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The traumatized brain

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2013

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Chalavi, S. (2013). *The traumatized brain: gray and white matter morphology in dissociative identity disorder and Posttraumatic Stress Disorder*. University of Groningen and Wöhrmann Print Service.

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Chapter 7

Summary and General Discussion

The etiology of dissociative identity disorder (DID) has been the focus of controversy for many years (Bremner, 2010, Coons, 2005, Fraser, 2005, Giesbrecht et al., 2008 and 2010, Piper and Merskey, 2004a, 2004b and 2005, Sar, 2005). Mental health professionals disagree about the etiology of DID as well as DID's status as a valid mental disorder (for reviews see Reinders (2008) and Boysen and Vanbergen (2013)). Objective and empirical research in individuals with DID is limited (Dalenberg et al., 2012) allowing the proponents of the non-trauma-related model to question the genuineness of DID as a childhood-trauma-related disorder (Lilienfeld et al., 1999, Merckelbach and Muris, 2001, Merckelbach et al., 2002, Paris, 2012, Pope et al., 2006, Spanos, 1994 and 1996), postulating that individuals with DID either consciously or subconsciously simulate their different identity states.

Objective neuroscientific information, such as structural brain imaging data of individuals with DID and PTSD, could help in better understanding the neural correlates of these disorders. Investigating the neural correlates of DID may provide support for either of the etiology models for DID. This thesis aimed to provide this type of objective empirical evidence to increase the current understanding of the neuroanatomy of DID. To this end, three studies were conducted examining the neuroanatomical abnormalities in DID patients (who all had a co-morbid posttraumatic stress disorder (PTSD)) in comparison with PTSD patients (without a DID diagnosis) and to healthy controls (HC). Comparing neuroanatomical measurements between DID and PTSD patients allowed us to study the similarities and differences in the pattern of structural abnormalities between these disorders. Whereas similarities in neuroanatomical abnormalities between PTSD and DID patients may provide support for the trauma-related model of DID, differences between these disorders may indicate disorder-specific abnormalities.

Summary of findings

A reproducibility study

Finding individuals with DID willing and able to participate in a neuroimaging study was expected to provide a challenge. Therefore, we planned to include patients from all over The Netherlands as well as from the northern part of Belgium. Shortening travel time for participants was considered to increase the likelihood for participation. Therefore, we aimed to conduct MRI scans at two different centers in The Netherlands, i.e. Amsterdam and Groningen. An important confound of combining and analyzing images from different scanners is that the volumetric and surface-based brain measurements derived from MR images can be dependent on the quality of the MR images which is itself dependent on several other factors including MRI scanner properties (Han et al., 2006, Jovicich et al., 2009), MR sequence parameters (Jovicich et al., 2009, Kruggel et al., 2010) and MRI scanner upgrades (Jovicich et al., 2009). Slight differences in these factors can have considerable impact on the reliability and reproducibility of the segmentation results (Schnack et al., 2010), which ultimately could make the interpretation of results difficult. The two participating MRI centers in the studies for this thesis were equipped with MRI scanners with similar hardware configurations (both Philips 3T scanners). Nevertheless, it was still necessary (Jovicich et al., 2009) to determine an MR sequence with a high contrast to noise ratio for minimal differences in the anatomical measurements acquired across centers and over time. To this end, we collected five datasets, which included two within-subject within-center datasets, two between-subject between-center datasets and one between-subject within-center dataset after a scanner upgrade in one of the centers. The results of these steps helped us to realize an artifact-free MR sequence with high short-term and long-term reproducibility across the two centers. This sequence also showed to have high reproducibility after a scanner upgrade at one of the centers.

Conducting this study enhanced the reliability of the results presented in *chapter 4* and *chapter 5*. *Chapter 3* also emphasizes the importance of conducting reproducibility studies in general prior to any multicenter or longitudinal study. It

revealed that standard MR sequence as provided by the vendor, or other sequences frequently used at each MRI center, did not provide optimal scanner settings for our two-center study.

Gray matter abnormalities in DID and PTSD

So far, only a limited number of neuroimaging studies have investigated possible neuroanatomical differences between DID patients and healthy or traumatized controls and all of these studies have focused on volumetric differences in *a priori* specified brain regions (Ehling et al., 2008, Irle et al., 2007, Irle et al., 2009, Tsai et al., 1999, Vermetten et al., 2006, Weniger et al., 2008). In *chapter 4*, for the first time, whole-brain gray matter volumetric measurements of individuals with DID were compared to those of gender-, age- and education-matched HC and individuals with PTSD. To this end, volumetric measures (cortical volume, cortical surface-area, cortical thickness and subcortical gray matter volume) were extracted from the anatomical MR images of individuals with DID, individuals with PTSD and HC, and comparisons were made between the groups.

With regard to the cortical measurements we found smaller cortical volume of the whole brain, frontal, temporal and insular cortices in DID and PTSD groups, compared to HC, in accord with prior literature in PTSD (Eckart et al., 2011, Geuze et al., 2008, Kasai et al., 2008). Furthermore, we found that cortical gray matter of the left inferior parietal cortex was smaller in DID patients compared to PTSD patients and HC. The inferior parietal cortex is a posterior association area which combines sensory and cognitive information. Previously it has been suggested that this area is involved in the dissociation (Reinders et al., 2003, 2006 and 2012) and depersonalization (Blanke and Arzy, 2005, Simeon et al., 2000) symptoms. In fact, we found significant correlations between the volumetric measurements of this region and both dissociation and depersonalization scores (see page 93 of this thesis). Therefore, we suggest that functional as well as structural abnormalities of this region have a role in the neurobiological processes involved in dissociative phenomena in DID.

With regard to subcortical gray matter structures we found smaller left and right hippocampal volumes in DID as compared to HC (see Figure 4.2 on page 87). The right hippocampal volume also showed a trend to be smaller in DID relative to PTSD. This finding is in line with prior studies in DID (Ehling et al., 2008, Irle et al., 2009, Tsai et al., 1999, Vermetten et al., 2006) and several other volumetric studies in traumatized individuals (Gurvits et al., 1996, Kitayama et al., 2005). Furthermore, the current findings confirm smaller bilateral hippocampal volume as reported by Vermetten et al. (2006) despite concerns expressed by proponents of the non-trauma-related model (Smeets et al., 2006).

Furthermore, the subcortical volumetric results showed preserved amygdala size in DID and PTSD patients relative to HC. Smaller amygdalar volume has been reported in two prior volumetric studies in DID patients (Ehling et al., 2008, Irle et al., 2009, Vermetten et al., 2006). However, reports of smaller amygdalar volume in traumatized individuals have not been consistent across studies. Our finding of preserved amygdalar volume does not rule out the possibility of a functionally hyperactive amygdala as reported in patients with DID (Reinders et al., 2003, 2006 and 2012) and PTSD (Lanius et al., 2006 and 2010b).

Another interesting finding of this study was a larger dorsal striatum (including caudate, pallidum and putamen) in DID patients relative to PTSD patients and HC. Importantly, these findings were not related to antipsychotic medication (see sub-study on page 117). FMRI studies have shown involvement of the striatum during dissociative identity state switching (Savoy et al., 2012, Tsai et al., 1999) and PET studies have shown the dorsal striatum to be involved in identity state dependent processing of trauma-related information (Reinders et al., 2006 and 2012). The latter study suggests that stress may cause a shift from the hippocampus to the dorsal striatum (Reinders et al., 2012). Furthermore, studies in patients with focal lesions in the dorsal striatum reported involvement of the dorsal striatum in task switching and inhibition of irrelevant information (Yamasue et al., 2003, Yehene et al., 2005 and 2008). Evidence from studies in rodents has suggested that glucocorticoid (stress hormone) injections into the dorsal striatum enhance memory

consolidation (Quirarte et al., 2009, Sanchez-Resendis et al., 2012) and a recent fMRI study showed that stress impaired the functioning of the hippocampal system, which coincides with higher activation in the dorsal striatum (Schwabe and Wolf, 2012). Altogether, we speculated that the dorsal striatum might be involved in the recurrent alternation between different dissociative identities, the self-stabilization of these identities for a period of time, and the dominance of trauma-related procedural memory for trauma-related dissociative identities, but we also stressed the importance of further research to confirm this hypothesis.

In sum, on a cortical level, the results of this study showed similarities in the pattern of smaller cortical volume in both DID and PTSD groups relative to a HC group, and on a subcortical level our findings revealed larger gray matter volume of the striatum in the DID patients than in the PTSD patients. This study provides important objective and empirical data in line with the trauma-related model suggesting that DID is a trauma-related disorder, as cortical GM abnormalities showed similarities in the DID and PTSD patients and hippocampal volume were smaller in DID patients compared to HC.

Hippocampal morphology and childhood trauma

Smaller hippocampal volume has been repeatedly found in studies investigating neuroanatomical differences between traumatized individuals, with or without psychiatric disorders, and HC (Andersen et al., 2008, Bremner et al., 2003). An important study by Teicher et al. (2012) confirmed a relationship between childhood maltreatment (as measured with the childhood trauma questionnaire (CTQ)) and smaller hippocampal volume. Although we did indicate a trauma-related nature of DID in *chapter 4*, the direct etiological relationship to childhood maltreatment was still unconfirmed. Therefore, in *chapter 5* we focused on investigating differences in morphology of the hippocampus between DID, PTSD and HC in relation to childhood maltreatment. Both volumetric changes and regional shape deformations were investigated in individuals with DID and PTSD. Of note, in order to be able to manually trace the hippocampal boundaries with precision, the acquired anatomical images should have a high contrast between the brain's white and gray matter

tissues. Hence, this study benefited from the optimization and calibration study presented in *chapter 3* since that study provided us with an MR sequence which produced MR images with a high gray/white matter contrast.

The results of the study presented in *chapter 5* showed that individuals with DID had smaller left and right hippocampal volume compared to PTSD and HC. The right hippocampal volume also showed a trend to be smaller in PTSD patients relative to HC. These results are in agreement with previous structural imaging studies in DID (Ehling et al., 2008, Irle et al., 2009, Tsai et al., 1999, Vermetten et al., 2006), PTSD (Gurvits et al., 1996, Kitayama et al., 2005) and victims of childhood maltreatment (Dannlowski et al., 2012). These findings are also in agreement with the results presented in *chapter 4*. Furthermore, in the DID and PTSD groups, as compared to HC, hippocampal regional shape contractions were found in different hippocampal subfields, i.e. the CA1, CA2-3 and subiculum. These deformations were more widespread in the DID group. These findings are consistent with previous animal and human studies investigating the effects of (childhood) trauma on hippocampal subfield morphology (Andersen and Teicher, 2004, Gould et al., 1997, Kadar et al., 1998, McEwen, 1999, Teicher et al., 2012, Wang et al., 2010). Although the shape analysis results should be interpreted with caution, as they did not survive multiple comparison correction, these findings indicate important implications for future research.

The most important findings of *chapter 5* are the associations of childhood trauma with hippocampal volume and radial distance (i.e. shape) in the DID and PTSD patients. These findings are in line with previous studies (Andersen et al., 2008, Dannlowski et al., 2012, Teicher et al., 2012) and again provide objective and empirical support for the clinical observations that DID is a childhood trauma-related disorder.

Structural connectivity in DID and PTSD

In *chapter 6*, a diffusion tensor imaging (DTI) study was presented investigating white matter (WM) integrity in DID and PTSD patients, relative to HC. Our findings indicated that both DID and PTSD groups were associated with lower WM integrity

in several major fiber tracts. The lower WM integrity in the DID group, compared to HC, was found to be most prominent in the genu of the corpus callosum (CC). These findings are in line with previous DTI studies in individuals with a history of (childhood) stress (for a review see Daniels et al. (2013)). We proposed that lower WM integrity in DID and PTSD patients can be linked to impaired emotion regulation and memory in these patient groups. The patterns of observed WM integrity disruption in the DID and PTSD groups consists of: lower fractional anisotropy, higher mean and radial diffusivity, and to a lesser extent higher axial diffusivities. These patterns suggest that WM integrity disruptions can be related to the abnormalities in both myelination and organization of the fiber tracts (see pages 180-181 of this thesis).

In contrast to our a priori hypothesis, comparing the DID or PTSD groups to HC, we found that WM integrity differences were more widespread in the PTSD group. Furthermore, direct comparison of the DTI measures between DID and PTSD patients showed lower WM integrity of some fiber tract most prominently the splenium of the CC in the PTSD group. In *chapter 6* (see pages 176-180) we proposed that these findings can be related to differences in medication use and history, timing of traumatizing events as well as differences in dissociative and depersonalization symptoms between the DID and PTSD groups. Inspection of the traumatic experiences checklist (Nijenhuis et al., 2002) revealed that the DID patients participated in this study reported severe potentially traumatizing experiences including sexual harassment and abuse beginning before the age of 6. The PTSD group, on the other hand, reported experiencing sexual harassment and abuse during the age range of 7 to 12 years old. Our DTI analyses showed the largest cluster with a lower white matter integrity in the DID vs. HC to be located in the genu of the CC, whereas in the PTSD vs. HC comparison it was located in the splenium of the CC. It has been documented that CC maturation occurs in a rostral-caudal pattern (Giedd et al., 1996) and thus different regions of CC have different sensitive periods. Given this pattern of CC maturation, our results of DTI analyses are in line with the reports of traumatizing experiences in DID, i.e. early childhood trauma in the age rage of 0-6 (see Table 6.3 on page 178) and PTSD,

i.e. no reported trauma in the age range of 0-6, but later in life.

Furthermore, DID patients reported higher dissociative and depersonalization symptoms as compared to PTSD patients. It is believed that dissociation is a self-protecting mechanism used by a maltreated child in response to severe and chronic abuse and neglect. We speculate that DID patients developed dissociative mechanisms in early childhood when the maltreatments started and continued using these as the abuse and neglect continued throughout the developmental period. It is known that the maintenance of axonal connections is activity dependent (Steele et al., 2013, Zatorre et al., 2012), and during pruning active connections remain while inactive connections would be eliminated. Therefore, we speculate that the use of dissociative mechanisms by the DID patients served as an iterative learning process for these patients and they benefited from development of this highly complex cognitive mechanism which avoids pruning and leaves a relatively more intact WM integrity, especially as compared to PTSD in which potential traumatizing events started later in life and protective dissociative mechanisms were not developed. Alternatively, it may be argued that in DID patients WM was re-organized in order to (at least partly) compensate for the gray matter loss (and subsequent functional loss) due to neurotoxic effects of elevated stress hormones. Correlation analyses showed a significant positive correlation in the right cingulum-parahippocampal fiber tract between total TEC scores and FA measures. Considering that in Chapter 4 and Chapter 5 we reported negative correlations between severity of childhood traumatic experiences and hippocampal volume, this positive correlation between TEC and the FA of the right cingulum-parahippocampal fiber tract is in line with our hypothesis of re-organization of brain network to compensate the detrimental effect of stress on the gray matter regions. However, these hypotheses are speculative and future research is needed to confirm them.

Although maps of statistical tests comparing DTI measures between the DID group and HC or PTSD groups did not survive multiple comparison correction, the uncorrected maps provided indications for a trauma-related etiology for DID, and

may guide future research in DID and therefore they were reported as exploratory results.

Methodological considerations and future directions

In the studies presented in *chapter 4*, *chapter 5* and *chapter 6* we were able to overcome several methodological limitations noted in the prior literature. Firstly, the participants were matched for gender, age and education. Secondly, to pool the data from different MRI centers we balanced the number of participants in each center, and conducted a reproducibility study to ensure that the quality of MR images from the different centers were very similar. Nevertheless, there are some remaining methodological considerations which are divided in two main categories and are discussed below: i) participants, and ii) methods.

i) Participants

Sample size

The same sample of seventeen DID patients, sixteen PTSD patients and thirty-two HC were included in the studies presented in *chapter 4*, *chapter 5* and *chapter 6*. This sample size is a modest but relatively standard for neuroimaging studies. Performing analyses on this sample of participants allowed us to identify several structural abnormalities in DID and PTSD patients. It is worth mentioning that for the correlation analyses reported in chapter 4, 5 and 6 we combined the DID and PTSD patient data (n = 33) to increase statistical power for this type of analyses. However, this sample size was unfortunately not large enough to provide sufficient statistical power for volumetric analyses of individual cortical regions within the superparcels in *chapter 4*, of the hippocampal surface deformation in *chapter 5*, or brain wise correlation analyses.

Furthermore, the studies presented in *chapter 4*, *chapter 5* and *chapter 6* are based on the same sample of participants and it might be argued that these combined gray and white matter findings are specific to this sample size. Therefore, it is essential that these studies are replicated preferably by different research groups and in different cross-cultural samples, to further confirm

neuroanatomical features of individuals with DID.

Male and female DID patients

All participants were female as early trauma (Putnam, 2003) and dissociative disorders (Putnam, 2000) are more frequent in females and moreover only female DID patients volunteered to take part in this study. Given that brain maturation and morphological abnormalities in psychiatric disorders can differ between males and females, our results cannot be generalized to the male population. Therefore, future research in male populations is needed to be able to generalize these findings.

Trauma matching

For the studies in this thesis we included PTSD patients who had a history of interpersonal trauma and who were closely matched with the DID patients with respect to gender, age and education. Therefore the nature of the trauma background of the PTSD patients was matched as close as possible to those of the DID patients. Our clinical investigations revealed that the PTSD patients reported a range of low to severe childhood trauma. Also, we found that the timing of the traumatizing experiences were different between the DID and PTSD groups (see *chapter 6*, Table 6.3 and 6.4). It might be that these differences in the timing and onset of the traumatizing events between DID and PTSD are intrinsically related to the disorder, but it makes a one-to-one comparison more challenging. For future research it would be interesting to be able to include a HC group with a background of childhood maltreatment and/or a more complex PTSD group (Thomaes, 2013) who are closely matched with the DID group with respect to the timing of the childhood traumatizing experiences. Such a match with the DID group with respect to the childhood trauma will make it possible to directly compare brain morphological differences due to early childhood trauma.

Medication

Given that some psychotropic medications may change the morphology and function of brain, using drug-naïve subjects or matching groups for medication

history seems an important issue in neuroimaging studies of neuropsychiatric disorders (Lanius et al., 2010a). The majority of DID patients who participated in the studies of this thesis reported a history of using various types of medication, most importantly antipsychotics, anti-epileptics and antidepressants. We addressed this issue in our analyses (*chapter 4,* page 117; *chapter 5,* pages 152-156; and *chapter 6,* pages 176-177). However, it was a challenge particularly in the DTI study to disentangle the effects related to DID from the effects related to medication (*chapter 6,* pages 176-177). When investigating the effect of medication on neuroanatomical measurements, we noticed that medication use led to less significant differences (*chapter 4*, page 117; *chapter 5,* pages 152-156) and therefore the current results may represent an underestimation of the effects. Nevertheless, future studies need to take this factor into consideration or further assess the effects of psychiatric drugs on brain morphology (Chakos et al., 1994, Corson et al., 1999, Gur et al., 1998, Massana et al., 2005, Minami et al., 2003, Okugawa et al., 2004).

ii) Methods

Volumetric analysis

In *chapter 4* we used the program *FreeSurfer* to extract cortical and subcortical volumetric measures. Several other techniques are available which can be used for volumetric analysis such as voxel based morphometry (VBM) methods. There were several reasons why we chose FreeSurfer over VBM: 1) using FreeSurfer several aspects of brain morphology can be explored, e.g. cortical thickness, surface-area and volume, and subcortical volume, while VBM only permits the assessment of cortical and subcortical volumes. This is particularly important as cortical thickness and surface-area provide distinct information about cortical morphology (Panizzon et al., 2009); 2) automatic non-uniformity intensity correction on the basis of the nonparametric non-uniformity intensity normalization method (N3) (Sled et al., 1998) is built in FreeSurfer; 3) FreeSurfer uses geometry to do inter-subject registration and this kind of registration results in a better matching of homologous cortical regions than other volumetric techniques (e.g. VBM) (Fischl et

al., 1999); 4) the target that FreeSurfer uses for registration is the white matter surface geometry, which is completely invariant to gray matter atrophy, so pathological gray matter changes will not result in a different registration.

One of the limitations regarding FreeSurfer is that it does not provide detailed information about the white matter volume. As *chapter 6* shows differences in white matter integrity, it would be interesting for future studies to look at the white matter volumetric differences between individuals with DID and healthy or traumatized controls using other volumetric methods such as VBM.

Manual tracing versus automatic methods

In this thesis, hippocampal volume was obtained using two different methods, automatic segmentation (*chapter 4*) and manual tracing (*chapter 5*). While significant differences in bilateral hippocampal volume between DID and HC was the common finding of both of these methods, there were differences between these methods in the results of hippocampal volume comparisons of DID vs. PTSD and PTSD vs. HC. It should be noted that the reliability of the results obtained across the two studies is high, and the intra-class correlation coefficients (ICCs) for the left and right hippocampal volumes were 0.81 and 0.77, respectively, which are in agreement with the previous publications (Morey et al., 2010, Shen et al., 2010). Therefore, the differences observed between the results obtained using these two methods are likely due to the differences in the segmentation procedure.

Morphological differences in hippocampal subfields between groups were obtained on the basis of a manual tracing method. At the beginning of this project (July 2008) this was the only way to investigate shape deformations in different hippocampal subfields. More recently a new method has been developed and included in FreeSurfer which automatically extracts volumes of different hippocampal subfields. This method has attracted the attention of researchers in the field of neuropsychiatry (Kuhn et al., 2012, Teicher et al., 2012). It should be noted that both manual and automatic methods have their advantages and drawbacks. Automatic methods are fast and could be highly reproducible, but they could be sensitive to noise and artifacts could lead to segmentation errors. Also, for

multicenter studies care should be taken that differences in center specific image quality do not lead to segmentation differences, which affect the results. On the other hand, manual tracing methods are not as sensitive to noise, but they are time consuming and their reproducibility could depend on the rater's skill.

The recently released new FreeSurfer methodology allows for the additional investigation of morphological abnormalities of the CA4-dentate gyrus subfield, which is located inside the hippocampus structure. The dentate gyrus is involved in neurogenesis and it has been suggested that childhood trauma can suppress neurogenesis and hence result in smaller CA4-dentate gyrus subfield (Teicher et al., 2012). As *chapter 5* has revealed that hippocampal volume is correlated with childhood trauma it would be most interesting to acquire information about the CA4-dentate gyrus subfield in future studies involving DID or other (childhood) trauma-related disorders to test the hypothesis that childhood trauma affects neurogenesis.

Genetic and epigenetic

Not everybody exposed to childhood maltreatment develops psychopathological disorders such as DID and PTSD. This suggests that genetic factors as well as interaction of genetic and environmental factors (epigenetic) may modulate the consequences of childhood maltreatment. In *chapter 4* we found that the cortical surface-area of several cortical regions was smaller in DID and PTSD patients compared to HC. It has been shown that cortical surface-area is highly heritable (Chen et al., 2012, Yoon et al., 2012). Therefore, smaller cortical surface-area of several cortical regions in DID and PTSD, relative to HC, and other morphological differences between DID or PTSD and HC can be due to genetic factors, and gene-environmental factors (Becker-Blease et al., 2004, Jaffee and Price, 2012). Future studies investigating the influence of genetic factors on neuroanatomical and neurobiological measurements of DID patients are needed to shed more light on the biological underpinning of this disorder.

The etiology of DID

The etiology of DID has been a topic of debate between proponents of the diametrically opposed trauma-related and non-trauma-related models. This thesis sought to use objective empirical data in a quest to provide empirical data to inform holders of either model. Furthermore, the results presented in this thesis informs about the neuropathology and etiology of DID. The subjectively reported and neurobiological data presented in this thesis (*chapters 4-6*) are generally in line with the trauma-related model.

The DID patients participating in the studies presented in this thesis (*chapter 4-6*) reported severe childhood maltreatment (see page 132 of this thesis) including emotional neglect and abuse, and physical and sexual abuse, as measured with the childhood trauma questionnaire (CTQ) (Bernstein et al., 1994) and the traumatic experience checklist (TEC) (Nijenhuis et al., 2002). Furthermore, compared to HC, the DID patients reported lower parental attachment, as measured with the parental bonding instrument (PBI) (Parker et al., 1979)). Freyd's betrayal trauma theory (Freyd, 1996) poses that children who are abused and betrayed by their caregivers use dissociation to block the memory of abuse out of their conscious awareness. This makes it possible to still engage in attachment relationships. Putnam (1997) proposed a developmental model, i.e. the "discrete behavioral states" model. He theorized that infants and children create distinct behavioral states in different environments and interpersonal interactions, and the process of maturation is consolidating an integrated sense of self from theses discrete behavioral states which predominate in infancy until these discrete states eventually unify, and present as a continuous self across differing situations. Putnam posits that an abusive child-caregiver relationship is inadequate to allow a child to complete the developmental task of consolidating an integrated sense of self from the discrete behavioral states. Functional neuroimaging studies have provided support for identity state-dependent differences in the integration of self-relevance information in DID patients (Reinders et al., 2003). It was shown that in response to traumatic memories different identity states in DID activate different

regions of brain (Reinders et al., 2003 and 2006).

Studies investigating effects of childhood maltreatment on brain maturation have proposed that early stress produces a cascade of neurobiological changes in the brain on neuro-hormonal, functional and structural levels (Teicher et al., 2003). It had been proposed that these changes can cause a long lasting impact on brain development (Teicher et al., 2003). If DID is a childhood trauma-related disorder neurobiological and structural changes should be similar to those reported in traumatized individuals.

DID as a trauma-related disorder

Similar abnormality of gray matter volume/surface-area of the frontal, temporal and insular cortices were found in DID and PTSD patients, as compared to HC. On a subcortical level, it was found that as compared to HC, bilateral hippocampal volume was smaller in the DID patients (*chapter 4* and *chapter 5*) and the right hippocampal volume showed a trend to be smaller in the PTSD patients (*chapter 5*). Furthermore, relative to HC, in both the DID and PTSD groups contractions were observed in several hippocampal subfields (*chapter 5*). Taken together, these findings indicate that DID is a trauma-related disorder related to (early) antecedent trauma.

Further testing revealed smaller hippocampal volume to be correlated with childhood trauma scores reported by DID and PTSD patients. If the claim of the non-trauma-related model would hold and the memories of childhood maltreatment are fabricated it was unlikely to find correlations between childhood maltreatment scores and hippocampal volumes.

Results of the DTI study (*chapter 6*) showed brain (micro)structural differences between patient groups (DID or PTSD) and HC. The most prominent WM integrity difference between DID and HC was found in the genu of the CC whereas comparing PTSD to HC the most prominent difference in WM integrity was found in the splenium of the CC. We speculated that this finding can be indicative of the early childhood trauma related origin of DID, as evidenced by the relationship

between timing of trauma and CC maturation and myelination. Studies have shown that CC maturation occurs in a rostral-caudal pattern, i.e. the genu matures earlier in life and the splenium matures in later ages. Hence, early childhood trauma results in WM integrity disruption in the genu, as it was observed in DID patients, and later childhood trauma leads to WM integrity disruption of the splenium, as it was found in the PTSD group.

DSM-5

DID was officially recognized as a mental disorder in the DSM-III (as multiple personality disorder) and DSM-IV, and is still included in the DSM-5, despite some attempts to remove DID from the DSM-5 (Gharaibeh and Merskey, 2009). Even today this debate continues and while writing this discussion a new opinionated publication emerged from proponents of the non-trauma related view by (Paris, 2012), which named DID as a psychiatric "fad" and argued against the inclusion of DID in DSM-5 as a valid diagnosis. The latter paper was criticized by experts in the field of DID in letters to the editor (Brand et al., 2013, Martinez-Taboas et al., 2013) as it focused on a single case report, disregarded a number of neurobiological and psychophysiological studies in DID (for example: Elzinga et al. (2007), Reinders et al. (2003, 2006 and 2012), Sar et al. (2001, 2007) and Vermetten et al. (2006)) and only cited relatively old studies conducted in the US, instead of recent international studies of DID. Numerous studies and empirical data including cross-cultural epidemiological studies indicate a trauma-related etiology for DID. It remains interesting that the DID diagnosis has been indicated to be overdiagnosed, misdiagnosed and an iatrogenic artifact created by a variety of non-traumagenic origins. There is no doubt that cases of individuals who try to imitate DID exist (Draijer and Boon, 1999), but this does not preclude the existence of genuine DID patients. We believe that it is essential that mental health professionals consider the existence of genuine cases of DID as these patients are at risk to spend several years of unsuccessful therapy in mental healthcare institutes (Arbour, 1998, Ross et al., 1989). Mrs. IB whose case report was presented in *chapter 1* serves as an example of mental health mismanagement. If such patients were diagnosed

correctly as suffering from DID at a younger age they could have benefited from a phase-orientated treatment specific to DID earlier in life (Brand et al., 2012, Ellason and Ross, 1997) and consequently could have had a better quality of life.

General conclusion of the thesis

Using neuroimaging techniques, this thesis aimed to provide more insight into the neural correlates underlying dissociative identity disorder. The findings presented in chapter 4-6 of this thesis mainly provide objective empirical support in favor of a trauma-related etiology for DID and thereby, hopefully, can move the etiology discussion forward. Therefore, the current thesis may help to resolve the controversies surrounding DID's genuineness and etiological discussion. Although we realize that much remains still unknown about brain function in DID we feel that the findings of this thesis can make an important contribution to the ongoing debate concerning the etiology of DID. More knowledge about the neurobiology of DID may ultimately lead to a better clinical understanding and the development of innovative treatment strategies.

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