CHAPTER 6

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.


SUMMARY AND GENERAL DISCUSSION

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.
SUMMARY AND GENERAL DISCUSSION

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.

**Neurostructural: 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 & Midedis 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
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 & Mikesid 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 semantic 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 diagnoses6 (Boon, Draijer 1993a) and without any psychiatric disorder7 (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.

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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 reliably 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
SUMMARY AND GENERAL DISCUSSION

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.
REFERENCES


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CHAPTER 6


SUMMARY AND GENERAL DISCUSSION


SUMMARY AND GENERAL DISCUSSION


CHAPTER 6


