). This can happen unconsciously by recognizing their own affective lability and identity confusion in the DID profile. Characteristic to this imitated disorder is the usually undue and histrionic presentation (Draijer, Boon 1999). Inclusion of factitious or imitative DID in future studies can provide an intermediate between diagnosed genuine DID and DID simulating healthy controls. Whereas genuine DID generally present their dissociative symptoms with great reluctance, the factitious group displayed, among others, more dramatic presentations, exaggeration of symptoms, "la belle indifference" and selective amnesia (Coons, Milstein 1994). In spite of criticisms of the sociocognitive model as an explanation of DID, it may explain some features of imitated DID (Van der Hart, Nijenhuis 2009). In order to find more evidence

for the possibility to reliable simulate DID, it would be of particular interest to include a DID imitative group (Draijer, Boon 1999) and compare patterns of brain activation with genuine DID patients.

Methodological

Since current diagnostics are complicated and can be prone to false-positives and negatives, a machine-learning approach might open avenues for differentiating genuine and imitative DID. Nouretdinov et al. (2011) pointed out that applying machine learning methods is promising to achieve clinically useful diagnostic and prognostic neurobiomarkers based on the pattern of brain activity and structure in psychiatric disorders. Studies using vector machine algorithms (Vapnik 1995) found 86% accuracy in identifying individual patients from the functional MRI pattern of brain activity to sad faces as a diagnostic marker of depression (Fu et al. 2008). In line with the discussion of findings in this thesis, the neural features of verbal working memory however showed a lower diagnostic accuracy (Marquand et al. 2008). Furthermore, with regard to an individual patient's clinical response to antidepressant medication, features of structural MRI were highly predictive (Costafreda et al. 2009). Karstoft et al. (2015) concluded that the ability to increase prediction versatility with machine learning is a promising step towards developing knowledge-based, personalized prediction of posttraumatic psychopathology. Clark et al. (2014) also used a machine learning classifier and multivariate pattern analysis (MVPA) and showed that, based on peri-traumatic brain activation, it was possible to predict later intrusive memories across participants with 68% accuracy, and within a participant with 97% accuracy.

Developments in the quantitative analysis of complex networks, based largely on graph theory, have been rapidly translated to studies of brain network organization (Bullmore, Sporns 2009). The brain's structural and functional systems have features of complex networks, both at the whole-brain scale of human neuroimaging and at a cellular scale in non-human animals (Bullmore, Sporns 2009). Graph theory analyses (Stam, Reijneveld 2007, Reijneveld et al. 2007, Bullmore, Sporns 2009) could aid showing intrinsic connectivity patterns in the brain. If network differences between NPS and TPS are found in such studies this would substantially contribute to neurobiological evidence regarding authenticity of personality-state-dependent functioning.

Furthermore, combined analyses of functional and structural data, that is multimodal imaging, could increase knowledge on structure-function relationships. For example, a relatively recent study investigated whether the gray matter volume of a selected group of structures was correlated with the fMRI response to a working memory task, within a mask of regions previously identified as involved with working memory (Harms et al. 2013). The same could be applied to studies in this thesis, investigating the structure-function relationship.

Also a relation between hippocampal size and short-term true and false memory was reported (Zhu et al. 2015). It might be of interest to combine data from chapter 2 and 3 to investigate the relationship reported by Zhu and colleagues in our sample of participants.

Concluding remarks

The results of this thesis have provided insights into the psychological, anatomical and neuronal profile of dissociative identity disorder as compared with several control groups. To date, no empirical studies concerning the etiological factors in DID existed that accommodated methodological concerns by both advocates of a trauma as well as advocates of a fantasy model. We have attempted to include measures from both the trauma and fantasy models in one comprehensive design and delineate findings in terms of the two models and have discussed clinical implications of the results presented here.

Concerning the etiology discussion in DID: From the studies conducted in this thesis, it has become apparent that childhood trauma is associated with hippocampal volume and shape differences in both the DID and PTSD patients. This provides empirical support for the clinical observations that DID is a childhood trauma-related disorder. In addition, it was shown that suggestibility and fantasy proneness did not differ between DID, PTSD, HC and DID simulating controls, opposing the main premise of the fantasy model. Furthermore, for trauma related symptom measures we found a continuum across groups that would be consistent with the idea that more severe and chronic trauma exposure, particularly in childhood, is associated with elevated dissociative symptoms. These results argue in favor of the trauma model and can be interpreted as a validation of the inclusion of DID in DSM-5 as a genuine

psychiatric disorder. On the other hand, our direct comparison of functional activation differences between simulated and genuine DID, yielded only subtle differences. This illustrates the difficulties in distinguishing between phenomenologically similar states, although methodological factors could play a role (limited sensitivity due to sample size, choice of fMRI task, etc.). Thus, strong conclusions cannot be drawn on the basis of these preliminary studies and further research is highly needed.

Concerning clinical implications: Both the study on symptom measures and the studies on neural correlates of working memory functioning revealed differences between neutral and trauma-related personality states that could not be mimicked by simulating controls. This supports previous notions regarding the importance of acknowledging and investigating personality-state differences in DID research. In contrast to NPS, TPS performed worse and showed difficulty activating the prefrontal parietal network accordingly, which might help explain symptomology as seen in different personality states of DID. NPS seems to be able to keep up apparent normality by additional recruitment of working memory related brain areas, whereas TPS' difficulty with activating the prefrontal parietal network might be related to a flooding of working memory with hyperaroused re-experiencing phenomena. These results appear to be in line with a previously proposed neurobiological model of DID (Reinders et al. 2014). The lack of an interaction between group (DID-G vs. DID-S) and state (TPS vs. NPS) with regard to brain activation is at odds with these results, however, and underlines the need for further research. We propose that acknowledging different dissociative personality states in DID treatment is essential and that communication between and cooperation of TPS and NPS, could be a strategy to achieve better working memory functioning, which is supportive for phase-oriented treatment in DID.

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CHAPTER 7

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NEDERLANDSE SAMENVATTING

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Dissociatieve identiteitsstoornis (DIS) is een psychiatrische aandoening die wordt gekenmerkt door de aanwezigheid van twee of meer verschillende persoonlijkheidstoestanden die herhaaldelijk de controle over het gedrag van de persoon nemen. DIS werd eerder ook wel meervoudige persoonlijkheidsstoornis genoemd. Elk van deze persoonlijkheidstoestanden heeft een eigen patroon van waarnemen en denken over de omgeving en het zelf. Verschillende prototypische persoonlijkheidstoestanden kunnen worden onderscheiden in DIS. In een neutrale persoonlijkheidstoestand (NPS) focussen DIS patiënten op het functioneren in het dagelijks leven en bestaat er volledige of gedeeltelijke amnesie voor trauma-gerelateerde herinneringen. In een trauma-gerelateerde persoonlijkheidstoestand (TPS) hebben DIS patiënten toegang tot trauma-gerelateerde herinneringen en wordt er emotioneel en lichamelijk sterk gereageerd op triggers die aan het trauma doen denken.

Ondanks dat DIS sinds 1980 in de DSM (Diagnostic and Statistical Manual, de standaard voor psychiatrische diagnostiek) is opgenomen, bestaat er een voortdurende discussie tussen aanhangers van het zogenaamde trauma- en fantasiemodel over de ontstaanswijze en diagnostische validiteit van de stoornis. Jaren van misdiagnose zijn vaak eerder de regel dan uitzondering bij DIS patiënten.

Voorstanders van het traumamodel nemen aan dat DIS is gerelateerd aan vroegkinderlijke traumatisering, waarbij factoren zoals ernstig verstoorde hechting en chronische mishandeling en verwaarlozing van invloed zijn. DIS wordt daarbij gezien als een ernstige trauma-gerelateerde stoornis, doorgaans samen voorkomend met posttraumatische stress stoornis. Aan de andere kant zijn voorstanders van het fantasiemodel van mening dat DIS bewust of onbewust wordt gesimuleerd en dat het een gevolg is van suggestieve psychotherapie of socioculturele invloeden, zoals bijvoorbeeld de media, kerk of televisie. Er wordt gedacht dat suggestibiliteit en fantasierijkheid belangrijke mediërende factoren zijn. De controverse rondom DIS kan blijven bestaan zolang er slechts beperkt neurowetenschappelijke evidentie voorhanden is.

Objectieve informatie zoals structurele en functionele beeldvorming van de hersenen bij DIS patiënten en patiënten met posttraumatische stress stoornis (PTSS), kan inzicht bieden in overeenkomsten en verschillen in neurale correlaten van deze aandoeningen en aanwijzingen geven over in welke mate een traumacomponent van invloed is. Door daarnaast ook actrices te includeren die DIS nabootsen kan er meer worden gezegd over de mate waarin DIS te simuleren is, zowel op een scala aan psychologische maten, als voor patronen van activatie in de hersenen. Door PTSS patiënten en actrices die DIS simuleren mee te nemen als controlegroep voor gediagnosticeerde DIS patiënten, kan het huidige onderzoek nieuwe inzichten bieden die zowel voorstanders van het trauma- als van het fantasiemodel kunnen informeren. Dit proefschrift is er op gericht om, naast nieuwe inzichten uit psychologische maten, neurobiologische gegevens aan de hand van structurele en functionele beeldvorming van de hersenen te bieden.

In een review werd enige tijd geleden de wetenschappelijke evidentie voor het trauma- en fantasiemodel van dissociatie besproken. Hierin werd geconcludeerd dat wanneer er gecontroleerd wordt voor fantasierijkheid, pathologische dissociatie nog steeds voorspellend is voor een verleden met traumatische ervaringen. Er werd weinig bewijs gevonden voor de veronderstelling dat de relatie tussen trauma en dissociatie het gevolg is van suggestibiliteit of onechte herinneringen aan trauma. Voorstanders van het fantasiemodel hebben echter gereageerd op dit review en suggereren dat er te snel causale conclusies worden getrokken op basis van correlationele verbanden. Hoewel reviews zeer waardevol zijn voor het debat tussen aanhangers van beide modellen, zijn ze gebaseerd op studies die geen van alle DIS direct hebben vergeleken met PTSS, actrices die DIS nabootsen en gezonde controles. In hoofdstuk 2 hebben wij voor het eerst deze groepen met elkaar vergeleken op een aantal goed gevalideerde psychologische maten waarmee beoogd werd zowel hypothesen uit het traumamodel als uit het fantasiemodel te testen. Voor een deel van deze maten hebben we eveneens gekeken of de gevonden patronen afhankelijk zijn van de persoonlijkheidstoestand (NPS of TPS) en of dit al dan niet nagebootst kan worden door actrices die DIS simuleren. Er werden meer significante verschillen gevonden tussen groepen op trauma-gerelateerde maten, dan op lijsten die gerelateerd zijn aan de ideeën van het fantasiemodel. Betreffende de trauma-gerelateerde lijsten rapporteerden DIS patiënten de hoogste scores, gevolgd door PTSS en daarna HC. Wanneer er werd gekeken naar persoonlijkheidstoestand afhankelijke resultaten, werden

hogere scores in de TPS gevonden voor trauma-gerelateerde maten. Verder werden er nauwelijks verschillen gevonden tussen de groepen op lijsten die fantasierijkheid en suggestibiliteit meten, hetgeen pleit tegen de belangrijkste hypothesen van het fantasiemodel.

Er is slechts beperkt neurowetenschappelijke onderzoek gedaan naar mogelijke neuroanatomische verschillen tussen DIS patiënten en gezonde of getraumatiseerde controles. Hoewel er in eerder onderzoek aanwijzingen zijn gevonden voor een trauma-gerelateerde oorsprong van DIS, is de directe etiologische relatie tot vroegkinderlijke traumatisering niet eerder onderzocht. Een kleiner volume van de hippocampus is herhaaldelijk beschreven in onderzoeken naar neuro-anatomische verschillen tussen getraumatiseerde personen, met of zonder psychiatrische stoornissen, en gezonde controles. In hoofdstuk 3 hebben we ons gericht op het onderzoeken van verschillen in morfologie van de hippocampus tussen DIS, PTSS en gezonde controles in relatie tot vroegkinderlijke traumatisering. Zowel veranderingen van volume als regionale veranderingen van vorm werden onderzocht bij personen met DIS en PTSS. De resultaten van de studie in hoofdstuk 3 tonen aan dat mensen met DIS een kleiner volume in de linker en rechter hippocampus hebben in vergelijking met PTSS en gezonde controles (HC). Voor de rechter hippocampus werd een statistische trend gevonden met een kleiner volume in PTSS in vergelijking tot HC. Verder werden er regionale vormcontracties in verschillende sub-gebieden van de hippocampus, te weten CA (Cornu Ammonis)1 , CA2 - 3 en subiculum, gevonden bij DIS en PTSS in vergelijking met HC. Deze bevindingen zijn in lijn met eerdere studies in DIS, PTSS en slachtoffers van vroegkinderlijke traumatisering. De belangrijkste bevinding van hoofdstuk 3 was de relatie tussen traumatisering in de kindertijd en volume en vorm van de hippocampus in patiënten met DIS en PTSS. Deze resultaten bieden empirische ondersteuning voor het klinische concept dat DIS een stoornis is gerelateerd aan vroegkinderlijke traumatisering.

In eerder onderzoek is aangetoond dat ernstige en chronische stress het functioneren beperkt op taken die betrokkenheid van de prefrontale cortex vereisen. Eerder taak-gebonden hersenonderzoek heeft laten zien dat er bij PTSS tekorten in het functioneren van het werkgeheugen bestaan, welke geassocieerd zijn met verminderde activatie van de prefrontale cortex. Hoewel DIS door het traumamodel wordt beschouwd als een ernstige trauma-gerelateerde stoornis, zijn er nog geen studies geweest die de neurale

activatie tijdens een werkgeheugentaak hebben onderzocht in DIS, PTSS en gezonde controles. In hoofdstuk 4 hebben we de patronen van hersenactiviteit tijdens een zogenaamde n-back werkgeheugentaak bestudeerd in deze groepen en hebben we daarnaast ook gekeken naar verschillen in prestatie en hersenactivatie tussen de verschillende persoonlijkheidstoestanden in DIS, de NPS en TPS. Gedragsdata liet zien dat DIS patiënten in TPS langzamer en minder accuraat presteerden op de n-back taak in vergelijking met NPS, HC en PTSS. De resultaten van het functionele hersenonderzoek laten zien dat NPS, HC en PTSS grotendeels dezelfde gebieden activeren in het prefrontale pariëtale netwerk, welke geassocieerd is met werkgeheugen processen. In TPS werd beperktere activatie van dit netwerk gevonden, onafhankelijk van de mindere taakprestatie. TPS heeft toegang tot en een voortdurende focus op traumatische herinneringen en het kan zijn dat het werkgeheugen daarmee wordt overspoeld. De bevindingen zijn vergelijkbaar met eerdere resultaten in PTSS die hypoactivatie van werkgeheugengebieden in het brein lieten zien. TPS zou kunnen worden ondersteund door bijvoorbeeld EMDR of exposure toe te passen en daarmee de heftigheid van traumatische herinneringen te verminderen, waardoor het werkgeheugen kan verbeteren. Hoewel NPS een vergelijkbare prestatie laat zien ten opzichte van HC, werden wel extra hersengebieden gebruikt die mogelijk nodig waren om deze prestatie te bereiken. Bovenstaande bevindingen tonen het belang van differentiatie tussen de verschillende prototypische persoonlijkheidstoestanden in DIS in relatie tot het functioneren van het werkgeheugen.

Hoewel er in hoofdstuk 4 verschillen zijn gevonden tussen neutrale en trauma-gerelateerde persoonlijkheidstoestanden, kunnen voorstanders van het fantasiemodel suggereren dat deze resultaten ook door simulatie tot stand zijn gekomen. Wanneer patronen van activatie in het brein systematisch verschillen tussen DIS patiënten en DIS simulerende gezonde controles, kan dit voor toegenomen inzicht in de validiteitsdiscussie van de diagnose zorgen. Eerder hersenonderzoek heeft reeds aangetoond dat er persoonlijkheidstoestand afhankelijke patronen van activatie zijn gevonden in DIS, welke niet door DIS simulerende controles konden worden nagebootst. In hoofdstuk 5 is onderzocht of de eerder gevonden verschillen tussen NPS en TPS op een werkgeheugentaak stand houden wanneer wordt gecontroleerd voor factoren van simulatie. DIS patiënten in zowel NPS als TPS zijn hiervoor vergeleken met DIS simulerende gezonde actrices, die een NPS als TPS hebben nagebootst na daarin te zijn getraind.

Het bleek dat er verschillen tussen beide groepen zichtbaar waren op het vlak van hersenactivatie en daarnaast presteerden de actrices beter op de werkgeheugentaak dan de DIS patiënten. Deze verschillen zouden een traumacomponent kunnen weerspiegelen, aangezien uit een aantal eerdere onderzoeken is gebleken dat zowel trauma als dissociatie verband houden met verminderd functioneren van het werkgeheugen. De verschillen tussen persoonlijkheidstoestanden binnen de patiëntengroep waren minder consistent in hoofdstuk 5 dan in hoofdstuk 4, hetgeen kan komen door het gebruik van een ander model in de analyses. De interactie-effecten tussen groep, met patiënten en controles, en toestand, met NPS en TPS, waren minder uitgebreid dan verwacht en de resultaten van hoofdstuk 5 ondersteunen slechts ten dele het traumamodel. Mogelijk is ook dat de huidige studie relatief weinig statistische power bevat om subtiele verschillen betrouwbaar weer te geven. Indien dit het geval is, kunnen grotere groepen in de toekomst uitkomst bieden. Wanneer we concluderen dat het patroon van NPS en TPS in DIS op een werkgeheugentaak nagebootst kan worden door actrices, betekent dat echter niet dat authentieke trauma-gerelateerde DIS niet bestaat. Mogelijk is een werkgeheugentaak niet sensitief genoeg om verschillen te detecteren en zijn er stimuli nodig die meer stoornis specifiek zijn. In overeenstemming hiermee heeft eerder onderzoek, waarbij trauma-gerelateerd materiaal werd aangeboden, laten zien dat de persoonlijkheidstoestand afhankelijke verschillen niet door DIS simulerende actrices konden worden nagebootst.

Samengevat is met dit proefschrift gepoogd om met behulp van psychologische maten en neuroimaging technieken meer inzicht te bieden in de correlaten van dissociatieve identiteitsstoornis. De bevindingen in hoofdstuk 2-4 van dit proefschrift geven voornamelijk empirische steun ten gunste van een trauma-gerelateerde etiologie van DIS en erkenning voor de validiteit van de diagnose. En hoewel hoofdstuk 5 een meer gemengd beeld toont, met resultaten die deels pleiten voor het fantasiemodel en deels voor het traumamodel van dissociatie, kan geredeneerd worden dat een werkgeheugentaak mogelijk niet stoornis specifiek genoeg is om onderscheid te maken tussen DIS patiënten en actrices die de stoornis nabootsen. Hoewel we ons er van bewust zijn dat er nog veel onbekend is over de hersenstructuur en functies in DIS, draagt het huidige proefschrift belangrijke informatie aan ten behoeve van het debat betreffende de etiologie van DIS. Verbeterde kennis over de neurobiologie van DIS draagt verder bij aan een toegenomen klinisch begrip en een vermindering van misdiagnoses.