Theoretical Review

WHITE MATTER INTEGRITY AND ITS RELATIONSHIP TO PTSD AND CHILDHOOD TRAUMA—A SYSTEMATIC REVIEW AND META-ANALYSIS

Judith K. Daniels, Ph.D.,[1]* Jan-Peter Lamke,[1] Michael Gaebler,[1] Henrik Walter, Ph.D.,[1] and Michael Scheel, Ph.D.[2]

Recent reviews and meta-analyses reported structural gray matter changes in patients suffering from adult-onset posttraumatic stress disorder (PTSD) and in subjects with and without PTSD who experienced childhood trauma. However, it remains unclear if such structural changes are also affecting the white matter. The aim of this systematic review is to provide a comprehensive overview of all empirical investigations measuring white matter integrity in populations affected by PTSD and/or childhood trauma. To this end, results from different methodological approaches were included. Twenty-five articles are reviewed of which 10 pertained to pediatric PTSD and the effects of childhood trauma measured during childhood, seven to the effects of childhood trauma measured during adulthood, and eight to adult-onset PTSD. Overall, reductions in white matter volume were reported more often than increases in these populations. However, the heterogeneity of the exact locations indicates only a weak overlap across published studies. In addition, a meta-analysis was carried out on seven whole-brain diffusion tensor imaging (DTI) studies in adults. Significant clusters of both increases and decreases were identified in various structures, most notably the cingulum and the superior longitudinal fasciculus. Future research directions are discussed. Depression and Anxiety 30:207–216, 2013.

Key words: ***posttraumatic stress disorder; childhood maltreatment; fractional anisotropy; diffusion tensor imaging; white matter***

INTRODUCTION

Recent reviews and meta-analyses reported structural gray matter changes in patients suffering from adult-onset posttraumatic stress disorder (PTSD)[1,2] and in subjects with and without PTSD who experienced childhood trauma.[3] However, it remains unclear if such structural changes are also affecting the white matter, that is, the fiber tracts connecting populations of neurons with each other. Longitudinal studies demonstrated that the trajectories of maturational effects vary considerably over the cortex. While visual, auditory, and limbic cortices myelinate early, the frontal and parietal neocortices continue myelination into adulthood.[4] The neurotoxic impact of childhood trauma might inhibit white matter myelination, especially during certain sensitive periods.[3] Childhood maltreatment has been associated with vulnerability to a host of psychiatric disorders.[5,6] It is a severe stressor known to result in a cascade of physiological, neurochemical, and hormonal changes, which in turn can lead to enduring alterations in brain structure and brain function.[7] However, structural changes in white matter connectivity have also been reported in PTSD due to adult trauma. To date it remains unclear if such structural changes are best understood as the result

[1]**Department of Psychiatry, Universitätsmedizin Charité, Berlin, Germany**

[2]**Department of Neuroradiology, Universitätsmedizin Charité, Berlin, Germany**

Contract grant sponsor: Volkswagen Foundation; Contract grant number: II/84051; Contract grant sponsor: Charité Foundation.

*Correspondence to: Judith K. Daniels, Division of Mind and Brain Research, Universitätsmedizin Charite, Chariteplatz 1, D-10117 Berlin, Germany. E-mail: judith.daniels@charite.de

Received for publication 16 June 2012; Revised 19 October 2012; Accepted 29 November 2012

DOI 10.1002/da.22044

Published online 14 January 2013 in Wiley Online Library (wileyonlinelibrary.com).

of trauma exposure and PTSD as suggested by the neurotoxicity hypothesis or as a pretraumatic vulnerability factor for the development of PTSD.

Previous studies investigating structural white matter changes predominantly used manual tracing or volumetric morphometry based on structural, T1-weighted magnetic resonance images. Most of the early white matter studies in children were limited to the corpus callosum, which was manually traced on one midsagittal slice. The area of this slice was then divided into seven sections and the extents of the resulting planes were measured. This methodology only allows for the assessment of a two-dimensional, cross-sectional area. Group comparisons therefore refer to predefined sections of the corpus callosum and do not provide an exact localization of morphological differences within these large sections (for an illustration of this approach see[8]). Although this was the best methodological approach at the time, these studies pale in comparison to modern, three-dimensional analyses and their results are seen as less meaningful. The small sample sizes of many of these earlier studies further call the reliability of the reported results into question. The subsequently introduced voxel-based morphometry approach enables a segmentation into gray and white matter as well as cerebrospinal fluid based on voxel intensities. Group comparisons are then carried out on the segmented white matter in a voxel-wise manner. The introduction of this method constituted a significant advancement in white matter analysis, as it enabled the representation of white matter structures in three-dimensional space as well as an exact localization of group differences. However, as this approach relies on a precise segmentation of gray and white matter, it is quite vulnerable to partial volume effects (for a discussion of this problem see[9]).

In recent years, diffusion tensor imaging (DTI) has emerged as a new, even more powerful technique for studying the role of structural brain connectivity. DTI provides a much more detailed assessment of fiber tracts than conventional magnetic resonance imaging by analyzing the restricted diffusion of water molecules. It has increasingly been utilized to detect neuroanatomical changes regarding the structural connectivity of white matter tracts in psychiatric populations in vivo. A common parameter obtained from DTI measurements is the fractional anisotropy (FA) value, which is regarded as a quantitative indicator of white matter integrity, reflecting fiber density, axonal diameter, and myelination. As each voxel is characterized by a diffusion tensor with a specific directionality, this enables a differentiation between fiber bundles with different orientations. Selecting a specific voxel as a starting point, probabilistic fiber tracking now also allows for the identification of the fiber tract this voxel is most likely a part of. Although the morphometry approach only allows detecting volumetric differences within the white matter as a whole, DTI allows for a differentiation between fiber tracts and thus an even more precise localization of group differences within specific white matter regions.

However, both voxel-based morphometry and DTI require the employment of a stringent statistical threshold as large brain volumes are analyzed in a voxel-wise manner. Insufficient adjustment for multiple comparisons thus results in a large number of false-positive findings.

AIMS OF THE STUDY

The aim of this systematic review is to provide a comprehensive overview of all available empirical investigations measuring white matter integrity in populations affected by PTSD and/or childhood trauma. In preparation for this manuscript, we carried out an extensive literature search using PubMed, MedLine, ISI Web of Knowledge, PsycInfo, and PsycArticles databases. The search terms *diffusion tensor imaging*, *white matter*, and *fractional anisotropy* were fully crossed with the search terms *psychological trauma*, *posttraumatic stress disorder*, *early life trauma*, *child** and *childhood trauma*, *child** and *childhood abuse*, *child** and *childhood adversity*, and *child** and *childhood maltreatment*. This search yielded 159 articles published in English, which were thoroughly inspected. Recent reviews were identified[10,11] and their reference lists were screened for additional studies. After exclusion of reviews, studies including subjects with severe head trauma or combat-related brain injuries, and articles presenting original data exclusively on gray matter or activation differences, 25 articles were included in the final analysis. Of these 25 articles, 10 pertained to pediatric PTSD and the effects of childhood trauma measured during childhood, 7 to the effects of childhood trauma measured during adulthood, and 8 to adult-onset PTSD. For a listing of all included publications see Table 1.

In addition to the systematic review, a meta-analytic investigation of the convergence across studies was carried out. To this end, all studies examining the whole brain and reporting exact coordinates (instead of vague region-of-interest [ROI] descriptions or labels) were further inspected. For DTI studies, only those reporting significant differences in FA values were included. Applying these criteria, only one volumetric study in children and seven DTI studies in adults were identified. All coordinates from the studies on adults were included in the meta-analysis, independent of the thresholds applied to *P*-values and cluster sizes. For decreases in FA values, 18 foci from five experiments on a total 92 participants were analyzed. For increases in FA values, seven foci from three experiments on 39 subjects were analyzed. An activation-likelihood meta-analysis was carried out using the GingerAle software package (www.brainmap.org/ale/). All coordinates were computed in Montreal Neurological Institute (MNI) space. The more conservative brain mask and the nonadditive Activation Likelihood Estimation (ALE) method by Turkeltaub were employed. The statistical threshold was set to False Discovery Rate (FDR) $pN = 0.05$ and the minimum cluster-size to the recommended value

TABLE 1. Listing of all reviewed publications, studies included in the meta-analysis in bold print

Population	Authors (year)	Population studied	Method	Brain region assessed	PTSD diagnosis	Childhood trauma	Main finding	Increase/ decrease
Trauma-exposed children	De Bellis[12]	44 children with PTSD vs. 61 HCs	Manual tracing	Corpus callosum	Yes	Yes	Corpus callosum	Decrease
	De Bellis[13]	28 children with PTSD vs. 66 HCs	Manual tracing	Corpus callosum	Yes	Yes	Corpus callosum	Decrease
	De Bellis et al.[14]	[Conjunction analysis of the 1999 and 2002 studies: 61 children with PTSD vs. 122 HCs]	[Manual tracing]	[Corpus callosum]	[Yes]	[Yes]	[Corpus callosum]	[Decrease]
	Eluvathingal et al.[19]	7 orphans with emotional neglect vs. 7 HCs	DTI:FA	Uncinate fasciculus, stria terminalis, fornix, and cingulum	No	Yes	Left uncinate fasciculus	Decrease
	Hanson et al.[21]	31 physically abused vs. 41 nonabused children	Volumetric analysis	Whole brain	Assessed but not reported	Yes	Cerebellum, prefrontal cortex	Increase
	Jackowski et al.[15]	17 children with PTSD vs. 15 HCs	DTI:FA	Corpus callosum	Yes	Yes	Medial and posterior corpus callosum	Decrease
	Mehta et al.[17]	14 orphans with emotional neglect vs. 11 HCs	Volumetric analysis	Corpus callosum	No	Yes	Corpus callosum	-
	Richert et al.[20]	23 children with PTSD symptoms vs. 24 HCs	Volumetric analysis	PFC	12 with PTSD, 11 with subclinical levels of PTSD symptoms	Yes	Prefrontal cortex	-
	Seckfort et al.[18]	118 healthy subjects aged 8–73 with and without childhood trauma	DTI:FA	Genu of corpus callosum	No	Yes	Genu of corpus callosum	Decrease
	Teicher et al.[16]	51 trauma-exposed children vs. 115 unexposed HCs	Volumetric analysis	Corpus callosum	One half of the abuse/neglect sample had PTSD	Yes	Corpus callosum	Decrease
Adults with childhood trauma exposure	Andersen et al.[22]	26 women with childhood sexual abuse vs. 17 HCs	Manual tracing	Corpus callosum	Mixed	Yes	Corpus callosum	Decrease
	Choi et al.[23]	**16 adults after parental verbal abuse vs. 16 HCs**	**DTI:FA, TBSS, $P = .0005$, uncorrected**	**Whole brain**	**No**	**Yes**	**Arcuate fasciculus, cingulum bundle, left body of fornix**	**Decrease**

TABLE 1. Continued

Population	Authors (year)	Population studied	Method	Brain region assessed	PTSD diagnosis	Childhood trauma	Main finding	Increase/ decrease
	Choi et al.[24]	**20 adults who witnessed domestic violence during childhood vs. 27 HCs**	**DTI:FA, TBSS, covaried for parental verbal aggression, $P < .05$, corrected**	**Whole brain**	**2/20 had PTSD, 10/20 had other current diagnoses**	**Yes**	**Left inferior longitudinal fasciculus**	**Decrease**
	Frodl et al.[26]	21 unaffected first-degree relatives of MDD patients vs. 24 HCs	DTI:FA, TBSS, $P < .05$, corrected	Whole brain	No	Yes	Corpus callosum, fornix, inferior fronto-occipital fasciculus, superior longitudinal fasciculus	Decrease and increase
	Kitayama et al.[27]	9 women with PTSD following childhood trauma vs. 9 HCs	Manual tracing	Corpus callosum	Yes	Yes	No difference in total corpus callosum area	-
	Teicher et al.[25]	63 adults with varying degrees of peer abuse	DTI:FA, TBSS, $P = .005$, corrected	Whole brain	No	Yes	Splenium of corpus callosum, corona radiata	Decrease
	Villareal et al.[28]	12 adults with PTSD vs. 10 HCs	Manual tracing	Corpus callosum	Yes	Half of the sample	Corpus callosum	Decrease
Adult-onset PTSD	**Abe et al.[31]**	**9 adults with PTSD vs. 16 HCs**	**FA**	**Whole brain**	**Yes**	**No**	**Cingulum**	**Increase**
	Hedges et al.[29]	6 veterans with PTSD vs. 5 HCs	Volumetric analysis	Various ROIs across the whole brain	Yes	Not reported	Right temporal lobe	Decrease
	Kim et al.[32]	**20 adults with PTSD vs. 20 HCs, republished in 2006**	**DTI:FA**	**Whole brain**	**Yes**	**Excluded all subjects with childhood trauma**	**Left anterior cingulate**	**Decrease**
	[Kim et al.[33]]	[21 adults with PTSD vs. 21 HCs]	[DTI:FA]	[8 cingulum ROIs]	[Yes]	[Excluded all subjects with childhood trauma]	[Left cingulum bundle]	[Decrease]
	Schuff et al.[30]	**19 veterans with PTSD vs. 19 veterans w/o PTSD**	**DTI:FA, TBSS, .001 uncor-rected**	**Whole brain**	**Yes**	**Some, not excluded**	**Anterior cingulate cortex, prefrontal cortex, precentral gyrus, posterior internal capsule, posterior angular gyrus**	**Decrease**

TABLE 1. Continued

Population	Authors (year)	Population studied	Method	Brain region assessed	PTSD diagnosis	Childhood trauma	Main finding	Increase/ decrease
	Wang et al.[34]	10 adults with PTSD vs. 10 trauma-exposed HCs	DTI:FA, manual tracing, $P = .05$ uncorrected	5 ROIs in hippocampus and cingulum	Yes	15 previously experienced traumatic events, including childhood abuse	Right posterior cingulum	Decrease
	Zhang et al.[36]	**17 adults with PTSD vs. 20 adults with GAD vs. 28 HCs**	**DTI:FA, whole brain: $P = .001$, uncorrected, ROIs: $P = .05$, corrected**	**Whole brain and ROIs**	**Yes**	**Not reported**	**Increase in left superior frontal gyrus; Decrease in right anterior cingulate**	**Decrease and Increase**
	Zhang et al.[35]	**Cross-sectional: 13 adults with PTSD vs. 14 trauma-exposed HC; Longitudinal: 8 adults with PTSD**	**DTI:FA, $P = .005$, uncorrected**	**Whole brain**	**Yes**	**Not reported**	**Cross-sectional: increase in bilateral posterior cingulate gyrus, precuneus, left middle temporal gyrus;** Longitudinal: increase in posterior cingulate gyrus; decrease in bilateral temporal regions, right prefrontal regions, cuneus	**Cross-sectional: increase; Longitudinal: decrease and increase**

calculated by the GingerALE software (48 for decreases, 24 for increases).

RESULTS

WHITE MATTER INTEGRITY IN TRAUMA-EXPOSED CHILDREN

Several studies have investigated the impact of childhood trauma on white matter integrity in children, both in pediatric PTSD and in healthy populations (for an illustration of the results see Supporting Information Fig. S1A). However, most of these studies did not analyze white matter integrity across the whole-brain volume, but only in circumscribed brain structures or brain regions. The majority of these studies focused on the largest fiber bundle, the corpus callosum, which connects the two cerebral hemispheres. De Bellis et al. published three studies analyzing the corpus callosum in children with PTSD. In the first study,[12] they reported on midsagittal corpus callosum area in 44 children with pediatric PTSD due to abuse and 61 healthy, nonabused controls using manual tracing. Total corpus callosum area as well as most of the seven analyzed divisions of this structure were significantly reduced in the PTSD group as compared to the healthy controls. The most prominent reduction was reported for the anterior midbody region. In an independent replication study, the group reported on data from 28 children with pediatric PTSD due to abuse and 66 healthy, nonexposed controls using the same methodological approach.[13] Again, they found significant reductions in total corpus callosum area, this time with the most significant reduction being identified in the splenium, which is the most posterior section of the corpus callosum. Combining the data from these two studies, they analyzed sex differences in corpus callosum area.[14] Although the findings were replicated for both sexes separately, a significant sex by group interaction emerged for two subregions of the corpus callosum, with boys showing greater reductions than girls.

In a DTI study, Jackowski et al.[15] also found reductions with a maximal effect size of $d = -0.87$ in the midbody of the corpus callosum in a sample of 17 children with PTSD and 15 matched healthy, nonexposed controls. Teicher et al.[16] studied 28 children reporting childhood trauma, half of which met diagnostic criteria for PTSD, and 115 healthy, nonexposed controls. Analyzing group differences in the corpus callosum, they described a reduction in total corpus callosum area in the traumatized group that was driven by significant reductions in the midbody and posterior regions. The most significant reduction emerged for the anterior midbody region. Although neglect was identified as the strongest predictor for the whole group, sexual abuse emerged as the strongest predictor in girls. Interestingly, severe socioemotional neglect did not lead to significant corpus callosum reductions in an investigation of 14 adolescents who had experienced early deprivation in Romanian orphanages as compared to 11 noninstitutionalized controls.[17] One study employed a lifespan approach, comparing the effect of childhood trauma on white matter integrity in the genu of the corpus callosum within four different age groups.[18] In each age bracket, subjects were classified as to whether or not they had been exposed to three or more early life stressors such as premature birth, life threatening illness, surgery, death of a loved one, and war exposure. Comparison of these low and high exposure groups revealed significant volume reductions in the frontal part of the corpus callosum both in the youngest age group ranging from 8 to 12 years and in the oldest age group ranging from 51 to 73.

Additional studies focused on different circumscribed brain regions. In a study of seven neglected orphans, FA values in the uncinate fasciculus, the stria terminalis, the cingulum, and the fornix were analyzed as these fiber tracts connect brain regions previously characterized as hypoactivated in this sample.[19] Only the uncinate fasciculus was found to be significantly smaller in the neglected group than in a control group of seven healthy children. No significant alterations were identified in a sample of children with clinical and subclinical PTSD symptomatology as compared to healthy controls in a study analyzing white matter integrity exclusively in the prefrontal cortex.[20]

Hanson et al. carried out a volumetric analysis of the whole-brain volume.[21] They reported significant increases in white matter volume in a sample of 31 physically abused children as compared to 41 nonexposed controls in the bilateral cerebellum as well as in the left frontal lobe. The white matter increase in the frontal lobe, possibly in the cingulum, was significantly associated with stronger behavioral problems.

WHITE MATTER INTEGRITY IN ADULTS WITH A HISTORY OF CHILDHOOD TRAUMA

Seven studies analyzed the long-term effect of childhood trauma in adults (for an illustration of their results see Supporting Information Fig. S1B). Teicher and coworkers published four of the seven studies on this topic. Typically, the authors did not exclude current and lifetime PTSD, but conducted a thorough diagnostic to identify subjects who were repeatedly exposed to one type of childhood trauma, but no other traumatic incidents. In the study by Andersen et al.,[22] the majority of the trauma-exposed sample (19 out of 26) had developed a mental disorder at some point in time, but at the time of study only eight of the subjects still qualified for a current diagnosis. In a multiple regression analysis predicting reductions in corpus callosum area, lifetime PTSD diagnosis was not identified as a significant predictor. Instead, sexual abuse at ages 9–10 emerged as a significant predictor. A different study from this group investigated the effect of parental verbal abuse on white matter integrity using tract-based spatial statistics (TBSS) in a whole-brain approach.[23] They reported significantly reduced FA values in three regions in a sample of 16 trauma-exposed young adults compared to 16 unexposed subjects: the left cingulum (26% reduction), the left body of the fornix (23% reduction), and the left arcuate fasciculus (22% reduction). In addition, the reduction in the cingulum was associated with higher levels of depression, dissociation, and "limbic irritability." No alteration of white matter integrity emerged for the corpus callosum. In this investigation, the trauma-exposed group was free of PTSD, but four participants met criteria for a current diagnosis and seven reported lifetime depression. In a subsequent study of adults who had witnessed domestic violence during childhood, Teicher's group reported a significant white matter reduction of 13% in the inferior longitudinal fasciculus using the same methodological approach.[24] Again, the sample consisted of healthy, unexposed ($n = 27$) and exposed ($n = 20$) subjects, of which 12 met criteria for a current diagnosis. The observed white matter reduction was significantly correlated with depression, anxiety, anger, dissociation, somatization, and "limbic irritability" scores. Again, no reductions in corpus callosum size were identified. As not only parental figures, but also peers can be the source of traumatic stress, they also studied the impact of peer verbal aggression on brain development in a sample of 63 adults with varying degrees of exposure.[25] They reported significant positive correlations between exposure to peer verbal abuse and mean diffusivity values in the most posterior part of the corpus callosum and between exposure and radial diffusivity scores in the adjacent corona radiata.

Frodl et al. studied the effect of childhood trauma exposure on white matter integrity in two groups of healthy adults, one of which consisted of 21 unaffected first-degree relatives of patients suffering from depression while the second group ($n = 24$) did not contain any first-degree relatives of such patients.[26] Although they did not find a significant main effect for childhood trauma exposure, they reported a two-way interaction. Differences between high and low childhood trauma exposure subgroups emerged with opposed directions in both groups, although the groups did not differ overall

in the amount of childhood trauma exposure. Although the first-degree relatives with high exposure showed an increase in FA in the midbody and posterior regions of the corpus callosum, the fornix, the left superior longitudinal fasciculus, and the inferior fronto-occipital fasciculus in comparison to the low trauma subgroup, the high exposure subgroup without family relations to patients with depression showed a decrease of FA in these areas as compared to the low trauma subgroup.

Only two studies investigated the effect of PTSD due to childhood trauma in adults. Kitayama et al.[27] compared the midsagittal corpus callosum area in nine adults with PTSD due to childhood trauma and nine healthy controls. No significant differences for total corpus callosum volume or any of the seven subregions were identified. Villarreal et al.[28] analyzed data from 12 adults suffering from chronic PTSD. Although half of the sample developed PTSD in reaction to adult trauma such as accidents, rape, assault, or combat, the other half reported PTSD chronicity of up to 35 years following childhood sexual abuse. All of the subjects had comorbid current or lifetime diagnoses of depression. In comparison to 10 matched healthy controls, the PTSD group exhibited smaller total midsagittal corpus callosum area. The most significant reductions were observed in the genu, that is, the most frontal part of the corpus callosum. Interestingly, corpus callosum area was positively correlated with anxiety scores in the PTSD group. No significant correlations emerged for time since the traumatic event, PTSD symptom severity and chronicity, or depression. Unfortunately, the effect of trauma exposure during childhood was not analyzed as a separate factor.

WHITE MATTER INTEGRITY IN ADULT-ONSET PTSD

In order to determine if trauma-induced white matter alterations only occur during the early, formative years of brain development, or if the neurotoxicity of PTSD itself may be driving white matter alterations, it is interesting to compare white matter integrity in adult PTSD populations without aversive childhood experiences (for an illustration of the results pertaining to this section see Supporting Information Fig. S1C).

Two studies investigated the impact of combat-related PTSD on white matter integrity. Comparing combat-exposed veterans with ($n = 6$) and without ($n = 5$) PTSD with manual tracing, Hedges et al.[29] described white matter reductions in the temporal lobe which were significant in a multivariate test of temporal white matter as a whole, but failed to reach significance in post hoc univariate tests for specific structures within the temporal lobe. In a DTI study comparing veterans with ($n = 19$) and without ($n = 19$) PTSD,[30] reduced values for FA were observed in the PTSD group in the bilateral prefrontal cortex, probably located in the cingulum, as well as in the bilateral posterior internal capsule and close to the angular gyrus. No differences in corpus callosum volume emerged in these two studies.

As subjects with a history of blast exposure were not excluded in these studies, the observed morphological changes could be due to physical force rather than neurotoxic effects of stress. Interestingly, two studies investigating civil PTSD with adult-onset also reported white matter alterations in the left anterior cingulum. Analyzing data from 25 subjects who were exposed to a terrorist attack, Abe et al.[31] compared those subjects who had subsequently developed PTSD ($n = 9$) to those who did not ($n = 16$). Only one of the PTSD subjects was diagnosed with current PTSD at the time of study, while the other eight subjects from this group were in remission. The PTSD group exhibited increased values of FA within the left anterior cingulum, which were not significantly correlated with a measure of PTSD symptom severity. In contrast, reduced FA within the cingulum was reported in a sample of PTSD patients ($n = 21$) who were all exposed to the same subway fire as compared to nonexposed healthy controls ($n = 21$). Reduced cingulum integrity was reported in this sample using both a whole-brain approach[32] as well as an ROI approach[33] to analyze these data. After the whole-brain approach had detected significant group differences within the cingulum, the data were reanalyzed placing four ROIs in the cingulum of each hemisphere to compare the effect on subregions of this structure. This investigation determined that the left rostral, subgenual, and dorsal subregions of the anterior cingulum were affected, while the left upper subregion and the four right subregions did not exhibit significant alterations.

Two investigations reported alterations of white matter integrity within the posterior section of the cingulum in PTSD due to coalmining accidents.[34,35] At 6 months post trauma, Wang et al.[34] reported significantly lower FA values in the PTSD group ($n = 10$) for both the right posterior cingulum and the bilateral hippocampal body as compared to trauma-exposed, healthy controls ($n = 10$) using an ROI approach. At 24 months post trauma, Zhang et al.[35] assessed FA in 16 ROIs. They observed increased FA values in the bilateral white matter in the posterior cingulate cortex, probably within the posterior cingulum, in the PTSD ($n = 13$) as compared to the healthy control group ($n = 14$). A subgroup of this study ($n = 8$) had already undergone an MRI scan at 10 months post trauma. Comparison of both time points in these subjects revealed a significant increase in white matter in the left posterior cingulate as well as significant decreases in various right-sided temporal and prefrontal regions (e.g., white matter within the transverse and superior temporal gyri as well as the medial, middle, and superior frontal gyri). FA values within the posterior cingulate region correlated negatively with intrusion frequency.

The only study to date testing the specificity of white matter alterations compared subjects with PTSD ($n = 17$) to a clinical control group of subjects with generalized anxiety disorder ($n = 20$) as well as healthy controls ($n = 28$). This study demonstrated decreased FA values in the right anterior cingulate regions, probably within the

TABLE 2. Results of the meta-analysis

FA decreases	Cluster center	Cluster size	Cluster range	Most probable label	Studies reporting significant group difference within this cluster
	10.5, 33.8, 28	96 mm^3	8, 32, 26 to 12, 36, 30	Right cingulum	Schuff et al.[30]: 19 veterans with PTSD vs. 19 veterans w/o PTSD
	2.6, 28.2, 28	80 mm	0, 26, 26 to 4, 30, 30	Unclassified	Kim[33]: 20 adults with PTSD vs. 20 HCs
	−6, 30, 29	80 mm	−8, 28, 28 to −4, 32, 30	Left cingulum	Kim[33] : 20 adults with PTSD vs. 20 HCs
	19, −13, 5	64 mm	18, −14, 4 to 20, −12, 6	Posterior limb of internal capsule	Schuff et al.[30]: 19 veterans with PTSD vs. 19 veterans w/o PTSD
	27, 31, 27	64 mm	26, 30, 26 to 28, 32, 28	Right anterior thalamic radiation	Schuff et al.[30]: 19 veterans with PTSD vs. 19 veterans w/o PTSD
	−2, −30, −6	56 mm	−4, −32, −8 to 0, −28, −4	Unclassified	Kim[33]: 20 adults with PTSD vs. 20 HCs
	14, 32, −6	56 mm	12, 30, −8 to 16, 34, −4	Right anterior corona radiata	Zhang et al.[36]: 17 adults with PTSD vs. 20 adults with GAD
	−32, −52, 36	56 mm	−34, −54, 34 to −30, −50, 38	Left superior longitudinal fasciculus	Schuff et al.[30]: 19 veterans with PTSD vs. 19 veterans w/o PTSD
	−30, −20, 48	56 mm	−32, −22, 46 to −28, −18, 50	Unclassified	Schuff et al.[30]: 19 veterans with PTSD vs. 19 veterans w/o PTSD
FA increases	Cluster center	Cluster size	Cluster range	Most probable label	Study
	−56, −54, −2	56 mm	−58, −56, −4 to −54, −52, 0	Left superior longitudinal fasciculus	Zhang[35]: 13 adults with PTSD vs. 14 trauma-exposed HC
	12, −56, 28	56 mm	10, −58, 26 to 14, −54, 30	Right cingulum	Zhang[35]: l 13 adults with PTSD vs. 14 trauma-exposed HC
	−8, −44, 30	56 mm	−10, −46, 28 to −6, −42, 32	Left cingulum	Zhang[35]: 13 adults with PTSD vs. 14 trauma-exposed HC
	40, −38, 36	56 mm	38, −40, 34 to 42, −36, 38	Right superior longitudinal fasciculus	Zhang[35]: 13 adults with PTSD vs. 14 trauma-exposed HC
	8, −60, 40	56 mm	6, −62, 38 to 10, −58, 42	Unclassified	Zhang[35]: 13 adults with PTSD vs. 14 trauma-exposed HC
	−18, 48, 42	56 mm	−20, 46, 40 to −16, 50, 44	Unclassified	Zhang[36]: 17 adults with PTSD vs. 28 HCs

cingulum, in comparison to the clinical control group as well as increased white matter integrity in the left superior frontal gyrus as compared with the healthy control group.[36]

META-ANALYSIS

The meta-analysis of seven DTI studies in trauma-exposed adults identified significant FA decreases in nine clusters and FA increases in six clusters in the trauma-exposed groups (see Supporting Information Fig. S2). The largest identified cluster pertained to an FA decrease in the right cingulum (see Table 2). Further increases and decreases were identified bilaterally in different sections of the cingulum. For the superior longitudinal fasciculus, decreased FA values were identified in the left and increased FA values in the left and the right structure. However, for all of these clusters only one study each was identified that reported significant differences in FA values within the designated cluster. The meta-analytic results of this rather small sample of studies are therefore best interpreted as a preliminary indication of possible group differences.

SUMMARY

This review identified 25 empirical investigations of white matter integrity in populations exposed to childhood trauma or with adult-onset PTSD. Overall, reductions in white matter volume were reported more often than increases in these populations. As would be expected statistically, most publications reported alterations in one of the larger white matter tracts. Some investigators exclusively analyzed the volume of circumscribed brain structures, while others employed a whole-brain approach. Therefore the number of significant findings per brain structure may be misleading. The majority of the findings concern the corpus callosum, that is, the fiber bundle connecting the two hemispheres. Reduced corpus callosum volume was identified in four studies investigating trauma-exposed children, in two studies investigating the effect of childhood trauma in adults, and

in two studies analyzing data from adult-onset PTSD samples. Of the eight studies reporting significant corpus callosum reductions, the majority was located within the posterior section. Three studies failed to replicate significant reductions in corpus callosum volume, two of these in trauma-exposed children and one in adults who had experienced childhood trauma. Interestingly, one study even demonstrated divergent effects of childhood trauma in two groups of healthy adults.

The second most prevalent finding concerns the cingulum bundle. Convergently, the largest cluster identified by the meta-analysis is also located in the cingulum. The cingulum bundle is classified as a long association fiber uniting more distant parts within one hemisphere. It is the most prominent white matter tract in the limbic system and is contained within the cingulate gyrus. It connects the anterior cingulate and entorhinal gyri and projects to and from the amygdala. Reductions of white matter volume within the cingulum bundle were reported in six studies. Five of these six studies analyzed data from adult-onset PTSD samples, while one demonstrated reductions in a sample of adults exposed to childhood trauma. Two of these six studies reported left-lateralized reductions in the posterior section of the cingulum, three in the left-lateralized anterior section, and one in the right-lateralized anterior section. In addition, one study reported a significant increase in white matter volume in the cingulum bundle in a sample with adult-onset PTSD. Furthermore, the only available prospective study identified a significant increase in the left posterior cingulate during the recovery phase following acute adult trauma. Two studies analyzed the cingulum volume without finding any significant alterations, one in trauma-exposed children and one in adults exposed to childhood trauma. Again, the exact locations of the reported reductions do not converge across studies. However, the meta-analysis did identify significant clusters for both FA decreases and increases within the cingulum. These findings are limited by the fact that for each identified cluster, only one study is available that reports significant differences within this cluster. Taken together with the three publications reporting null findings or even an increase, no robust conclusions can be drawn and more whole-brain DTI studies are called for.

LIMITATIONS

At the current date, the available empirical literature does not converge and thus does not provide a conclusive answer as to structural white matter alterations following childhood trauma or PTSD. Although the meta-analysis resulted in some significant findings, these results have to be interpreted with caution, as only a very limited number of studies could be included due to missing information. As evident from the systematic review and the meta-analysis, both increases and decreases in white matter have been reported for nearly all affected structures. This surprising finding is still awaiting a conclusive interpretation. Differences in type of trauma, chronicity of trauma exposure, illness duration, and comorbid psychiatric disorders limit the comparability of the samples studied so far. Particularly in children, previous studies have shown that even extreme levels of traumatization do not necessarily lead to the development of PTSD,[37] and not meeting diagnostic criteria for PTSD at one moment in time does not mean that these children will not meet these in the future or do not exhibit functionally impairing levels of symptomatology. For this reason, a fully controlled study of trauma-exposed children with and without current PTSD as well as a never-exposed control group is called for. In addition, differences in imaging parameters, methodological approaches, and software used for data analysis could account for discrepant findings. Overreporting of group differences may also be a problem as most studies used lenient statistics without controlling for multiple comparisons. In addition, a file-drawer bias has to be assumed as a recent meta-analysis of morphological abnormalities in psychiatric patients[38] indicates that 81% more significant results are reported than would statistically be expected.

FUTURE RESEARCH DIRECTIONS

To our knowledge, no studies on pediatric PTSD due to noninterpersonal trauma such as accidents and natural disasters are available. It therefore needs to be tested if potential alterations might be specific to interpersonal forms of childhood trauma. As no study directly compared trauma-exposed children with and without PTSD, it also remains unknown if the trauma exposure itself or the development of PTSD might lead to structural changes. In adults, no whole-brain study regarding the long-term effects of PTSD due to childhood trauma is currently available. Studies comparing age of trauma onset groups might prove helpful for the identification of critical developmental stages. Future studies should employ a whole-brain approach, include chronicity of trauma exposure as a covariate of interest, control for comorbid symptoms by covariation, and, most importantly, use stringent statistics.

Acknowledgments. The work of Judith Daniels, Michael Gaebler, and Jan-Peter Lamke was funded by the Volkswagen Foundation grant no. II/84051. Michael Scheel was supported by the "Friedrich C. Luft" Clinical Scientist Pilot Program funded by Volkswagen Foundation and Charité Foundation.

REFERENCES

1. Heim C, Nemeroff CB. Neurobiology of posttraumatic stress disorder. CNS Spectr 2009;14(1, Suppl 1):13–24.
2. Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. Neurosci Biobehav Rev 2006;30(7):1004–1031.
3. Heim C, Binder EB. Current research trends in early life stress and depression: review of human studies on sensitive periods,

gene-environment interactions, and epigenetics. Exp Neurol 2012;233(1):102–111.
4. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci 2003;6(3):309–315.
5. Cutajar MC, Mullen PE, Ogloff JR, Thomas SD, Wells DL, Spataro J. Psychopathology in a large cohort of sexually abused children followed up to 43 years. Child Abuse Negl 2010;34(11):813–822.
6. Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am J Psychiatry 2012;169(2):141–151.
7. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. Neurosci Biobehav Rev 2003;27(1–2):33–44.
8. Witelson SF. Hand and sex differences in the isthmus and genu of the human corpus callosum. A postmortem morphological study. Brain 1989;112(Pt 3):799–835.
9. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006;31(4):1487–1505.
10. Hart H, Rubia K. Neuroimaging of child abuse: a critical review. Front Hum Neurosci 2012;6:1–24.
11. Ayling E, Aghajani M, Fouche JP, van der Wee N. Diffusion tensor imaging in anxiety disorders. Curr Psychiatry Rep 2012 (March). DOI 10.1007/s11920-012-0273-z
12. De Bellis MD, Keshavan MS, Clark DB, et al. A.E. Bennett Research Award. Developmental traumatology. Part II: brain development. Biol Psychiatry 1999;45(10):1271–1284.
13. De Bellis MD, Keshavan MS, Shifflett H, et al. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. Biol Psychiatry 2002;52(11):1066–1078.
14. De Bellis MD, Keshavan MS. Sex differences in brain maturation in maltreatment-related pediatric posttraumatic stress disorder. Neurosci Biobehav Rev 2003;27(1–2):103–117.
15. Jackowski AP, Douglas-Palumberi H, Jackowski M, et al. Corpus callosum in maltreated children with posttraumatic stress disorder: a diffusion tensor imaging study. Psychiatry Res Neuroimag 2008;162(3):256–261.
16. Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL. Childhood neglect is associated with reduced corpus callosum area. Biol Psychiatry 2004;56(2):80–85.
17. Mehta MA, Golembo NI, Nosarti C, et al. Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees Study Pilot. J Child Psychol Psychiatry 2009;50(8):943–951.
18. Seckfort DL, Paul R, Grieve SM, et al. Early life stress on brain structure and function across the lifespan: a preliminary study. Brain Imag Behav 2008;2(1):49–58.
19. Eluvathingal TJ, Chugani HT, Behen ME, et al. Abnormal brain connectivity in children after early severe socioemotional deprivation: a diffusion tensor imaging study. Pediatrics 2006;117(6):2093–2100.
20. Richert KA, Carrion VG, Karchemskiy A, Reiss AL. Regional differences of the prefrontal cortex in pediatric PTSD: an MRI study. Depress Anxiety 2006;23(1):17–25.
21. Hanson JL, Chung MK, Avants BB, et al. Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. J Neurosci 2010;30(22):7466–7472.
22. Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. J Neuropsychiatry Clin Neurosci 2008;20(3):292–301.
23. Choi J, Jeong B, Rohan ML, Polcari AM, Teicher MH. Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. Biol Psychiatry 2009;65(3):227–234.
24. Choi J, Jeong B, Polcari A, Rohan ML, Teicher MH. Reduced fractional anisotropy in the visual limbic pathway of young adults witnessing domestic violence in childhood. Neuroimage 2012;59(2):1071–1079.
25. Teicher MH, Samson JA, Sheu Y-S, Polcari A, McGreenery CE. Hurtful words: association of exposure to peer verbal abuse with elevated psychiatric symptom scores and corpus callosum abnormalities. Am J Psychiatry 2010;167(12):1464–1471.
26. Frodl T, Reinhold E, Koutsouleris N, Reiser M, Meisenzahl EM. Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. J Psychiatr Res 2010;44(13):799–807.
27. Kitayama N, Brummer M, Hertz L, Quinn S, Kim Y, Bremner JD. Morphologic alterations in the corpus callosum in abuse-related posttraumatic stress disorder: a preliminary study. J Nerv Ment Dis 2007;195(12):1027–1029.
28. Villarreal G, Hamilton DA, Graham DP, et al. Reduced area of the corpus callosurn in posttraumatic stress disorder. Psychiatry Res Neuroimag 2004;131(3):227–235.
29. Hedges DW, Thatcher GW, Bennett PJ, et al. Brain integrity and cerebral atrophy in Vietnam combat veterans with and without posttraumatic stress disorder. Neurocase 2007;13(5–6):402–410.
30. Schuff N, Zhang Y, Zhan W, et al. Patterns of altered cortical perfusion and diminished subcortical integrity in posttraumatic stress disorder: an MRI study. Neuroimage 2011;54:S62-S68.
31. Abe O, Yamasue H, Kasai K, et al. Voxel-based diffusion tensor analysis reveals aberrant anterior cingulum integrity in posttraumatic stress disorder due to terrorism. Psychiatry Res Neuroimag 2006;146(3):231–242.
32. Kim MJ, Lyoo IK, Kim SJ, et al. Disrupted white matter tract integrity of anterior cingulate in trauma survivors. Neuroreport 2005;16(10):1049–1053.
33. Kim SJ, Jeong D-U, Sim ME, et al. Asymmetrically altered integrity of cingulum bundle in posttraumatic stress disorder. Neuropsychobiology 2006;54(2):120–125.
34. Wang HH, Zhang ZJ, Tan QR, et al. Psychopathological, biological, and neuroimaging characterization of posttraumatic stress disorder in survivors of a severe coalmining disaster in China. J Psychiatr Res 2010;44(6):385–392.
35. Zhang L, Li W, Shu N, et al. Increased white matter integrity of posterior cingulate gyrus in the evolution of post-traumatic stress disorder. Acta Neuropsychiatr 2012;24(1):34–42.
36. Zhang L, Zhang Y, Li L, et al. Different white matter abnormalities between the first-episode, treatment-naive patients with posttraumatic stress disorder and generalized anxiety disorder without comorbid conditions. J Affect Disord 2011;133(1–2):294–299.
37. Klasen F, Oettingen G, Daniels J, Post M, Hoyer C, Adam H. Posttraumatic resilience in former Ugandan child soldiers. Child Dev 2010;81(4):1096–1113.
38. Ioannidis JP. Excess significance bias in the literature on brain volume abnormalities. Arch Gen Psychiatry 2011;68(8):773–780.