The traumatized brain

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Structural Connectivity in Dissociative Identity Disorder and Posttraumatic Stress Disorder: A Diffusion Tensor Imaging Study

Chapter

6

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Abstract

Background: Childhood maltreatment as an early life stressor has been found to have damaging effects on brain development. Dissociative identity disorder (DID) has been associated with childhood trauma and has been indicated to be a severe form of posttraumatic stress disorder (PTSD). Thus far, neuroimaging studies have identified gray matter morphological abnormalities in DID patients which were similar to that of PTSD patients. However no study has yet investigated abnormalities of structural connectivity of white matter (WM) in DID patients.

Methods: Diffusion tensor imaging (DTI) data were collected from seventeen DID patients, sixteen PTSD patients and thirty-two healthy controls (HC), all matched for gender, age and education. Maps of DTI measures, including fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) were generated and analyzed using tract-based spatial statistics (TBSS) and were compared between the groups.

Results: DID was associated with lower FA and higher MD, RD and AD in several regions and most prominently in the genu of the corpus callosum (CC), as compared to HC. PTSD was associated with widespread regions of significant lower FA and higher MD and RD, compared to HC. Direct comparisons of DTI measures between DID and PTSD revealed lower WM integrity in PTSD most prominently in the splenium of CC.

Conclusions: DID and PTSD groups showed more differences in WM integrity when compared to HC than when compared to each other. We propose that our findings of more pronounced WM integrity disruption in PTSD as compared to DID might be due to the differences in timing of the experienced trauma and in dissociative symptoms. We hypothesize that in DID patients the development of dissociation mechanisms in response to repeated maltreatment may protect WM during pruning. Furthermore, due to plasticity of the brain the effects of early life trauma can possibly be reversed or result in brain WM re-organization, whereas the effects of stress after the brain's sensitive developmental period, e.g. in PTSD,

might be irreversible. However, effects of (antipsychotic) medication in the DID group might also have contributed to this finding. In sum, our findings indicate that both DID and PTSD are associated with changes in structural connectivity and therefore can help in better understanding the neural correlates of both disorders.

Introduction

Severe stress can cause functional and structural alterations of the brain (Bremner, 1999, McEwen, 2000). As an early stressor, childhood maltreatment (i.e. emotional, physical and sexual abuse as well as emotional neglect) tend to have short-term and long-term effects on the developing brain by altering neurogenesis, myelination, and synaptic overproduction and pruning during sensitive periods of brain maturation (Kaufman et al., 2000, Teicher et al., 2003). Previous volumetric studies have reported several structural abnormalities associated with childhood maltreatment including attenuated left hemisphere maturation (Teicher et al., 1997), and smaller size of the hippocampus (Bremner et al., 2003, Teicher et al., 2012), amygdala (Aas et al., 2012), anterior cingulate cortex (Kitayama et al., 2006) and several sub-regions of the corpus callosum (CC) (Andersen et al., 2008, De Bellis et al., 1999 and 2002, De Bellis and Keshavan, 2003, Kitayama et al., 2007, Teicher et al., 1997 and 2004, Villarreal et al., 2004). These adverse effects of childhood maltreatment on brain development could partly be the reason that childhood maltreatment has became a major risk factor for developing several psychiatric disorders in adulthood, for example anxiety disorders (Gibb et al., 2007), posttraumatic stress disorder (PTSD) (Bremner et al., 2003, Wolfe et al., 2006), mood-related disorders (Wolfe et al., 2006), psychosis (Aas et al., 2012, Hoy et al., 2012) and schizophrenia (Sideli et al., 2012).

Clinical observations and empirical research indicate that dissociative symptoms and dissociative identity disorder (DID) are causally related to severe and chronic maltreatment that started in early childhood. It includes physical and emotional neglect and abuse, and sexual abuse, often combined with disorganized attachment and a lack of affect-regulation by caregivers (Boon and Draijer, 1993, Chu and Dill, 1990, Mulder et al., 1998, Nijenhuis and Den Boer, 2009, Spiegel,

2006, Van der Hart et al., 2006). DID has been indicated to be at the far end of the spectrum of trauma-related disorders (Spiegel, 1984) and thereby to be a severe form of (dissociative) PTSD (Lanius et al., 2006b, Van der Hart et al., 2006). According to the DSM-IV, DID is characterized by the presence of two or more different identity states that recurrently take control of a person's behavior and consciousness. Different prototypical identity states have been found to be related to different patterns of brain activation (Reinders et al., 2003, 2006 and 2012). Episodes of dissociative amnesia, depersonalization, derealization, and sensorimotor dissociative symptoms are other characteristic features of this disorder. So far, neuroimaging studies investigating morphological changes in DID have only focused on gray matter morphology and have reported cortical and subcortical volumetric differences between DID and healthy controls (HC) (Chalavi et al., submitted, Ehling et al., 2008, Tsai et al., 1999, Vermetten et al., 2006), as well as cortical volumetric similarities between DID and PTSD (Chalavi et al., submitted). To the best of our knowledge white matter (WM) morphological abnormality in DID patients has not been studied to date.

White matter of the brain, which transmits signals from one region of the cerebrum to another and between the cerebrum and lower brain regions and vise versa, can be studied using ‘diffusion tensor imaging’ (DTI). DTI is a relatively new magnetic resonance imaging technique (Le Bihan et al., 2001), which provides a quantitative method to assess structural connectivity and integrity of WM tracts in the brain by measuring the directionality of water diffusion (Basser and Pierpaoli, 1996). Water diffusion in the brain is modified by its physical environment and in WM tissue water diffusion is restricted by myelin sheaths, and axonal membranes. This leads to diffusion being greater along fiber tracts than across them, which is known as fractional anisotropy (FA). FA is believed to reflect the degree of fiber organization, fiber directional coherence, or WM integrity.

Long axonal connections are established in early development, but it has been suggested that the diameter and structure of axons and their myelination continue to develop into adulthood (Keshavan et al., 2002). Therefore (lack of) stimulation or

adversity during life can affect WM development and thereby affect WM integrity (De Bellis and Keshavan, 2003, Denenberg, 1981, Juraska and Kopcik, 1988, Sanchez et al., 1998). Thus far, a limited number of DTI studies have investigated abnormalities in WM integrity in traumatized individuals (see Daniels et al. (2013) for a review). In children, adolescents and adults with a history of childhood maltreatment, compared to matched HC, lower WM integrity has been reported in several WM tracts including the medial and posterior CC (Huang et al., 2012, Jackowski et al., 2008, Paul et al., 2008, Teicher et al., 2010), uncinate fasciculus (Eluvathingal et al., 2006, Govindan et al., 2010), superior longitudinal fasciculus (Govindan et al., 2010, Huang et al., 2012), cingulum (Choi et al., 2009b, Eluvathingal et al., 2006, Huang et al., 2012) and corona radiata (Teicher et al., 2010). These reports suggest that childhood maltreatment is associated with abnormal structural connectivity of WM. Investigating WM integrity in DID can therefore inform about the etiology and neurobiology of DID.

In the current study we aimed to investigate whole-brain WM integrity in individuals with DID in comparison to gender-, age- and education-matched PTSD patients and HC. Based on prior DTI reports in traumatized individuals, we expected to find disruptions in white matter integrity in both DID and PTSD patients as compared to HC. In addition, we hypothesized that disruptions in WM integrity would be more pronounced in the DID group than in the PTSD group.

Methods

Subjects

Sixty-five subjects underwent magnetic resonance imaging (MRI): seventeen individuals with DID, sixteen individuals with PTSD and thirty-two HC. The sample used in this chapter is similar to the sample used in chapters 4 and 5. All participants were female as only female DID patients volunteered to take part in this study. In addition, all subjects were matched for age, level of education and Western European ancestry. DID and PTSD patients were recruited via mental health care institutions and internet advertisements. The diagnosis of DID was

assessed by one of two DID experts (E.N. and N.D.) using the Structural Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) (Boon and Draijer, 1993, Steinberg, 1993) and PTSD comorbidity was determined using the PTSD section of the SCID-D (Steinberg, 1993). All DID patients met the criteria for either comorbid PTSD (82.35%) or PTSD in remission (17.65%). PTSD patients were diagnosed by researchers E.V. and M.G. using the Clinician Administered PTSD Scale (CAPS) interview (Blake et al., 1995). Only PTSD patients with inter-personal trauma were included in the current study.

Exclusion criteria for DID and PTSD patients were: age outside the range of 18-65, pregnancy, systemic or neurological illness, claustrophobia, presence of metal implants in the body and alcohol/drug abuse. HC were recruited through advertisements in local newspapers. Additional exclusion criteria for HC were: the presence of dissociative symptoms, as determined with the Dissociative Experiences Scale (DES) (Bernstein and Putnam, 1986) and Somatoform Dissociation Questionnaire (SDQ-20) (Nijenhuis et al., 1996), a high score on the Traumatic Experience Checklist (TEC) (Nijenhuis et al., 2002) or mental illness in the past or at present. All participants were given a complete description of the study and gave written informed consent according to procedures approved by the Medical Ethical Committee (METc) of the University Medical Center Groningen (UMCG) and of the Amsterdam Medical Center (AMC).

Demographical and clinical data

Table 6.1 lists clinical and demographical characteristics of the participants. DID patients filled in the questionnaires in their most predominant identity state. Depersonalization and dissociative symptoms were evaluated using the Cambridge Depersonalization Scale (CDS) (Sierra and Berrios, 2000), DES (Bernstein and Putnam, 1986) and SDQ-20 (Nijenhuis et al., 1996). Reports of potentially traumatizing events were assessed using the TEC (Nijenhuis et al., 2002). This questionnaire quantifies the presence of potentially traumatizing events during lifetime and additionally the severity of the potentially traumatizing events can be

studied in more details during the developmental period (i.e. 0-6, 7-12 and 13-18 years old). Participants' psychotropic medication was not discontinued in this study. The past medical history in the DID group included: antipsychotics (n=2), antidepressants (n=2), anti-epileptics (n=1). The present medications in the DID group included antipsychotics (n=8), antidepressants (n=10), anti-epileptics (n=3). Two PTSD patients reported using antidepressants at the time of scanning. All HC were free of present and past psychiatric medication.

DTI data acquisition

Participants were scanned on a 3T MR scanner (Philips Medical Systems, Best, NL) in one of the participating centers in The Netherlands (Groningen (UMCG) and Amsterdam (AMC)) and balanced over the two centers (ten DID patients, ten PTSD patients and nineteen healthy controls were scanned at the UMCG). High resolution echo-planar DTI acquisition parameters at both centers were: TR/TE=8749/86 ms, flip angle=90, FOV= 256 mm sampled on a 128x128 matrix, 69 axial slices with slice thickness of 2 mm and in images were acquired in an interleaved slice order. Images were collected with diffusion sensitizing gradients applied along 60 directions with a b-factor of 1300 s/mm^2, along with six images with no diffusion sensitization gradients. The total scan time was 9.77 minutes. Two DTI scans were collected from each subject whenever possible (successful in fifteen DID patients and fourteen HC). Where both scans were artifact-free, the first scan was used.

Table 6.1. *Demographical and clinical characteristics of the participants*

	Mean (SD)			ANOVA		Post hoc (P-value)		
	DID (n=17)	**PTSD (n=16)**	**HC (n=32)**	**Statistic**	***P*-value**	**DID vs. HC**	**DID vs. PTSD**	**PTSD vs. HC**
Demographics								
Age, years	43.82 (9.85)	40.75 (12.05)	41.91 (12.16)	F(2,62)=0.30	0.74			
Education, years	14.88 (0.99)	14.94 (0.85)	15.09 (1.14)	F(2,62)=0.65	0.52			
Clinical measures								
Dissociative symptoms								
psychoform (DES)	54.41 (16.18)	22.18 (13.83)	6.92 (10.79)	F(2,62)=72.78	**<0.001***	**<0.001***	**<0.001***	**<0.001***
somatoform (SDQ-20)	57.06 (17.26)	32.69 (13.43)	22.53 (4.01)	F(2,62)=51.63	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Depersonalization symptoms (CDS)								
frequency	1.91 (0.51)	0.85 (0.44)	0.27 (0.30)	F(2,62)=93.44	**<0.001***	**<0.001***	**<0.001***	**<0.001***
duration	2.73 (0.70)	1.37 (0.72)	0.44 (0.46)	F(2,62)=82.09	**<0.001***	**<0.001***	**<0.001***	**<0.001***
total	134.76 (33.46)	64.56 (32.70)	20.56 (20.94)	F(2,62)=94.55	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Traumatic Experience Checklist (TEC) – total								
emotional neglect	12.23 (3.15)	7.5 (5.82)	2.31 (4.17)	F(2,62)=29.04	**<0.001***	**<0.001***	**0.003***	**<0.001***
emotional abuse	11.06 (4.11)	6.81 (5.36)	0.81 (2.26)	F(2,62)=29.04	**<0.001***	**<0.001***	**0.002***	**<0.001***
physical abuse	10.76 (4.56)	3.69 (4.19)	1.09 (3.16)	F(2,62)=44.60	**<0.001***	**<0.001***	**<0.001***	**0.030***
sexual harassment	8.76 (5.32)	2.56 (2.58)	0.53 (1.27)	F(2,62)=35.72	**<0.001***	**<0.001***	**<0.001***	**0.037***
sexual abuse	9.17 (5.13)	2.37 (3.07)	0.16 (0.63)	F(2,62)=39.12	**<0.001***	**<0.001***	**<0.001***	**0.021***
total trauma score	17.53 (4.08)	11.06 (4.01)	2.62 (2.95)	F(2,62)=103.57	**<0.001***	**<0.001***	**<0.001***	**<0.001***

DID= dissociative identity disorder; PTSD= posttraumatic stress disorder; HC= healthy controls; DES= dissociative experiences scale; SDQ-20= somatoform dissociation questionnaire; CDS= Cambridge depersonalization scale; TEC= traumatic experience checklist.
** P-Value<=0.05*

DTI data acquisition

Participants were scanned on a 3T MR scanner (Philips Medical Systems, Best, NL) in one of the participating centers in The Netherlands (Groningen (UMCG) and Amsterdam (AMC)) and balanced over the two centers (ten DID patients, ten PTSD patients and nineteen healthy controls were scanned at the UMCG). High resolution echo-planar DTI acquisition parameters at both centers were: TR/TE=8749/86 ms, flip angle=90, FOV= 256 mm sampled on a 128x128 matrix, 69 axial slices with slice thickness of 2 mm and in images were acquired in an interleaved slice order.

Images were collected with diffusion sensitizing gradients applied along 60 directions with a b-factor of 1300 s/mm^2, along with six images with no diffusion sensitization gradients. The total scan time was 9.77 minutes. Two DTI scans were collected from each subject whenever possible (successful in fifteen DID patients and fourteen HC). Where both scans were artifact-free, the first scan was used.

DTI data analysis

FMRIB software library (FSL version 4.1.9; www.fmrib.ax.ac.uk/fsl) was used for image analysis. Images were skull stripped using the FSL brain extraction tool (Smith, 2002) and then corrected for motion and eddy current (Jenkinson and Smith, 2001). Maps of fractional anisotropy (FA), which quantifies the directionality of diffusion of water within a voxel, were generated by fitting a tensor model at each voxel using the DTIfit in FSL. Voxel-wise group comparisons were then performed using FSL-TBSS (Tract-Based Spatial Statistics) (Smith et al., 2006).

All subjects' FA data were aligned into a common space (the Montreal Neurological Institute (MNI)-152) with non-linear registration. Thereafter, the mean FA map, which represents the centers of all tracts common to all subjects, was calculated and then thresholded at an FA>0.2. Each subject's aligned FA map was then projected onto this skeleton by searching the data around it for each subject's FA map in the direction perpendicular to each tract, finding the highest local FA and assigning this value to the skeleton. The diffusion tensor is represented by three

eigenvectors and corresponding eigenvalues that define an ellipsoid, and can be quantified in terms of a number of scalar measures; besides FA, other quantities that can be derived from the DTI images include mean diffusivity (Basser and Pierpaoli, 1996), axial diffusivity and radial diffusivity (Basser, 1995).

Mean diffusivity (MD) is the average of the three eigenvalues and provides a measure of the degree of restriction to the diffusion of water molecules irrespective of direction. Axial diffusivity (AD), which represents the diffusivity of water in the direction parallel to the fiber bundles, is defined as the major eigenvalue. Radial diffusivity (RD), which measures water diffusion perpendicular to the axonal wall, is defined as the average of the two minor eigenvalues. It has been suggested that the directional diffusivities (i.e. MD, RD and AD) may reflect specific biological processes such as myelin and axonal changes (Song et al., 2002, Song et al., 2005). In general, the relationship between measurements obtained from DTI is such that FA decreases when RD increases and/or AD decreases; in contrast, MD increases when AD and/or RD increases and vice versa (Qiu et al., 2008). In this study the skeletonized MD, RD and AD were similarly extracted by applying the deformations determined in the original non-linear registration of the FA images to the vectors from the FA data).

Statistical analysis

Demographical and clinical data were compared between the three groups using analysis of variance (ANOVA) followed by pairwise *t*-tests. Voxel-wise *t*-tests were conducted on all diffusion parameters using a permutation-based inference tool for nonparametric statistical thresholding (the randomise function, part of FSL)(Smith et al., 2006) and the number of permutations was set to 5000. The following group comparisons were made: 1) DID vs. HC, 2) DID vs. PTSD and 3) PTSD vs. HC. For the initial exploratory analyses the uncorrected maps ($p< 0.05$) were investigated (Fani et al., 2012). Then, the maps were corrected for multiple comparisons correction ($p<0.05$, family-wise error (FWE)) based on the threshold-free cluster enhancement (TFCE) option in the randomise function in FSL. All randomise tests included age and center as covariates, which were de-meaned

prior to analyses (Cole et al., 2012). Anatomical localization of each significant cluster was determined using John Hopkins University (JHU) DTI-based WM atlas (Wakana et al., 2004) provided by FSL.

Results

Demographical and clinical assessment

The DID, PTSD and HC groups did not differ significantly with respect to age and education (Table 6.1). Depersonalization and dissociative (including psychoform and somatoform) symptom scores were significantly higher in the DID group as compared to the HC or PTSD groups. PTSD patients also reported significantly higher depersonalization and dissociative symptoms compared to HC. Furthermore, potentially traumatizing events (as measured with the TEC) were significantly higher in DID compared to both HC and PTSD. The total TEC scores were also higher in the PTSD patients compared to HC.

White matter integrity

The exploratory analyses revealed that compared to HC, DID was associated with lower FA and higher MD, RD and AD in multiple commissural, association and projection fiber tracts including the genu, body and splenium of the CC as well as the superior longitudinal fasciculus, posterior thalamic radiation, anterior corona radiata, internal and external capsules (see Figure 6.1 and Table 6.2). However, these differences did not reach a significant level after applying FWE correction.

Comparing PTSD to HC, the exploratory analyses revealed widespread regions of significantly lower FA (see Table 6.2 and supplementary Figure SF6.1) in PTSD in, among others, the genu, body and splenium of the CC, the cingulum and cingulum-parahippocampal region, the anterior and superior and posterior corona radiata, the anterior and posterior limbs of internal capsule, the external capsule, superior longitudinal fasciculus, sagittal stratum and fornix/stria terminalis. Furthermore, significantly higher MD, RD and AD were observed in a widespread region in PTSD, with a distribution very similar to the FA results (Table 6.2). Except for the AD results, most results of the FA, MD and RD measures survived FWE

multiple comparison correction (Figure 6.2 and supplementary Table ST6.1).

The exploratory analyses of the direct comparisons of DTI measures between DID and PTSD groups (Table 6.2, Figure 6.3) revealed lower FA and/or higher MD and RD and AD in PTSD in, among others, the body and splenium of the CC, the right superior longitudinal fasciculus, the external capsule, and subsections of the internal capsule, superior longitudinal fasciculus and cingulum-parahippocampal tracts. However, these results did not survive multiple comparison correction.

No clusters (corrected or uncorrected) with a significant higher FA and/or lower MD, RD or AD were observed in the DID and PTSD groups, when compared to HC, or in the PTSD group when directly compared to the DID group.

Table 6.2. *Location (tract) and size (mm3) of clusters where a significant difference in white matter integrity was found between the groups*

Tracts	DID vs. HC[a]				DID vs. PTSD[a]				PTSD vs. HC[a]			
	FA[b]	MD[c]	RD[c]	AD[c]	FA[d]	MD[e]	RD[e]	AD[e]	FA[f]	MD[g]	RD[g]	AD[g]
Commissural tracts												
Genu of corpus callosum	1074	120	1009	11	-	-	-	199	**1039***	647	**1007***	126
Body of corpus callosum	92	103	298	-	294	216	252	216	**956***	**1254***	**1529***	568
Splenium of corpus callosum	257	82	468	334	1028	199	627	-	**1835***	**1304***	**1826***	160
Association tracts												
Left superior longitudinal fasciculus	459	539	719	625	146	-	-	-	**850***	**1018***	**1027***	-
Right superior longitudinal fasciculus	412	40	645	167	410	13	88	10	**1093***	**1180***	**1252***	115
Left superior fronto-occipital fasciculus	32	27	35	-	-	14	-	-	29	60	**54***	12
Right superior fronto-occipital fasciculus	-	-	-	-	-	-	-	11	25	55	**50***	15
Left uncinate fasciculus	18	51	32	68	-	-	-	-	-	25	-	-
Right uncinate fasciculus	39	-	49	-	-	-	-	-	40	47	44	-
Left external capsule	111	530	321	880	18	243	15	16	**579***	**837***	**763***	401
Right external capsule	52	163	325	331	368	17	89	-	**634***	**539***	**585***	-
Left sagittal stratum	168	329	324	326	79	-	-	-	**366***	**367***	**393***	-
Right sagittal stratum	79	37	127	29	50	-	23	-	**381***	**372***	**412***	160
Left fornix (crus)/stria terminalis	-	54	39	42	-	-	-	-	**87***	51	**72***	-
Right fornix (crus)/stria terminalis	10	167	83	161	140	-	-	-	**154***	88	**72***	-
Left cingulum	37	59	107	70	-	-	-	163	-	300	**-**	343
Right cingulum	-	45	36	-	-	193	-	-	**19***	**301***	**124***	315

Table 6.2 (cont.). *Location (tract) and size (mm3) of clusters where a significant difference in white matter integrity was found between the groups*

Tracts	DID vs. HC[a]				DID vs. PTSD[a]				PTSD vs. HC[a]			
	FA[b]	MD[c]	RD[c]	AD[c]	FA[d]	MD[e]	RD[e]	AD[e]	FA[f]	MD[g]	RD[g]	AD[g]
Left cingulum-parahippocampal WM	37	30	53	16	157	-	75	-	**159***	-	92	-
Right cingulum-parahippocampal WM	35	170	122	224	204	-	-	-	158	179	**174***	103
Projection tracts												
Left anterior internal capsule	356	545	528	432	26	89	-	-	374	**443***	**471***	168
Right anterior internal capsule	239	136	131	239	-	34	-	28	**289***	276	**330***	50
Left posterior internal capsule	187	244	233	175	61	28	-	-	263	**130***	**172***	-
Right posterior internal capsule	233	237	338	172	142	99	130	10	**523***	**462***	**545***	16
Left retrolenticular internal capsule	-	69	66	146	244	-	-	-	**203***	**261***	**262***	-
Right retrolenticular internal capsule	22	80	117	60	257	-	146	-	**542***	**490***	**617***	163
Left anterior corona radiata	500	684	1017	353	-	-	-	-	**667***	946	**961***	19
Right anterior corona radiata	431	-	629	-	-	-	-	-	**897***	397	**1011***	117
Left superior corona radiata	296	129	493	93	43	-	-	-	**662***	**1036***	**1002***	12
Right superior corona radiata	35	-	269	-	240	221	209	90	**672***	**1148***	**1069***	316
Left posterior corona radiata	61	67	227	232	224	-	-	-	**337***	**441***	**472***	-
Right posterior corona radiata	40	19	139	14	171	-	11	-	**294***	**473***	**437***	128
Left posterior thalamic radiation	597	659	717	415	192	52	11	-	**870***	**825***	**900***	28
Right posterior thalamic radiation	646	278	807	64	69	-	-	-	**857***	**790***	**904***	116

[a] P-Value<=0.05 (uncorrected), unless marked with an additional ''*
[b] DID < HC; [c] DID > HC; [d] PTSD < DID; [e] PTSD > DID; [f] PTSD < HC; [g] PTSD > HC
** Clusters that survived multiple comparison correction (family-wise error, P-value<=0.05); For the exact number of voxels in the corrected statistical map see supplementary Table ST6.1.*

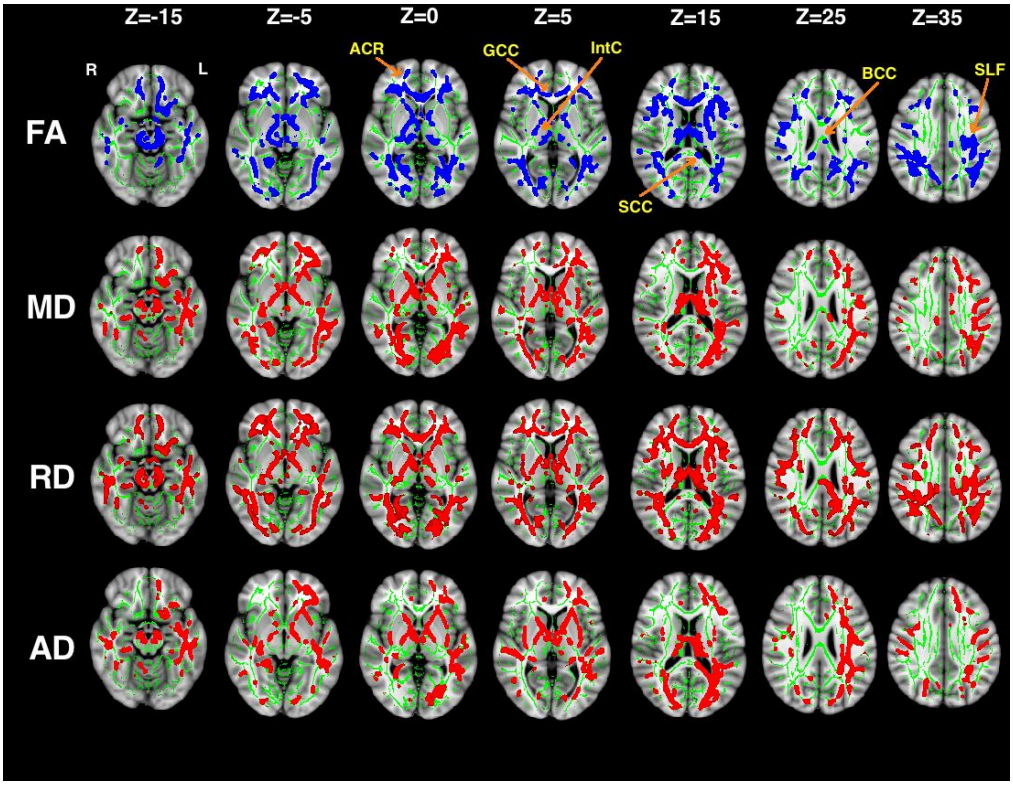

Figure 6.1. *Regions where a difference in DTI measures was found between DID and HC (uncorrected, p<0.05). Green coloration indicates the white matter skeleton where no significant differences were found. The blue colored regions indicate lower FA in DID compared to HC and the red colored regions indicate higher MD, RD or AD in DID compared to HC. Abbreviations: FA , fractional anisotropy; MD, mean diffusivity; RD , radial diffusivity; AD, axial diffusivity; DID, dissociative identity disorder; HC, healthy control; L, left; R, right; ACR, anterior corona radiata; GCC, genu of corpus callosum; BCC, body of corpus callosum; SCC, splenium of corpus callosum; IntC, internal capsule; SLF, superior longitudinal fasciculus.*

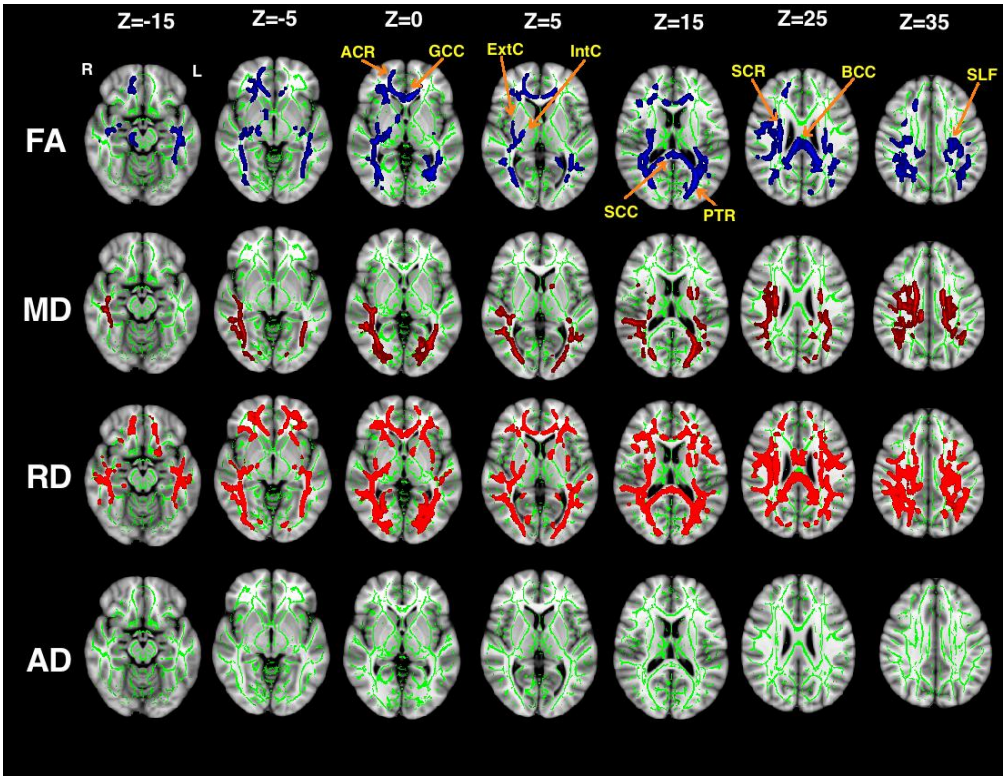

Figure 6.2. *Regions where a difference in DTI measures was found between PTSD and HC (family-wise error corrected, p<0.05). Green coloration indicates the white matter skeleton where no significant differences were found. The blue colored regions indicate lower FA in PTSD compared to HC and the red colored regions indicate higher MD, RD in PTSD compared to HC. Abbreviations: PTSD, posttraumatic stress disorder; HC, healthy control; L, left; R, right; ACR, anterior corona radiata; GCC, genu of corpus callosum; BCC, body of corpus callosum; SCC, splenium of corpus callosum; IntC, internal capsule; ExtC, external capsule; PTR, posterior thalamic radiation; SCR, superior corona radiata; SLF, superior longitudinal fasciculus.*

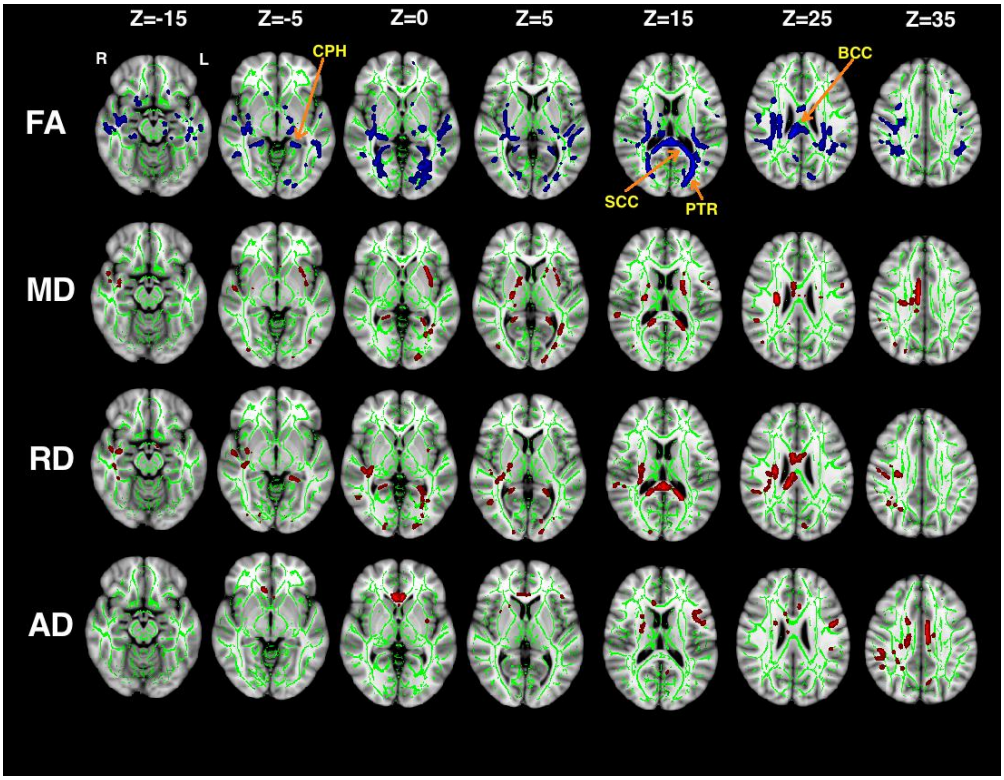

Figure 6.3. *Regions where a difference in DTI measures was found between DID and PTSD (uncorrected, p<0.05). Green coloration indicates the white matter skeleton where no significant differences were found. The blue colored regions indicate lower FA in PTSD compared to DID and the red colored regions indicate higher MD, RD in PTSD compared to DID. Abbreviations: DID, dissociative identity disorder; PTSD, posttraumatic stress disorder; L, left; R, right; CPH, cingulum-parahippocampal white matter; BCC, body of corpus callosum; SCC, splenium of corpus callosum; PTR, posterior thalamic radiation; SCR, superior corona radiata.*

Discussion

The present study is the first to investigate whole-brain structural connectivity in DID patients and to compare this to gender-, age- and education-matched PTSD patients and healthy controls. In the DID patients, compared to HC, we found lower FA and higher MD, RD and AD in several fiber tracts, most prominently in the genu of the CC, although these differences failed to meet a corrected threshold. Furthermore, widespread significant WM integrity disruptions were present in the

PTSD group, relative to HC, in several major commissural, association and projection tracts. Direct comparisons of DTI parameters between the DID and PTSD groups revealed a small number of regions with lower FA and higher MD, RD and AD in PTSD.

DID and PTSD versus HC

Corpus callosum (CC)

Our findings of lower WM integrity in several subregions of the CC (see Table 6.2) when comparing the DID or PTSD groups to HC are in accordance with prior DTI studies in children (Jackowski et al., 2008), adolescents (Huang et al., 2012) and adults (Paul et al., 2008, Teicher et al., 2010) with a history of childhood maltreatment. Furthermore, smaller CC volume has been reported in children with a history of abuse or neglect compared to healthy control subjects (De Bellis et al., 2002, Teicher et al., 2004). The CC is the largest commissural WM pathway in the human brain. The most rostral region of the CC, the genu, contains axons connecting the prefrontal brain regions of the two brain hemispheres. The caudal region of the CC consists of the body and splenium and contains fibers connecting occipital, temporal, parietal and insula regions of the two hemispheres. In line with the current results several functional MRI studies have indicated abnormal activity of the frontal, temporal, parietal and insular cortices in DID (Reinders et al., 2003, Sar et al., 2001) and PTSD (Lanius et al., 2006) patients. It has been documented that the prefrontal cortex and the insula have an important role in emotion modulation (Phan et al., 2002), the prefrontal cortex also having a key role in memory functions (Blumenfeld and Ranganath, 2007). These cognitive functions are known to be disturbed in DID (Dorahy, 2001, Reinders et al., 2003, Van der Hart et al., 2005) and PTSD (Lanius et al., 2010, Samuelson, 2011) patients. Furthermore, structural MRI studies in PTSD have reported smaller gray matter volume of the frontal (Geuze et al., 2008), temporal (Woodward et al., 2009) and insula (Kasai et al., 2008) cortices. A separate study in the current sample focused on gray matter volumetric measurements of DID and PTSD patients and reported smaller cortical volume of the bilateral frontal and temporal cortices and left insular

cortex in DID and PTSD patients as compared to HC (Chalavi et al., submitted). Although a direct link between function and brain morphology remains a topic of scientific research (Honey et al., 2010) we speculate that lower WM integrity of the CC subregions in the DID or PTSD patients as compared to HC could be linked to smaller GM volume of the frontal, temporal and parietal cortices and thereby to the abnormal cognitive functions such as memory and emotion regulation in DID and PTSD patients (Dorahy, 2001, Lanius et al., 2010, Reinders et al., 2003, Van der Hart et al., 2005).

Association fibers

Regarding the association fibers, the most prominent differences between the DTI measures of both the DID and PTSD groups, compared to HC, were present in the superior longitudinal fasciculus (SLF). These findings are in line with prior DTI studies in children and adolescents exposed to childhood maltreatment (Govindan et al., 2010, Huang et al., 2012). The SLF is a major pathway connecting cortical regions of the frontal to the parietal, temporal and occipital lobes and it is involved in a variety of cognitive and executive brain functions (Makris et al., 2007). Therefore, our findings of lower WM integrity of SLF in DID and PTSD patients could be related to impaired emotion regulation (Lanius et al., 2010). Furthermore, lower WM integrity of the SLF in DID and PTSD groups compared to HC could be also related to the smaller gray matter volumes of the frontal and temporal cortices in the DID and PTSD patients (Chalavi et al., submitted).

Limbic system

In both DID and PTSD groups, relative to HC, lower WM integrity was found in the cingulum and in its extension to the parahippocampal region, which are both part of the limbic system. Abnormal WM integrity of the cingulum has been previously reported in several DTI studies in children and adults with childhood maltreatment (Choi et al., 2009b, Eluvathingal et al., 2006, Huang et al., 2012) and also in PTSD patients who suffered from adulthood-trauma (Abe et al., 2006, Kim et al., 2005, Kim et al., 2006, Zhang et al., 2012). The cingulum bundle is the most prominent WM tract in the limbic system, connecting the cingulate gyrus to the entorhinal

cortex, hippocampus and amygdala. Therefore any damage to this fiber tract may affect processes related to the prefrontal-limbic system (Braun, 2011), including regulating the hypothalamic-pituitary-adrenal (HPA) axis during stress (Herman et al., 2005, Jankord and Herman, 2008) and emotion regulation (Phan et al., 2002). It is possible that the disrupted structural connectivity in the cingulum bundle is related to the dysregulation of the HPA axis and emotion regulation which have been implicated in the pathophysiology of PTSD (Yehuda, 1997) and dissociative disorders (Simeon et al., 2007).

Other fiber tracts

Other differences in WM integrity between DID or PTSD patients and HC were found in association fibers such as the fronto-occipital fasciculus, uncinate fasciculus, external capsule and sagittal stratum, and in the projection fibers including the corona radiata, internal capsule, thalamic radiation and in limbic fiber of the fornix. Some of these findings, i.e. the fronto-occipital fasciculus, uncinate fasciculus, internal capsule and fornix, have been reported in prior DTI studies in traumatized individuals (Admon et al., 2012, Choi et al., 2009a, Coplan et al., 2010, Eluvathingal et al., 2006, Govindan et al., 2010, Huang et al., 2012, Teicher et al., 2010).

DID versus PTSD

In contrast to our a priori hypothesis we found more pronounced WM integrity disruptions in the PTSD group than in the DID group, when compared to HC. Direct comparisons of the DTI measures between DID and PTSD groups revealed lower WM integrity in the PTSD group in, among others, the body and splenium of the CC, the right superior longitudinal fasciculus, the external capsule, and subsections of the internal capsule, superior longitudinal fasciculus and cingulum-parahippocampal tracts. One possible explanation for this finding is related to the effect of medication. In the current study, half of the DID patients were using antipsychotics (APs) at the time of scanning and one patient had previously used APs. In addition, the DID patients reported using anti-epileptics (current: 3; previously:1), and antidepressants (current:10; previously:2), whereas only two

PTSD patients had reported using antidepressants at the time of scan. So far, two DTI studies have shown that AP medications can have positive effects on WM integrity (Minami et al., 2003, Okugawa et al., 2004). Furthermore, in primates an association between exposure to chronic AP and increased glial proliferation has been observed (Selemon et al., 1999). However, reports of non-significant effects of APs on DTI measures have also been published (Szeszko et al., 2008). Effects of anti-epileptics and antidepressants on WM integrity are even less clear (Cole et al., 2012). Nevertheless, based on reports in the literature, medication usage by the DID patients in our study might have had a positive effect on the microstructural characteristics of the WM tracts in comparison to subjects with little or no medication use.

Another possible explanation of the more pronounced WM integrity disruptions in the PTSD group as compared to the DID group can be related to the differences between these patient groups in timing of the traumatizing experiences as well as differences in dissociative and depersonalization symptoms. In this study, the DID group reported severe potentially traumatizing events, i.e. emotional neglect and abuse and physical and sexual abuse and sexual harassment, which started before the age of 6 and continued throughout the developmental period (see Table 6.3). The PTSD group, on the other hand, only reported sexual abuse and harassment in the age range of 7 to 12 years (see Table 6.3). Table 6.4 shows that DID and PTSD groups differ significantly on reported timing and severity of potentially traumatizing events. Interestingly, these subjective reports appear to be corroborated by the DTI findings as we found that the largest cluster with a lower FA in the DID vs. HC was located in the genu of the CC, and in the PTSD vs. HC in the splenium of the CC. It has been reported that during brain development the most substantial increase in myelination in the CC occurs between the ages of 6 months to 3 years and continues into the third decade of life in a rostral-caudal pattern; i.e. the CC maturation starts from the genu in early ages and continues to the splenium in later ages (Giedd et al., 1996). Therefore, it has been suggested that different subregions of the CC have differing sensitive periods for example to life stressors (Teicher et al., 2002) with the genu being more sensitive in early

childhood and the splenium in later childhood (i.e., 9-10 years old (Andersen et al., 2008)). Although the findings in the CC need to be confirmed by future research, we speculate that our finding of lower WM integrity of the CC subregions in DID and PTSD patients relates to the differences in the timing of reported traumatizing experiences between these disorders.

***Table 6.3**. Potentially traumatizing experiences related to different developmental periods as measure using the TEC*

	Mean (SD)			Group comparison t-test: *P*-value		
	DID (n=17)	**PTSD (n=16)**	**HC (n=32)**	**DID vs. HC**	**DID vs. PTSD**	**PTSD vs. HC**
TEC: 0-6 years						
emotional neglect	5.00 (0.00)	2.50 (2.58)	0.66 (1.56)	**<0.001***	**<0.001***	**0.001***
emotional abuse	4.56 (1.26)	1.81 (2.43)	0.00 (0.00)	**<0.001***	**<0.001***	**<0.001***
physical abuse	4.56 (1.31)	0.62 (1.71)	0.28 (1.11)	**<0.001***	**<0.001***	0.40
sexual harassment	3.81 (1.97)	0.19 (0.75)	0.06 (0.35)	**<0.001***	**<0.001***	0.71
sexual abuse	3.94 (1.98)	0.56 (1.55)	0.00 (0.00)	**<0.001***	**<0.001***	0.15
TEC: 7-12 years						
emotional neglect	4.00 (0.00)	2.50 (2.00)	0.75 (1.46)	**<0.001***	**0.004***	<**0.001***
emotional abuse	3.62 (1.02)	2.31 (1.92)	2.81 (0.92)	**<0.001***	**0.005***	<**0.001***
physical abuse	3.62 (1.09)	1.50 (1.90)	0.34 (1.09)	**<0.001***	<**0.001***	**0.006***
sexual harassment	2.81 (1.76)	1.69 (1.49)	0.13 (0.55)	**<0.001***	**0.011***	<**0.001***
sexual abuse	2.94 (1.77)	1.50 (1.67)	0.00 (0.00)	**<0.001***	**0.001***	<**0.001***
TEC: 13-18 years						
emotional neglect	4.00 (0.00)	2.44 (1.96)	0.66 (1.40)	**<0.001***	**0.002***	<**0.001***
emotional abuse	3.56 (1.09)	2.62 (1.86)	0.28 (0.92)	**<0.001***	**0.039***	<**0.001***
physical abuse	3.25 (1.61)	1.56 (1.90)	0.22 (0.87)	**<0.001***	**0.001***	**0.002***
sexual harassment	3.00 (1.59)	0.69 (1.49)	0.34 (0.79)	**<0.001***	<**0.001***	0.36
sexual abuse	2.87 (1.75)	0.31 (1.01)	0.12 (0.49)	**<0.001***	<**0.001***	0.57

TEC= traumatic experience checklist; DID= dissociative identity disorder; PTSD= posttraumatic stress disorder;
HC= healthy controls.
** P-value<0.05*

Table 6.4*. Statistical comparison of the TEC scores between different age categories in the DID and PTSD groups*

	Mean (SD)			Paired t-test comparisons: *P*-values		
	Age 0-6	Age 7-12	Age 13-18	Age 0-6 vs. Age 7-12	Age 0-6 vs. Age 13-18	Age 7-12 vs. Age 13-18
DID						
Emotional neglect	5.00(0.00)	4.00(0.00)	4.00(0.00)	-[a]	-[a]	-[a]
Emotional abuse	4.56(1.26)	3.62(1.02)	3.56(1.09)	**<0.001***	**0.002***	0.79
Physical abuse	4.56(1.31)	3.62(1.09)	3.25(1.61)	**<0.001***	**<0.001***	0.19
Sexual harassment	3.81(1.97)	2.81(1.76)	3.00(1.59)	**<0.001***	**0.027***	0.33
Sexual abuse	3.94(1.98)	2.94(1.77)	2.87(1.75)	**<0.001***	0.063	0.88
PTSD						
Emotional neglect	2.50(2.58)	2.50(2.00)	2.44(1.96)	1.00	0.92	0.87
Emotional abuse	1.81(2.43)	2.31(1.92)	2.62(1.86)	0.31	0.15	0.43
Physical abuse	0.62(1.71)	1.50(1.90)	1.56(1.90)	0.069	0.14	0.90
Sexual harassment	0.19(0.75)	1.69(1.49)	0.69(1.49)	**0.002***	0.27	**0.027***
Sexual abuse	0.56(1.55)	1.50(1.67)	0.31(1.01)	**0.038***	0.62	**0.011***

TEC= traumatic experience checklist; DID= dissociative identity disorder; PTSD= posttraumatic stress disorder; HC= healthy controls.
[a] *Paired t-test was not calculated since standard deviation of the two variables were zero.*
** P-value<=0.05*

DID patients reported higher dissociative and depersonalization symptoms as compared to PTSD patients (see Table 6.1). It is believed that dissociation is a self-protecting mechanism that is used by the maltreated child to cope with overwhelming and inescapable abuse and neglect. It is likely that DID patients developed dissociative mechanisms in early childhood in line with the onset of maltreatment. Since in the DID group the abuse and neglect was continuous throughout the developmental period, the use of dissociative mechanisms by the DID patients may have served as an iterative learning process for these patients. It has been shown that the maintenance of axonal connections is activity dependent (Steele et al., 2013, Zatorre et al., 2012), implying that active connections remain during pruning, whereas other connections would be eliminated. Therefore, it is possible that the DID group benefited from the development of this highly complex cognitive dissociation mechanism which avoids pruning and maintains intact WM integrity to a greater extent, as compared to PTSD in which potential traumatizing events started later in life and protective dissociative mechanisms were not

developed. However, future research is obviously needed to further address this hypothesis.

It is also possible that in the DID patients WM was re-organized in order to (at least partly) compensate for gray matter loss due to neurotoxic effects of stress hormones and thereby to compensate the possible functional loss. In fact, correlation analyses between total TEC scores and FA measures showed a significant positive correlation in the right cingulum-parahippocampal fiber tract ($r=0.522$, $p=0.002$). Considering that in a previous volumetric study in the same patient groups, we reported negative correlations between the severity of childhood traumatic experiences and hippocampal volume (Chalavi et al., submitted), the positive correlation found between TEC and the FA of the right cingulum-parahippocampal fiber tract are in line with our hypothesis of re-organization of brain network to compensate the detrimental effect of stress on gray matter regions. Future research is needed to investigate the effect of both WM and GM abnormalities on brain functioning in DID.

Besides environmental factors such as stress and childhood maltreatment, genetic factors as well as the interaction of the environmental and genetic factors can influence WM development (Chiang et al., 2009, Kochunov et al., 2010). Therefore, an alternative explanation for our findings of abnormal WM integrity in the DID or PTSD patients is that lower WM integrity in these patients could be a predisposing (genetic) factor. This renders an individual more vulnerable to develop a psychopathological disorder such as DID or PTSD following exposure to stress. Future genetic studies in DID and PTSD groups are needed to investigate this hypothesis.

The pattern of WM integrity disruption of lower FA and higher MD, RD and AD as observed in the DID and PTSD groups, compared to HC, may reflect part of the neurobiological processes involved in the disrupted structural connectivity of DID and PTSD patients. It has been shown that while FA and MD reflect the maturity of structural connectivity, RD and AD reflect the changes in tissue morphology related to axonal myelination and/or organization (Beaulieu, 2002). Increased RD can be

related to delayed or disrupted myelination or to dysmyelination (Song et al., 2002, Song et al., 2005). In contrast, increased AD may be related to poor growth of neurofibrils, such as microtubules and neurofilaments, and the abnormal development of glial cells (Qiu et al., 2008, Wang et al., 2012). Therefore, the observed WM integrity disruptions in the DID and PTSD groups can be related to both disturbed myelination and/or poor neural development.

Limitations

Our findings are limited by the modest sample sizes of 17 DID patients and 16 PTSD patients. Furthermore, we were only able to study females in this study. Given that both normal (Giedd et al., 1996) and stress-related abnormal brain maturation (De Bellis et al., 1999, De Bellis et al., 2002, De Bellis and Keshavan, 2003, Paul et al., 2008, Teicher et al., 2004) are gender-specific, our findings cannot be generalized to male DID and PTSD populations. Another limitation of this study is the difference between the timing of potentially traumatizing experiences between the DID and PTSD groups which made it difficult to explain the WM integrity differences between these groups. Our suggestions for future research are to investigate the effects of medication on the traumatized brain in more detail and in a larger sample size. Furthermore, future studies need to investigate the effect of timing and duration of trauma, especially in relation to dissociative symptoms on the (developing) brain in both female and male individuals.

Conclusion

An interesting finding of the current study is that with regard to WM integrity measures, DID and PTSD groups differed more from HC than from each other. This finding may provide important neurobiological information concerning DID as well as an important contribution to its etiological discussion. In conclusion, this study shows that DID is associated with lower WM integrity in several fiber tracts and most prominently in the genu of the CC. In PTSD patients we additionally found widespread significant lower WM integrity in commissural, association, and projection fibers. These preliminary findings can aid in better understanding the

neurobiological underpinnings in DID and PTSD.

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Supplemental Material for:

Structural Connectivity in Dissociative Identity Disorder and Posttraumatic Stress Disorder: A Diffusion Tensor Imaging Study

Chapter 6

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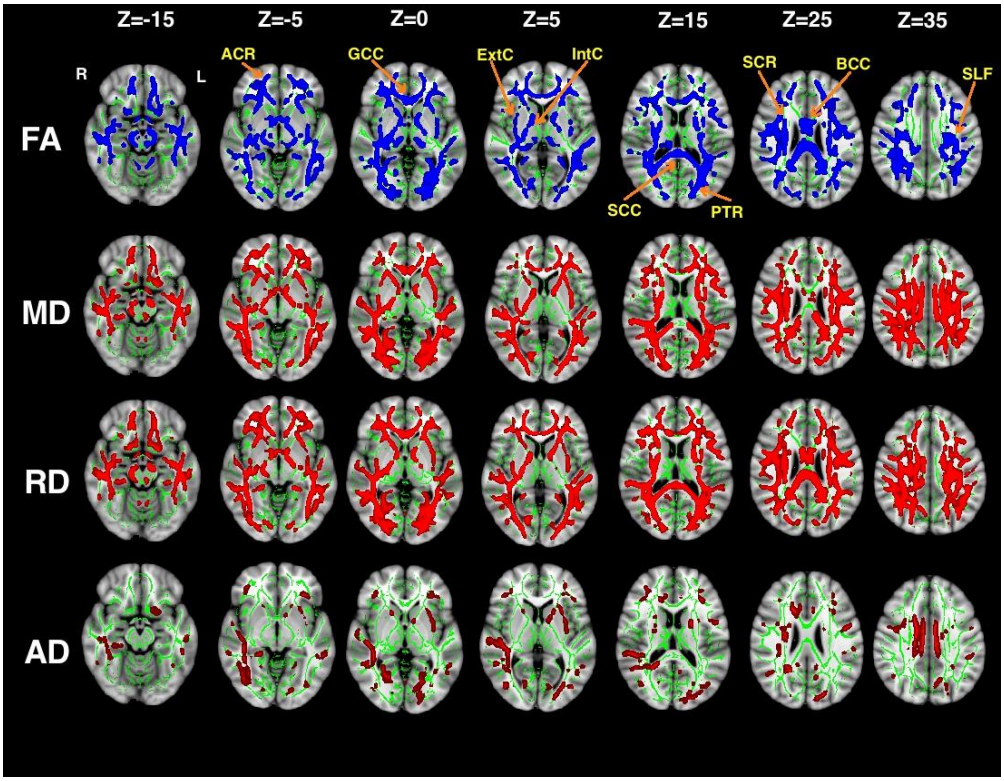
Supplementary Table ST6.1. *Location (tract) and size (mm3) of clusters where a significant difference in white matter integrity was found between PTSD and HC.*

Tract	FA[a]	MD[b]	RD[b]	AD[b]
Commissural tract				
Genu of corpus callosum	826	-	823	-
Body of corpus callosum	429	604	1150	-
Splenium of corpus callosum	1444	257	1452	-
Association tract				
Left superior longitudinal fasciculus	394	276	858	-
Right superior longitudinal fasciculus	856	860	1154	-
Left superior fronto-occipital fasciculus	-	-	40	-
Right superior fronto-occipital fasciculus	-	-	41	-
Left uncinate fasciculus	-	-	-	-
Right uncinate fasciculus	-	-	-	-
Left external capsule	34	55	480	-
Right external capsule	359	14	359	-
Left sagittal stratum	301	58	346	-
Right sagittal stratum	101	162	307	-
Left posterior thalamic radiation	700	484	785	-
Right posterior thalamic radiation	669	415	783	-
Left fornix (crus)/ stria terminalis	58	-	50	-
Right fornix (crus)/ stria terminalis	65	-	57	-
Left cingulum	-	-	-	-
Right cingulum	10	48	24	-
Left cingulum-parahippocampal WM	32	-	-	-
Right cingulum-parahippocampal WM	-	-	99	-

Supplementary Table ST6.1. *Location (tract) and size (mm3) of clusters where a significant difference in white matter integrity was found between PTSD and HC.*

Tract	FA[a]	MD[b]	RD[b]	AD[b]
Projection tract				
Left anterior internal capsule	-	131	352	-
Right anterior internal capsule	25	-	164	-
Left posterior internal capsule	-	29	41	-
Right posterior internal capsule	318	77	414	-
Left retrolenticular internal capsule	150	130	217	-
Right retrolenticular internal capsule	369	258	496	-
Left anterior corona radiata	212	-	754	-
Right anterior corona radiata	582	-	798	-
Left superior corona radiata	315	516	830	-
Right superior corona radiata	467	899	960	-
Left posterior corona radiata	252	291	418	-
Right posterior corona radiata	193	247	373	-
Left posterior thalamic radiation	700	484	785	-
Right posterior thalamic radiation	669	415	783	-

[a] *PTSD < HC (family-wise error corrected, p<0.05)*
[b] *PTSD > HC (family-wise error corrected, p<0.05)*



Supplementary Figure SF6.1. *Regions where a significant difference in DTI measures was found between PTSD and HC (uncorrected, p<0.05). Green coloration indicates the white matter skeleton where no significant differences were found. The blue colored regions indicate lower FA in PTSD compared to HC and the red colored regions indicate higher MD, RD in PTSD compared to HC. Abbreviations: PTSD, posttraumatic stress disorder; HC, healthy control; L, left; R, right; ACR, anterior corona radiata; GCC, genu of corpus callosum; BCC, body of corpus callosum; SCC, splenium of corpus callosum; IntC, internal capsule; ExtC, external capsule; PTR, posterior thalamic radiation; SCR, superior corona radiata; SLF, superior longitudinal fasciculus.*