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Structural white matter changes in adults and children with posttraumatic stress disorder: A systematic review and meta-analysis

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ABSTRACT

White matter plasticity occurs throughout life due to learning and can be a protective factor against as well as a vulnerability factor for the development of mental disorders. In this systematic review we summarize findings on structural white matter changes in children and adults with posttraumatic stress disorder (PTSD) and relate them to theoretical accounts of the pathophysiology of PTSD with a focus on the disturbed processing of contexts and associated problems in emotional and cognitive processing and PTSD symptomatology. We particularly examine studies reporting fractional anisotropy (FA) measured with diffusion tensor imaging (DTI). We further subdivided the studies in adult-onset PTSD with traumatic experience in adulthood, adult-onset PTSD with traumatic experience in childhood and children with PTSD. We included 30 studies comprising almost 1700 participants with 450 adults and 300 children suffering from PTSD. Our systematic review showed that for children with PTSD and adult-onset PTSD with childhood trauma, a decrease in FA in the corpus collosum, most prominently in the anterior and posterior midbody, the isthmus and splenium were reported. For adult-onset PTSD with traumatic experience in adulthood, changes in FA in the anterior and posterior part of the cingulum, the superior longitudinal fasciculus and frontal regions were found. Using GingerAle, we also performed a coordinate-based meta-analysis of 14 studies of adult-onset PTSD with traumatic experience in adulthood and did not find any significant clusters. Our results suggest that changes in white matter microstructure vary depending on traumatic experience and are associated with changes in brain circuits related to the processing of contexts. Finally, we present methodological considerations for future studies.

1. Introduction

1.1. Structural changes in posttraumatic stress disorder

A traumatic experience such as a life threatening event can lead to the development of posttraumatic stress disorder (PTSD). Structural changes in major white matter (WM) tracts have been reported in several studies in adult and juvenile patients suffering from PTSD (Fani et al., 2012; Kennis et al., 2015). This is in line with recent work demonstrating that WM plasticity occurs in adults (Sampaio-Baptista and Johansen-Berg, 2017; Scholz et al., 2009; Zatorre et al., 2012), suggesting a broader role of WM in learning and neural circuit formation. Traumatic experiences are an extremely aversive form of learning in a potentially life threatening situation. Changes in WM microarchitecture of certain tracts might also be a vulnerability factor similar to findings on smaller hippocampal volumes predicting susceptibility to posttraumatic symptoms (Gilbertson et al., 2002). Structural changes in major WM tracts have been reported in several studies in adult and juvenile patients suffering from PTSD. A recent review and meta-analysis (Daniels et al., 2013) on WM changes using data from diffusion tensor imaging (DTI) focused on individuals with trauma exposure with or without the diagnosis of PTSD. The authors subdivided the reviewed articles in the following three populations: a) pediatric PTSD and trauma exposure in childhood, b) adults with childhood trauma exposure and c) adult-onset PTSD. However, the definition of childhood trauma is not clearly mentioned and can only be assumed to be below the age of 18 years. Daniels et al. (2013) included 25 studies in their review and found a heterogeneous picture with studies reporting an

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increase or decrease of white matter volume in PTSD. The majority of studies reported a significant reduction in WM volume of major fiber tracts including the corpus callosum, the cingulum bundle as well as the left posterior cingulate. Changes in the anterior and posterior parts of the corpus callosum were most prominently reported in trauma-exposed children with or without the diagnosis of PTSD in comparison to healthy control subjects. Changes in WM volume in adult-onset PTSD in comparison to healthy control subjects with or without traumatic experience were found bilaterally in the cingulum and the left superior longitudinal fasciculus. The cingulum is one of the major fiber tracts for communication within the limbic system. The superior longitudinal fasciculus connects occipital, parietal and temporal regions to the frontal lobe and is involved in a wide range of functions including processing of visual spatial information. In addition, one longitudinal study observed a significant increase in the left posterior cingulate after remission of PTSD symptoms in adult-onset PTSD. The posterior cingulate is assumed to be a major hub for integrating information from different perspectives and feeding information into the precuneus for building up mental images (Burgess et al., 2001a, 2001b; Vann et al., 2009). Due to the small number of studies included and the differences in comparison groups (trauma controls, healthy controls), it remains unclear whether trauma exposure, predisposition or the development of PTSD is the driving factor of structural changes. Except for two studies that reported on adult patients with PTSD in comparison to healthy controls and either trauma control subjects or patients with generalized anxiety disorder (GAD), none of the reviewed studies used more than one control group (Sun et al., 2013; Zhang et al., 2011). Furthermore, the majority of studies employed only healthy control subjects without any traumatic experience and no trauma control subjects with trauma experience. However, trauma control subjects are essential to determine whether these changes are the result of trauma exposure or are related to PTSD or based on pretraumatic vulnerability (for a summary Brewin et al., 2000).

In this review, we focus on studies reporting DTI data in at least one population diagnosed with PTSD. We followed the subdivision by Daniels et al. (2013) in comparing adults with PTSD after traumatic experience in adulthood (aa-PTSD), adults with PTSD after traumatic experience in childhood (ac-PTSD) and children with PTSD after traumatic experience in childhood (cc-PTSD). This subdivision was related to the fact that increases in WM volume are part of a natural maturation from birth to young adulthood (Giedd et al., 2015; Giedd and Rapoport, 2010). A traumatic experience during this vulnerable period might have a different effect on WM microstructure than after maturation of the core WM network in young adulthood. Trauma in childhood or adolescence is defined as any traumatic event experienced before the completion of the 18th birthday and was chosen rather as a legal than a biological boundary definition. While, we include all three age groups in our review of the literature, we will only include studies with aa-PTSD in our meta-analysis. The small number of studies available for ac-PTSD and cc-PTSD make a reliable interpretation of the findings difficult at this stage for these two groups. In addition, we will provide guidelines for future studies on white matter changes in trauma-exposed populations suffering from PTSD.

1.2. Theoretical considerations related to WM changes in PTSD

PTSD is characterized by symptom clusters such as re-experiencing the traumatic event, avoidance and numbing, hyperarousal and negative thought and mood changes (Diagnostic and Statistical Manual of Mental Disorders (DSM) 5; American Psychiatric Association, 2013). In the past decades, theoretical frameworks have identified several key brain circuits involved in different cognitive and emotional processes contributing to the development of PTSD with a focus on disturbed contextual processing, an inability to extinguish aversive memories and an increase in threat detection and arousal (Bisby and Burgess, 2017; Brewin et al., 2010; Ehlers and Clark, 2000; Flor and Nees, 2014; Jacobs and Nadel, 1985; Liberzon and Abelson, 2016; Maren et al., 2013). Patients with PTSD have trouble to contextualize incoming visual-spatial information, which is associated with a functional down regulation in activity in the medial temporal lobe (MTL), most prominently in the hippocampus, and the retrosplenial cortex (RSC), which translates this information into a coherent egocentric mental image in the precuneus (Bisby and Burgess, 2017). At the same time, the processing of salient emotional cues involves areas like the amygdala, the insula and the anterior cingulate cortex (ACC), which are up-regulated in PTSD (Bisby and Burgess, 2017; Brewin et al., 2010; Liberzon and Abelson, 2016). Finally, the prefrontal control of subcortical regions involved in fear learning and extinction such as the medial-, dorso- and ventrolateral prefrontal cortex (mPFC, dlPFC, vlPFC) is diminished (Bisby and Burgess, 2017; Brewin et al., 2010; Liberzon and Abelson, 2016). As a result, patients show increased levels of arousal and anxiety as well as hypervigilance and might have difficulties putting these negative emotions in context and thus successfully extinguish acquired fear responses. In line with this, several reviews and meta-analyses on volumetric gray matter (GM) changes reported significant differences in GM in the hippocampus, mPFC, superior frontal gyrus and the ACC (Kühn and Gallinat, 2013; Li et al., 2014) in PTSD patients compared to controls. These studies need to be complemented by research on WM changes because they might, similar to GM changes, directly reflect changes in connections between functionally distinct brain areas. In this review, we will mainly focus on changes WM microstructure after negative experiences early or late in white matter development due to its centrality and importance and the small number of existing reviews in this area.

1.3. Methods for measuring structural changes

Changes in microstructural WM in individuals with adult-onset PTSD have been measured using manual tracing, volumetric morphometry and DTI. One of the earliest methods was manual tracing. In manual tracing, the corpus callosum is manually subdivided into seven parts (De Bellis et al., 2015). Manual tracing has particularly been used in underage populations suffering from traumatic experience and PTSD (Daniels et al., 2013), tracing mostly the corpus callosum. Here, differences in white matter are visible in a two dimensional plane only. Voxel-based morphometry (VBM) was introduced as an approach to segment the brain into GM, WM and cerebrospinal fluid (CSF). Groups are contrasted using voxel-wise comparisons, which increase the accuracy of localization and permit a three-dimensional representation of the WM. However, the precise segmentation is error-prone and vulnerable to partial volume effects, which occur if more than one type of tissue occupies the same voxel and in consequence can cause loss of contrast (Smith et al., 2006). In DTI, the directionality of water molecules is calculated as they diffuse in a substance-dependent manner. This is achieved by fitting a voxel-wise ellipsoid tensor to the diffusion-weighted magnetic resonance images (MRI) in three dimensions (Le Bihan and Johansen-Berg, 2012; Le Bihan, 2014). Three eigenvectors (λ_1, λ_2, λ_3) of this tensor are obtained, which, in combinations with their lengths eigenvalues, allow to describe different measures of diffusivity, such as the mean diffusivity (MD; $(\lambda_1 + \lambda_2 + \left(\mathrm{FA}; \frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_1-\lambda_3)^2}}{\sqrt{2(\lambda_1{}^2+\lambda_2{}^2+\lambda_3{}^2)}}\right)\lambda_3)/3$) assessing the total diffusion within one voxel, the axial diffusivity (AD, λ_1) assessing axonal injury or the radial diffusivity (RD; $(\lambda_2 + \lambda_3)/2$) assesses myelin injury. In addition, a fourth measurement can be obtained, the so called fractional anisotropy, which gives information about the shape of the diffusion tensor in each voxel. FA values range from 0 (isotropic; non-directional) to 1 (anisotropic diffusion; highly directional) and indicate the net directionality of water diffusion in the given tissue (Pierpaoli and Basser, 1996). Since the majority of diffusivity studies on PTSD report FA values we will focus on this measurement in this review. A decrease in FA or a more isotropic connection, is generally considered

to lead to a decrease in structural connectivity and functionality of the tract (Zatorre et al., 2012; Hänggi et al., 2010). An increase in FA or a more anisotropic connection, is considered to lead to an increase in structural connectivity and functionality of the tract (Scholz et al., 2009; Zatorre et al., 2012).

2. Aims

This paper seeks to systematically review the literature reporting structural changes using DTI in individuals with PTSD compared to healthy individuals with the experience of a traumatic event (trauma controls) and healthy individuals without the experience of a traumatic event (healthy controls). In the review part we subdivide three groups of studies: a) underage patients with PTSD after childhood/adolescence trauma (cc-PTSD), b) adult-onset PTSD following childhood trauma (ac-PTSD) and c) adult-onset PTSD following trauma experience in adulthood (aa-PTSD). We suggest that traumatic experiences might interact with naturally occurring maturation processes during childhood and adolescence (Giedd et al., 2015; Giedd and Rapoport, 2010) and might therefore have a different impact on WM tracts than traumatization in adulthood. Early traumatization might therefore interfere more strongly in the development of the corpus callosum (Teicher et al., 2003). In the meta-analysis, we will investigate overlapping clusters of FA change. We will only include studies from adult-onset PTSD following trauma experience in adulthood, which used a whole brain analysis (see also Table 2a).

3. Methods

3.1. Literature search

PubMed, Web of Science, PSYNDEX and PsychINFO databases were searched to identify studies on the role of structural changes measured via DTI in patients with PTSD in comparison to healthy control subjects and/or trauma-exposed control subjects. The systematic search was conducted with the following keywords: *structural changes* (OR diffusion tensor imaging OR DTI OR white matter integrity OR fractional anisotropy OR FA) AND *PTSD* (OR psychological trauma* OR posttraumatic stress* OR anxiety OR anxious* OR early life trauma OR childhood trauma OR childhood abuse OR childhood adversity OR childhood maltreatment).

3.2. Inclusion and exclusion criteria

Participants had to be clearly diagnosed with PTSD using the criteria of the fourth and fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2000, 2013) or the International Classification of Diseases (ICD 10; World Health Organization, 1992) available at the time of publication. We included all studies that examined structural changes using DTI. Studies on adult-onset PTSD were subdivided into studies with individuals suffering from PTSD after childhood trauma or trauma experienced in adulthood. In a third group, we included studies with children that suffered from PTSD. Studies were excluded, if no control group was included or if participants in the experimental group suffered from comorbid disorders such as substance abuse or psychotic symptoms.

3.3. Meta-Analysis using GingerAle

In our meta-analysis we included only DTI studies examining the whole brain, instead of specific predefined regions of interest (ROI). Although ROI-based analyses have several advantages such as theory guidance, a limited number of statistical tests performed on the ROIs and a definition of regions according to functional properties (Poldrack, 2007), the comparability between studies is impeded due to differences in the definition of ROIs and the masking of the same ROI. For studies using whole brain analysis, we included all coordinates in our meta-analysis, independent of the threshold applied to the p values or the cluster sizes used in the study. The small number of studies in the group of adults and children with trauma experience in childhood made it difficult to calculate any meaningful effects specific to this group. Thus we only included DTI studies from the group of adult-onset PTSD with traumatic experience in adulthood. We further subdivided the findings in this group in studies reporting a significant decrease or a significant increase of FA in patients with PTSD in comparison to at least one control group. The activation-likelihood (ALE) meta-analysis was computed separately for these two groups. The meta-analysis was carried out with the GingerAle software package (www.brainmap.org/ale/), a coordinate-based human brain mapping tool to perform meta-analyses of functional or structural datasets (Eickhoff et al., 2012; Eickhoff et al., 2009; Turkeltaub et al., 2012). All coordinates were either reported in the Montreal Neurological Institute (MNI) space or transformed using the Bretts transformation algorithm in GingerAle. The meta-analysis was computed in four steps. For the calculations, GingerAle needs the following information of each study in a text file: the contrast (e.g. PTSD vs. TC), the mask (MNI), the subject size and the finding (e.g. decrease). First, an ALE score is calculated in a 3D image for each group of foci, using the information given above. Second, a Modelled Activation map (MA; Eickhoff et al., 2009) is constructed, finding in our case the maximum across the Gaussian distributions of the foci (Non-Additive; Turkeltaub et al., 2012). Third, All the MA are united to form an ALE image. We set the statistical threshold to a False Discovery Rate (FDR) of pN = 0.05 and the threshold of the cluster level analysis to $p = 0.05$ with 1000 threshold permutations. The FDR with pN thresholding is the more conservative option of two possible thresholdings, making no assumptions about correlations in the data. The cluster-level inference simulates random data sets based on the characteristics of our input data. Finally, GingerAle calculates the volumes which are above the threshold (clusters) and tracks the distribution of their volume. An output table is created indicating which clusters survived after applying the indicated threshold.

4. Results

Initially, 1741 articles were identified in the searched databases after applying the search terms. Of these, 1183 articles did not meet inclusion criteria, because they either did not specifically investigate PTSD, focused on different techniques or non-human samples. Further, we fully reviewed 78 articles, resulting in 30 studies that were ultimately included in the qualitative review. We included 19 papers in the group of aa-PTSD, two papers in the group of ac-PTSD and nine papers on cc-PTSD (see Fig. 1 for details). In total, the articles reviewed comprise a population of 1687 individuals, of whom 744 were diagnosed with PTSD, 473 were trauma-exposed control subjects, 450 were healthy control subjects and 20 were individuals with Generalized Anxiety Disorder (GAD). For the change in FA, 16 studies found a decrease, 6 found an increase and 5 reported both, a decrease and an increase in FA in patients with PTSD in comparison to at least one control group. In addition, two studies found no significant change in FA (see Table 1 for details).

In the systematic review, we further subdivided the identified regions depending on the comparison made between either PTSD patients and healthy or PTSD and trauma control subjects (see also Appendix Tables 1, 2 and 3). In the group of aa-PTSD, studies predominantly used a whole brain approach and the majority of studies compared patients to trauma control subjects. In the group comparison between aa-PTSD patients and healthy control subjects, the most commonly mentioned regions were the cingulum, especially with its anterior and subgenual subparts (Abe et al., 2006; Kim et al., 2006) and the superior and orbital frontal gyrus (Sun et al., 2013; Zhang et al., 2011). In the cingulum, a significant increase, using whole brain (Abe et al., 2006), as well as

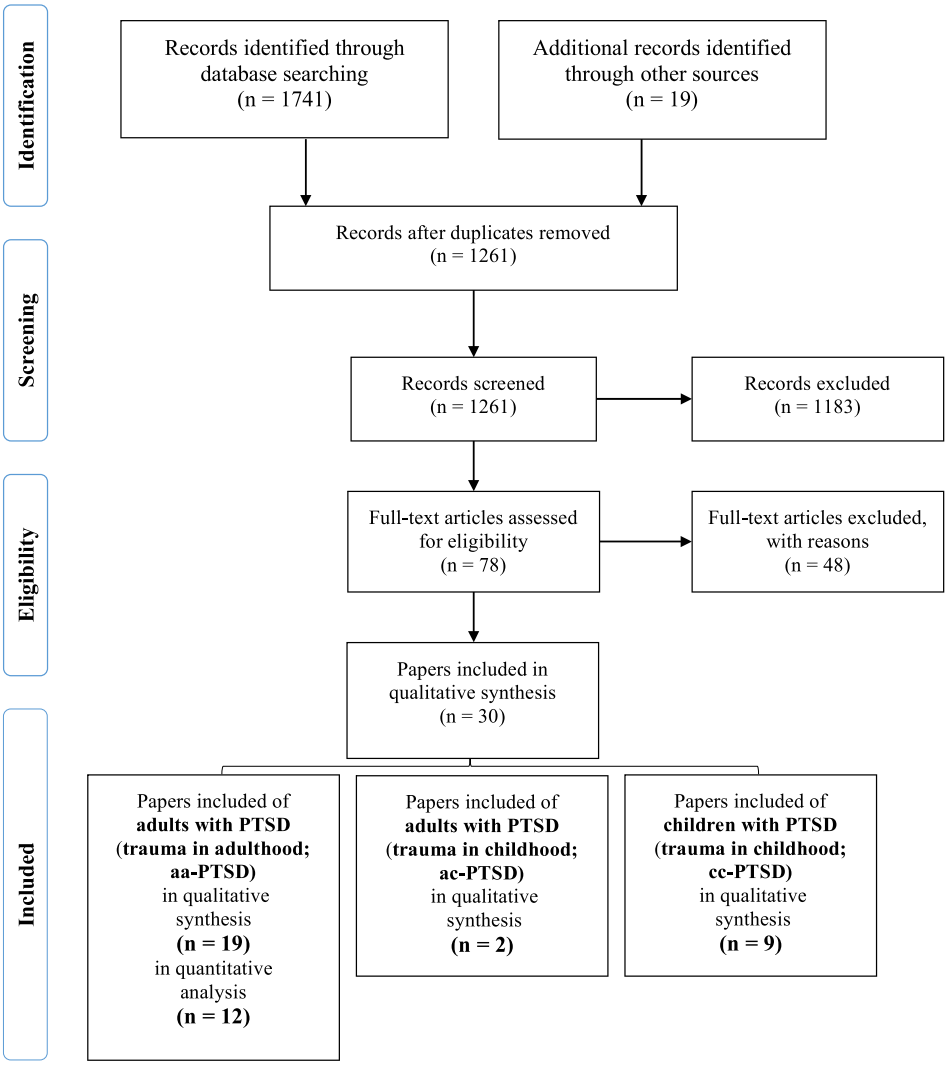

Fig. 1. Flowchart of literature review. The total number of studies reviewed in this article is printed in bold letters (taken from the guidelines of the PRISMA group (Moher et al., 2009)).

decrease, using ROI analysis (Kim et al., 2006), was found. In the group comparison between aa-PTSD patients and trauma control subjects, a larger range of regions were found (detailed overview Table 2a, Appendix Table 1). Again, the most prominent regions included several subparts of the cingulum (Bierer et al., 2015; Fani et al., 2012; Hu et al., 2016; Kennis et al., 2015; Kim et al., 2016; Sun et al., 2013; Wang et al., 2010; Zhang et al., 2012), frontal gyrus (Li et al., 2016; Sun et al., 2015; Sun et al., 2013) and in addition the longitudinal fasciculus (Fani et al., 2012; Hu et al., 2016; Olson et al., 2017). In the cingulum, a significant decrease in FA was found, using whole brain (Fani et al., 2012; Hu et al., 2016; Kim et al., 2016; Schuff et al., 2011; Sun et al., 2013) or ROI (Bierer et al., 2015; Wang et al., 2010) but also a significant increase in FA, using whole brain (Kennis et al., 2015; Zhang et al., 2012) or ROI (Kennis et al., 2015). In the frontal gyrus, all studies used whole brain analysis finding a decrease (Schuff et al., 2011; Sun et al., 2015; Sun et al., 2013) or increase (Li et al., 2016) in FA of several frontal areas. Within the inferior and superior longitudinal fasciculus, a decrease was found using whole brain analysis (Fani et al., 2012; Hu et al., 2016; Olson et al., 2017). In the group of ac-PTSD (detailed overview Table 2b, Appendix Table 2), both studies reviewed used ROI analysis of the corpus callosum, finding a decrease of the genu, mid-body and isthmus (Kitayama et al., 2007; Villarreal et al., 2004). Finally, in the group of cc-PTSD (detailed overview Table 2c, Appendix Table 3), the great majority studies focused on the corpus callosum and

Table 1
Summary of reviewed articles with the number of individuals included in each subgroup (PTSD – Posttraumatic Stress Disorder; TC – Trauma Controls; HC – Healthy Controls; GAD – Generalized Anxiety Disorder) and number of studies reporting changes in fractional anisotrophy (FA; dec. – decrease; inc. – increase; both – decrease and increase; no ch. – no change).

	N (PTSD)	N (TC)	N (HC)	N (GAD)	Total	FA dec.	FA inc.	FA both	FA no ch.	Total
Adult onset PTSD (adulthood trauma)	431	422	101	20	974	10	6	3	0	19
Adult onset PTSD (childhood trauma)	21	0	19	–	40	1	0	0	1	2
Child onset PTSD (childhood trauma)	292	51	330	–	673	5	0	2	2	9
Total	744	473	450	20	1687	16	6	5	3	30

Table 2a
Diffusion tensor imaging studies in adult onset posttraumatic stress disorder after traumatic experience in adulthood.

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood trauma	Increase	Decrease	Key findings [Cohen's d]
[1] **Abe et al. (2006)**	36; 9 PTSD vs. 16 HC	21 to 69; PTSD M ≈ 44	60% male; 100% Asian	CAPS	1.5 T GE	Whole brain/ROI	DTI/FA	No	Yes	No	Increase: Left anterior cingulum [d = 1.63]
[2] Aschbacher et al. (2017)	57; 31 PTSD vs. 26 TC	22 to 55; M ≈ 33	100% male; 54% Hispanic, 28% White, 23% African-American	CAPS; SCL-90-R; PDEQ;	3 T Siemens	ROI	DTI/FA	No	Yes	No	Increase: Superior fronto-occipital fasciculus [d = 0.56]
[3] Bierer et al. (2015)	20; 12 PTSD vs. 8 TC	Range not specified; M ≈ 43	100% male; 35% Latino, 30% White, 30% African-American	CAPS; SCID-I; CTQ; MS; BDI; STAI	3 T Siemens	ROI	DTI/FA and MD; TBSS	Yes	Yes	Yes	Increase: Right cingulum (MD) Decrease: Right cingulum (FA; $p = 0.071$) ROI: (bilateral anterior cingulum)
[4] **Fani et al. (2012)**	50; 25 PTSD vs. 26 TC	20 to 62; M ≈ 36	100% female; 100% African-American	TEI; CTQ; PSS; BDI	3 T Siemens	Whole brain	DTI/FA; TBSS	Yes	Yes	Yes	Increase: Right lateral occipital cortex [d = 0.61] Decrease: Left post. Cingulum [d = 0.63] Right post. Cingulum [d = 0.85] Left superior longitudinal fasciculus
[5] Fani et al. (2014)	82; 28 TC (CC) vs. 34 TC (CT) vs. 20 TC (TT)	Range not specified; M ≈ 39	100% female; 100%African American	TEI; PSS; CTQ	3 T Siemens	Whole brain	DTI/FA; TBSS	Yes	No	Yes	Decrease: Left posterior cingulum in carriers of two risk allele of type rs1360780
[6] **Huang et al. (2012)**	34; 17 PTSD vs. 17 TC	18 to 60; M ≈ 40	50% female; race not specified	CAPS; SCID-I; M.I.N·I; ASDI; BDI; PDI	3 T GE	Whole brain	DTI/FA; TBSS	No	No	Yes	Decrease: Anterior thalamic radiation with 1. Corticospinal tract, cingulum & inferior fronto-occipital fasciculus [d = 1.46] 2. Corticospinal tract, cingulum & superior fronto-occipital fasciculus [d = 1.28] 3. Forceps minor, inferior fronto-occipital fasciculus, superior longitudinal fasciculus [d = 1.99]
[7] **Kennis et al. (2015)**	61; 39 PTSD vs. 22 TC	22 to 57; M ≈ 36	100% male; race not specified	CAPS; SCID-I	3 T Philips	Whole brain/ROI	DTI/FA	No	Yes	No	Increase: Dorsal cingulum [d = 0.53] ROI: dorsal and hippocampal cingulum bundle [d = 0.57], stria terminalis [d = 0.69] and fornix [d = 0.53]
[8] **Kim et al. (2005)**	40; 20 PTSD vs. 20 TC	19 to 49; M ≈ 28	40% males; race not specified	CAPS; SCID-I; PDQ-4; HDRS	3 T GE	Whole brain	DTI/FA	no	no	yes	Decrease: Left anterior cingulate
[9] Kim et al. (2006)	42; 21 PTSD vs. 21 HC	19 to 49; M ≈ 28	38% male; race not specified	CAPS; SCID-I; PDQ-4; HDRS	3 T GE	ROI	DTI/FA	No	No	Yes	Decrease: Left cingulum bundle – Rostral anterior subregion [d = 1.57] – Subgenual anterior subregion [d = 1.34] – Dorsal anterior subregion [d = 1.11] ROI: upper cingulate, rostral cingulate, dorsal cingulate, supragenual cingulum

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Table 2a (*continued*)

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood trauma	Increase	Decrease	Key findings [Cohen's d]
[10] Koch et al. (2017)	77; 38 PTSD vs. 39 TC	Range not specified; M ≈ 40	53% male; race not specified	CAPS; SCID; HADS-A; HADS-D; IES-R; AUDIT; ETI-SF; PLES	3 T Philips	Whole brain	DTI/FA, MD	Yes	Yes (only MD)	No	Increase: Right uncinated fasciculus (MD); – Positively correlated with symptoms of anxiety in PTSD Positively associated with amygdala activity and vmPFC activity in response to happy and neutral faces whereas FA remained unchanged
[11] **Li et al. (2016)**	179; 88 PTSD vs. 91 TC	Range not specified; M ≈ 43	30% male; race not specified	CAPS; PCL	3 T GE	Whole brain	DTI/FA (AD and RD)	No	Yes	No	Increase: Left superior frontal gyrus [d = 0.81] Left middle frontal gyrus [d = 0.70] Left forceps major [d = 0.71]
[12] **Olson et al. (2017)**	37; 20 PTSD vs. 17 TC	21 to 56; M ≈ 36	62% female; race not specified	CAPS; TLEQ	3 T Siemens	Whole brain	DTI/FA; TBSS	Yes	No	Yes	Decrease: Inferior longitudinal fasciculus [left: d = 0.80; right d = 0.17]
[13] Saar-Ashkenazy et al. (2016)	30; 16 PTSD vs. 14 HC	Range not specified; M ≈ 35	67% male; race not specified	CAPS; STAI; PDS	1.5 T Philips	Whole brain	DTI/FA	No	No	Yes	Decrease (only significant correlations): Total FA in corpus callosum (CC) correlated negatively with arousal, avoidance, re-experiencing and total symptom severity. Central CC correlated highest with symptoms of arousal, avoidance and re-experiencing
[14] **Schuff et al. (2011)**	38; 19 PTSD vs. 19 TC (5 not exposed)	Range not mentioned; M ≈ 43	Not specified	CAPS; SCID-I; LSC-R	4 T Siemens	Whole brain	DTI/FA; TBSS, 0.001 uncorrected	Some not excluded	No	Yes	Decrease: Anterior cingulate cortex Prefrontal cortex Precentral gyrus Posterior internal capsule Posterior angular gyrus
[15] **Sun et al. (2013)**	60; 21 PTSD vs. 22 HC vs. 17 TC	18 to 60; M ≈ 38	45% male; race not specified	CAPS; M.I.N.I.; ASDI	3 T GE	Whole brain	DTI/FA	No	No	Yes	Decrease PTSD < TC (FA): Right middle temporal gyrus WM [d = 1.78] Right anterior cingulate cortex WM [d = 1.76] Right midbrain WM [d = 1.26] Left gyrus rectus/medial OFC WM [d = 1.55] Decrease PTSD < TC (MD): Right superior frontal gyrus WM Left subcallosal gyrus WM Decrease PTSD < HC (FA): Left superior frontal gyrus, orbital part WM [d = 1.55] Left superior temporal gyrus WM [d = 1.51] Right inferior occipital gyrus WM [d = 1.51]

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Table 2a (*continued*)

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood trauma	Increase	Decrease	Key findings [Cohen's d]
[16] **Sun et al. (2015)**	29; 15 PTSD vs. 14 TC	18 to 60; M ≈ 39	52% male; race not specified	CAPS; M.I.N.I.; ASDI	3 T GE	Whole brain	DTI/FA;	No	No	Yes	Decrease (FA): Commissural tract connecting bilateral superior/middle frontal gyrus [d = 0.84]
[17] Wang et al. (2010)	20; 10 PTSD vs. 10 TC	17 to > 40; not specified	Not specified	CAPS; PSQI; HDRS; SCL-90-R	3 T Siemens	Whole brain/ROI	DTI/FA; manual tracing, $p = 0.05$ uncorrected	Some not excluded	No	Yes	Decrease: right posterior cingulum [d = 1.14] hippocampus (body) [d = 1.21] ROI: hippocampus and cingulum
[18] **Zhang et al. (2011)**	65; 17 PTSD vs. 28 HC vs. 20 GAD	23 to 43; M ≈ 32	66% male; race not specified	CAPS; PSWQ	1.5 T GE	Whole brain/ROI	DTI/FA; whole brain: $p = 0.001$, uncorrected, ROIs: $p = 0.05$	No	Yes	Yes	Decrease (PTSD < GAD): right anterior cingulate [d = 2.91] Increase (PTSD > HC): left superior frontal gyrus [d = 1.18]
[19] **Zhang et al. (2012)**	27; 13 PTSD vs. 14 TC	Not specified; M ≈ 39	Gender not specified; race not specified	PCL-C; STAI; BDI	1.5 T GE	Whole brain	DTI/FA; $p = 0.005$, uncorrected	No	Yes	No	Increase: Left posterior cingulate gyrus Right posterior cingulate gyrus Right precuneus Right parietal sub-gyrus Left middle temporal gyrus

Table 2b
Diffusion tensor imaging studies concerning adult onset posttraumatic stress disorder after traumatic experience in childhood.

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood trauma	Increase	Decrease	Key findings
[20] Kitayama et al. (2007)	18; 9 PTSD vs. 9 HC Childhood Abuse	Not mentioned; M ≈ 37	100% female; not mentioned	CAPS; ETI; SCID	1.5 T GE	ROI	Manual tracing	Yes	No	No	No difference found in whole corpus callosum ROI: corpus callosum
[21] Villarreal et al. (2004)	22; 12 PTSD vs. 10 HC In most cases physical and sexual childhood abuse	Not mentioned; M ≈ 43	82% female; not mentioned	CAPS; SCID; BDI; BAI	1.5 T GE	ROI	Manual tracing	Yes (50% of the sample)	No	Yes	Decrease: Absolute and normalized corpus callosum; In subregions: 2 (genu) [d = 1.03]; 4 (anterior mid-body; trend) [d = 0.77]; 5 (mid-body) [d = 1.32]; 6 (isthmus) [d = 1.19] ROI: corpus callosum

Table 2c
Diffusion tensor imaging studies concerning childhood onset posttraumatic stress disorder after traumatic experience in childhood.

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood trauma	Increase	Decrease	Key findings
[22] De Bellis et al. (1999)	105; 44 PTSD vs. 61 HC	7 to 17; M ≈ 12	58% male; 75% white, 13% African American, 11% biracial	K-SADS-PL; CDI; CBCL; CDC; GAF; SES; WISC-R; PANESS	1.5 T GE	ROI (Corpus callosum)	Manual tracing	Yes	No	Yes	Decrease: Corpus callosum (total size) [d = 0.41] Corpus callosum (genu) [d = 0.31] Corpus callosum (ant. midbody) [d = 0.58] Corpus callosum (post. midbody) [d = 0.50] Corpus callosum (isthmus) [d = 0.39] Corpus callosum (splenium) [d = 0.48]
[23] De Bellis et al. (2002)	94; 28 PTSD vs. 66 HC	5 to 17; M ≈ 12	58% male; 78% white, 7% African American, 15% biracial	K-SADS-PL; CDI; CBCL; CDC; GAF; SES; WISC-R; PANESS	1.5 T GE	ROI (Corpus callosum)	Manual tracing	Yes	No	Yes	Decrease: Corpus callosum (ant. midbody) [d = 0.56] Corpus callosum (post. midbody) [d = 0.55] Corpus callosum (isthmus) [d = 0.61] Corpus callosum (splenium) [d = 0.74]
[24] De Bellis and Keshavan (2003)	[183; 61 PTSD vs. 122 HC] (pooled from studies 1999 and 2002 (see above))	5 to 17; M ≈ 12	51% male; Race not specified	K-SADS-PL; CDI; CBCL; CDC; GAF; SES; WISC-R; PANESS	1.5 T GE	ROI (Corpus callosum)	Manual tracing	Yes	No	Yes	Decrease: (females > males) Corpus callosum (total size) Corpus callosum (ant. midbody) Corpus callosum (post. midbody) Corpus callosum (isthmus) Corpus callosum (splenium) Decrease in white matter volume higher in females with PTSD than in males with PTSD
[25] De Bellis et al. (2015)	79; 23 PTSD vs. 27 TC vs. 29 HC	6.2 to 16.2; M ≈ 10	54% female; 45% African American, 42% Caucasian, 13% Multi-racial	K-SADS-PL; WISC-R; CBCL; CGAS	3 T Siemens	ROI (Corpus callosum)	DTI/FA	Yes	No	No	Decrease in AD: (PTSD < TC, HC) Corpus callosum (splenium)
[26] Jackowski et al. (2008)	32; 17 PTSD vs. 15 HC	6.3 to 14.4; M ≈ 11	56% female; 41% African American, 25% Caucasian, 18% Hispanic, 16% Biracial	K-SADS-PL; SCARD	1.5 T GE	ROI (Corpus callosum)	DTI/FA	Yes	No	Yes	Decrease: Corpus callosum (ant. midbody) [d = 3.00] Corpus callosum (post. midbody) [d = 3.50]
[27] Lei et al. (2015)	51; 25 PTSD vs. 24 TC	Range not specified; M ≈ 13	57% female; race not specified	CAPS; PCL	3 T GE	Whole brain	DTI/FA,MD, RD, AD	Yes	Yes	Yes	Increase: Left angular gyrus (MD) left angular gyrus (AD) Decrease: right thalamus (MD)
[28] Richert et al. (2006)	47; 23 PTSD (52% full diagnosis) vs. 24 HC	7 to 14; PTSD M ≈ 13	56% male in PTSD group; race not specified	CAPS-CA; K-SADS-PL	1.5 T GE	ROI	Volumetric analysis	Yes	No	No	No difference in white matter found ROI: prefrontal cortex

(*continued on next page*)

Table 2c (*continued*)

	Sample (N; groups contrasted)	Age in years (range; M)	Gender (%), race (%)	Diagnostic tools	Scanner	Brain regions assessed	Method	Childhood trauma	Increase	Decrease	Key findings
[29] Rinne-Albers et al. (2016)	40; 20 PTSD vs. 20 HC	Range not specified; M ≈ 16	87.5% female; race not specified	ADIS-C/P; PDS; TSCC	3 T Philips	Whole brain/ ROI	DTI (threshold $p < 0.075$) TBSS/ FA, AD, RD, MD	Yes	Yes	Yes	Decrease: Left splenium of the corpus callosum (FA) Increase: Left splenium of the corpus callosum (RD, MD) ROI: bilateral uncinated fasciculus, genu, splenium and body of the corpus callosum (RD, MD)
[30] Teicher et al. (2004)	166; 51 PTSD/TC (50% with diagnosis of PTSD) vs. 115 HC	Range not specified; M ≈ 12	58% male; race not specified	DSM-III-R	1.5 T GE	ROI (Corpus callosum)	Volumetric analysis	Yes	No	Yes	Decrease: [*detailed effect sizes in paper] Corpus callosum (total size) Corpus callosum (rostral body) Corpus callosum (ant. midbody) Corpus callosum (cost. midbody) Corpus callosum (isthmus) Corpus callosum (splenium)

AD – Axial Diffusivity; ASDI – Acute Stress Disorder Inventory; ADIS-C/P – Anxiety Disorders Interview Schedule Child and Parent Versions; AUDIT – Alcohol Use Disorders Identification Test; BAI – Beck Anxiety Inventory; BDI – Becks' Depression Inventory; CAPS – Clinician-Administered PTSD Scale; CAPS-CA – Clinician-Administered PTSD Scale for Children and Adolescents; CBCL – Child Behaviour Checklist; CDC – Child Dissociative Checklist; CDI – Childhood Depression Inventory; CGAS – Children Global Assessment Score; CTQ – Childhood Trauma Questionnaire; DMN – Default Mode Network; DSM-III-R – Diagnostic and Statistical Manual of Mental Disorders (revised 3rd edition); DTI – Diffusion Tensor Imaging; ETI-SF – Early Trauma Inventory; GAD – Generalized Anxiety Disorder; GAF – Children's Global Assessment Scale; HADS-A – Hospital Anxiety and Depression Scale – Anxiety; HADS-D – Hospital Anxiety and Depression Scale – Depression; HC – Healthy Control; HDRS – Hamilton Depression Rating Scale; IES-R – Revised Impact of Events Scale; K-SADS-PL – Schedule for Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime; LSC-R – Life Stressor Checklist-Revised; M – Mean; M.I.N.I. – Mini-International Neuropsychiatric Interview; MS – Mississippi Scale; OFC – Orbitofrontal Cortex; PANESS – Revised Physical and Neurological Examination for Subtle Signs; PCL – PTSD Checklist; PCL-C – PTSD Checklist Civilian Version; PDEQ – Peritraumatic dissociative experiences questionnaire; PDI – Peri-traumatic Distress Inventory; PDS – Puberty Development Scale; PDQ-4 – Personality Disorder Questionnaire-4; PLES – Police Life Events Scale; PSQI – Pittsburgh Sleep Quality Index; PSS – PTSD Symptom Scale; PSWQ – Penn State Worry Questionnaire; PTSD – Posttraumatic Stress Disorder; RD – Radial Diffusivity; ROI – Region of Interest; SCID-I – Structured Clinical Interview for DSM IV; SCARD – Screen for Child Anxiety and Related Disorders; SCID – Structured Clinical Interview for DSM-IV; SCL-90-R – Revised Symptom Checklist 90; SD – Standard Deviation; SES – Hollingshead four factor index of socioeconomic status; STAI – State-Trait Anxiety Inventory; TC – Trauma Control; TEI – Traumatic Events Inventory; TLEQ – Traumatic Life Events Questionnaire; TSCC – Trauma Symptom Checklist for Children; WISC-R – Wechsler Intelligence Scale for Children.

compared underage patients (< 18 years of age) with PTSD to healthy control subjects. Using ROI analysis, they found a decrease in FA, most prominently in the anterior and posterior midbody (De Bellis et al., 1999, 2002; De Bellis and Keshavan, 2003; Jackowski et al., 2008; Teicher et al., 2004) as well as the isthmus and splenium (De Bellis et al., 1999, 2002; De Bellis and Keshavan, 2003; Rinne-Albers et al., 2016; Teicher et al., 2004).

5. Meta-analysis

In the meta-analysis, we included only studies fulfilling the following five criteria: a) one group of adult patients (> 18 years of age) with PTSD and at least one control group; b) clearly stating if childhood trauma and comorbid disorders were present; c) using diffusion tensor imaging measuring fractional anisotropy; d) using whole brain analysis; e) reporting foci of significant cluster differences. In total, 14 DTI studies of patients with adult-onset PTSD were included in the meta-analysis. Seven studies reported a decrease of FA (Fani et al., 2012; Hu et al., 2016; Kim et al., 2005; Olson et al., 2017; Schuff et al., 2011; Sun et al., 2013; Sun et al., 2015; Zhang et al., 2011), including 9 contrasts with 22 foci. In this group of studies, 175 patients with PTSD, 130 trauma and 22 healthy control subjects and 20 subjects with GAD were included. In contrast, six studies reported an increase in FA (Abe et al., 2006; Fani et al., 2012; Kennis et al., 2015; Li et al., 2016; Zhang et al., 2011, 2012), including six contrasts with twelve foci. In this second group of studies, 191 patients with PTSD, 153 trauma and 44 healthy control subjects are comprised in the analysis (see Fig. 2).

6. Discussion

The aim of this systematic review was to provide a comprehensive evaluation of studies reporting structural WM changes in patients with PTSD. We identified 30 articles, including almost 1700 individuals comprising 450 adult patients and 300 children suffering from PTSD. Firstly, for aa-PTSD in comparison to trauma and healthy control subjects, the most common changes in white matter were reported in the cingulum (decrease and increase) and frontal regions (decrease and increase). Furthermore, changes in the longitudinal fasciculi (decrease) were shown in studies comparing adult patients with trauma control subjects. A meta-analysis using GingerAle, including 14 studies of adults with adult onset PTSD in comparison to trauma and healthy control subjects did not reveal any significant clusters. Secondly, for ac-PTSD in comparison to healthy control subjects, only two studies could be included both focusing on changes in the corpus callosum (decrease and no change). Thirdly, for children diagnosed with PTSD compared to healthy control subjects, all available studies found changes in the corpus callosum (decrease), most prominently in the anterior and posterior midbody, the isthmus and the splenium. Only one study in this subgroup also compared children suffering from chronic PTSD to trauma control subjects and found no change in FA in the corpus callosum. Our review revealed a high heterogeneity regarding significant changes of WM, measured via change in the FA, in patients with PTSD in comparison to trauma and healthy controls. The most prominent changes in fiber tracts included the corpus callosum (CC), the cingulum, the superior longitudinal fasciculus (SLF). These changes can be related to contextualization, the processing of emotionally salient cues and extinction of aversive memories. Changes in the white matter microarchitecture due to traumatic experiences could play an important role in the development of child- and adult onset PTSD.

Firstly, the corpus callosum, the largest connecting fiber bundle which facilitates inter-hemispheric communication, was reported to show a decreased FA mainly in patients with childhood trauma in comparison to healthy control subjects (see also Appendix Table 3; De Bellis et al., 1999, 2002; De Bellis and Keshavan, 2003; Jackowski et al., 2008; Kitayama et al., 2007; Lei et al., 2015; Richert et al., 2006; Rinne-Albers et al., 2016; Teicher et al., 2004; Villarreal et al., 2004). Only one study with adult-onset PTSD with trauma experience in adulthood found a significant negative CC and symptoms like arousal, avoidance and re-experiencing (Saar-Ashkenazy et al., 2016). The CC has been reported to be important for encoding and retrieval of memories (Gazzaniga, 2000; Tulving et al., 1994). A malfunctioning or reduction in volume was suggested to result in a lack of lateralization and specification in associative memory (Saar-Ashkenazy et al., 2014, 2016). These results point towards changes in WM maturation due to traumatic experiences rather than vulnerability. Interestingly, Saar-Ashkenazy et al. (2014, 2016) found a high negative correlation of 0.65 between WM in the mid-posterior, posterior and the total FA of the CC and associative memory encoding and retrieval of words in adult-onset

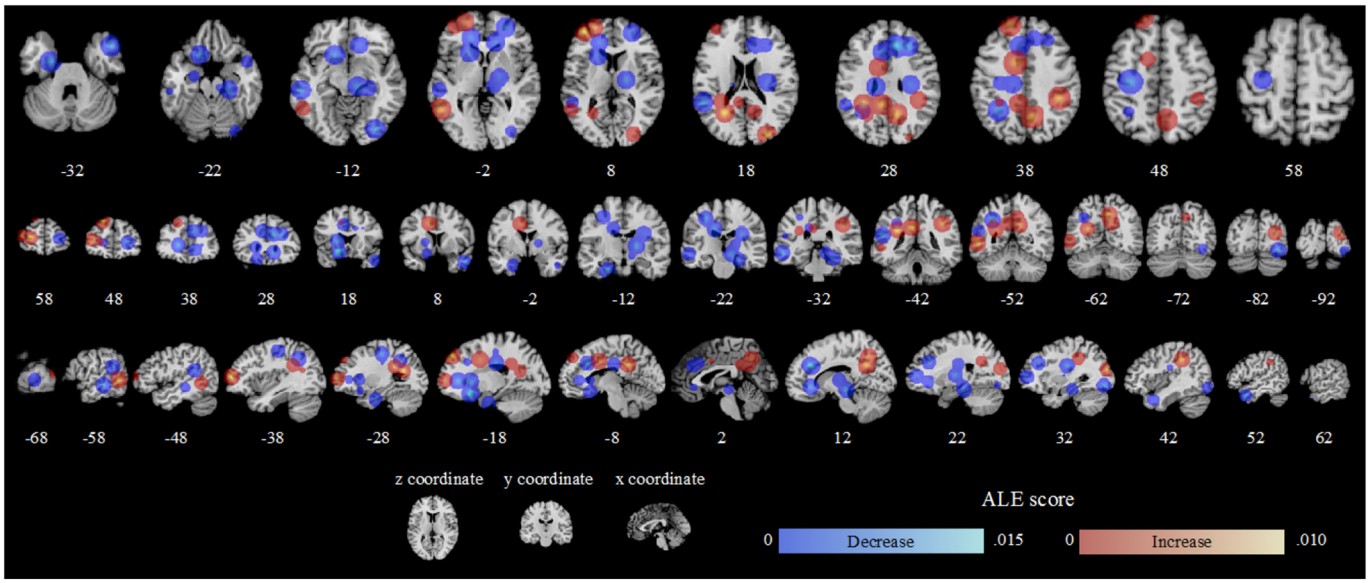


Fig. 2. Overview of thirteen studies reporting coordinates in MNI space on changes in FA in adult-onset PTSD. The ALE scores are displayed in colour (blue spectrum for decrease of FA, red spectrum for increase of FA). Due to the choice of showing the Gaussian distribution of each foci, weighted by the number of subjects included in each study, foci might appear in several slices.

PTSD. In addition, they found a strong negative correlation of 0.65 between WM in the anterior, central and total FA of the CC for the mean association reaction time for pictures. These findings indicate a deficit in associative encoding and memory, which is in line with the idea of a disturbance of brain circuits involved in contextual processing in PTSD (Bisby and Burgess, 2017; Brewin et al., 2010; Flor and Nees, 2014; Liberzon and Abelson, 2016). In their review, Daniels et al. (2013) observed a reduced volume of the CC in the majority of studies investigating trauma-exposed children. They found a similar amount of studies as in our review reporting volume loss in the CC in adult-onset PTSD. However, this is not surprising considering that the CC is developing most dramatically during childhood and adolescence, driven by additive genetic effects and environmental exposure (Giedd and Rapoport, 2010; Luders et al., 2010). Luders et al. (2010) found differences in males and females in colossal maturation patterns and segments. The authors suggested that a decrease in the thickness of the CC may reflect axonal redirection or pruning. Alternating periods of growth and shrinkage of the CC during childhood and adolescence were found to be normal in healthy development of the human brain. Interestingly, the only study in the subgroup of children with PTSD including a healthy as well as a trauma control group, did not find any differences in FA in the corpus callosum (De Bellis et al., 2015). However, in their well-designed study De Bellis et al. (2015) found a decrease in axial diffusivity in childhood patients in comparison to trauma controls in the section of splenium projecting to occipital regions. Although the authors discuss reasons for an innate vulnerability, they also mention the limited inference one can make from a cross-sectional design. Future studies should include healthy and trauma control groups in their design and take into account sex- and age-specific differences in WM development of the corpus callosum. Overall, a decrease in FA in the CC is more prominent in children with PTSD than adults, suggesting a more drastic change in white matter architecture given the central role of the CC in interhemispheric communication. However, in adults, a negative association between the decrease in FA in subparts of the CC and the performance in an association task with words and pictures was found, suggesting a role of the CC in associative encoding and processing.

Secondly, the cingulum was reported to show an alteration in FA in individuals with aa-PTSD (see also Appendix Table 1). Our findings rather support the hypotheses of the cingulum as a vulnerable WM tract, with several studies showing differences between patients with PTSD and trauma controls. Although the cingulum is the most frequently reported WM bundle to be affected by chronic stress besides the CC, the directionality of change in FA stays unclear with some studies reporting an increase (Kim et al., 2006; Schuff et al., 2011) and others a decrease (Abe et al., 2006; Zhang et al., 2013) in FA. In general, the cingulum has been associated with a variety of functions including the integration of negative affect and pain (Shackman et al., 2011) and verbal and spatial short-term memory (Kalisch et al., 2006; Vytal et al., 2012; Vytal et al., 2013). Robinson et al. (2014) demonstrated over a series of experiments that individuals with anxiety disorder but without PTSD showed an increased circuit coupling during processing of fearful faces in the amygdala and the anterior cingulate cortex (ACC). An increased trait anxiety was thereby associated with an increased connectivity of the amygdala and the ACC. Fani et al. (2014) found that traumatized females without the diagnosis of PTSD carrying two risk alleles of the FKBP5 gene showed a decreased FA in the posterior cingulum, pointing towards WM changes as a vulnerability factor. The posterior cingulate cortex (PCC) is assumed to be a major region involved in the integration of information from an ego- and allocentric perspective into a cohesive whole (Aggleton and Vann, 2004; Burgess et al., 2001a, 2001b; Hassabis et al., 2007; Vann et al., 2009). It is thought to play a part in combining spatial components to form mental images and episodic memories and was further found to be important for imagination and planning for the future (Vann et al., 2009). Recent findings found alterations in WM integrity in the PCC and dorsolateral PFC (dlPFC) in adults with PTSD and trauma experience in the adulthood (e.g. Kennis et al., 2015). Interestingly, individuals with PTSD showed similar WM alterations in the PCC and dlPFC during fear extinction (Li et al., 2016). In summary, mixed findings within the cingulum might be explained by the different functions of the ACC and PCC in human cognition and emotion. Whereas the ACC is important for the processing of negative emotions and spatial short-term memory (Brewin et al., 2010; Liberzon and Abelson, 2016), the PCC integrates and transforms information of different perspectives to create mental images and episodic memories. Furthermore, the PCC might play a role in contextualization as part of a salience, visual and default mode network, which was found to be distorted in individuals with PTSD (Liberzon and Abelson, 2016; Sripada et al., 2012) and has recently been associated with symptoms like intrusions (Brewin and Burgess, 2014; Brewin et al., 2010) or overgeneralization (Kheirbek et al., 2012; Maren et al., 2013). More speculatively, changes in white matter in the ACC and connected areas such as the amygdala or insula could be associated with an up-regulation in sensory emotional processing of the experience of the traumatic event (Brewin et al., 2010). In contrast, changes in WM in the PCC and connected areas such as the hippocampus or precuneus could be associated with a down-regulation of contextualization of traumatic events. This imbalance in information processing with, for example, an up-regulation of object recognition and a down-regulation of spatial and temporal scene recognition could be associated with the development of intrusions (Brewin et al., 2010; Flor and Wessa, 2010). A recent study by Hermann et al. (2017) showed a direct relationship between the hippocampal part of the cingulum, connecting the cingulate cortex and the hippocampus, and context dependent extinction recall. They found that healthy participants with a higher FA value in the hippocampal part of the cingulum showed higher renewal of conditioned skin conductance responses (SCRs). This is in line with research on adult-onset patients with PTSD after traumatic experience in adulthood, showing that they have an impaired extinction recall and fear renewal, making it difficult for them to distinguish safe and dangerous environments (Garfinkel et al., 2014; Milad et al., 2009; Steiger et al., 2015; Wicking et al., 2016). Further research is needed here to distinguish the role of different segments of the cingulum in contextualization and the role of distorted salience and contextual networks in adult-onset PTSD with trauma (see Fig. 2).

Thirdly, the superior longitudinal fasciculus (SLF) was found to be altered in individuals with aa-PTSD (see also Appendix Table 1).Here, two studies found a decrease in WM integrity in the left SLF (Fani et al., 2012; Schuff et al., 2011), while one study reported an increase in WM in the left middle temporal branch (arcuate fascicle (AF)) and the right parietal branch of the SLF (SLF II; Zhang et al., 2012). Interestingly, the SLF was only found to differ between patients with PTSD and trauma control subjects, suggesting changes due to traumatic experience. The SLF is one of the major fiber bundles connecting the parietal, occipital and temporal lobe with the frontal lobe. The SLF is subdivided into three major tracts and their major functions include higher aspects of motor behaviour (SLF I), the perception of visual (SLF II) and auditory space (AF) as well orofacial and hand actions (for a review see Makris et al., 2005). De Schotten et al. (2011) emphasized the key role of the SLF in a visuo-spatial network with an increased processing speed of visuospatial information along the right hemispheric SLF II. Alterations in the left SLF on the other hand are associated with decreased visual spatial processing in a variety of neurological and mental disorders including Williams Syndrome (Hoeft et al., 2007), spatial neglect (Shinoura et al., 2009), early-onset schizophrenia (Karlsgodt et al., 2008) and social anxiety disorder (Baur et al., 2011). Although a wide

range of literature found that the SLF is a key player in spatial attentional processing across different modalities, it stays unclear how its malfunctioning is connected to alterations in other major WM fiber tracts such as the CC or the ACC and PCC. In patients with PTSD, the SLF might play an important role in a wider network of visual-spatial attention in information processing and autobiographical memory. Changes in the WM microstructure of the SLF might have an overarching effect on several brain circuits involved in PTSD such as the early detection and processing as well the emotional response to the cue, which further influences how well the cue is embedded in the environment (see Fig. 2).

Fourthly, we want to briefly emphasize a growing evidence of changes in FA in white matter tracts in frontal regions including the superior- and middle frontal gyrus (SFG; MFG) in aa-PTSD in comparison to trauma control subjects (see also Appendix Tables 1 and 3; Li et al., 2016; Schuff et al., 2011; Sun et al., 2013; Sun et al., 2015) and healthy control subjects (Zhang et al., 2011). In our sample, two studies found a decrease in FA in the SFG and MFG (Sun et al., 2013; Sun et al., 2015) and two an increase specifically in the left SFG (Li et al., 2016; Zhang et al., 2011). Interestingly, the SFG was found to support cognitive functions like spatial cognition (Du Boisgueheneuc et al., 2006) or as being part of a lateralized parietal-frontal resting state network (van den Heuvel and Hulshoff Pol, 2010). Parts of the medial SFG, better known as mPFC are involved in top-down control of subcortical regions and executive functions and known to be impaired in patients with PTSD (Brewin et al., 2010; Flor and Wessa, 2010; Lang et al., 2009; Liberzon and Abelson, 2016). The mPFC was suggested to support association learning between contexts, events, locations and their emotional responses (Euston et al., 2013). A decreased functioning of the SFG as part of higher level working memory might play a role in how patients with PTSD can “keep up” with environmental changes, which in turn might influence more long-term learning processes like extinction recall or fear renewal mentioned above. Symptoms like biased attention or heightened impulsivity might be the result. This is in line with current neurobiological models of the development and maintenance of PTSD, similarly associating the MFG to executive networks. Liberzon and Abelson (2016) argue that the dorsolateral PFC (part of the MFG) in combination with other prefrontal regions is activated during reappraisal. These assumption stay of course highly speculative until more research is carried out specifically locating the areas of the SFG impacted by changes in WM and their specific cognitive functions it might support (see Fig. 2).

6.1. Critical evaluation and future directions

The recent development of GingerAle makes it possible to calculate brain-wide analyses of cluster changes across studies. Due to the heterogeneity of findings across studies and the small number of studies reported, we only included those studies using whole brain analysis. In addition, research groups tend to use different protocols for the DTI parameters. Following our approach, we were able to subdivide the studies in groups reporting a significant increase or decrease in FA across the whole brain. Due to the global comparison, the construction of Ale maps leading to a meta-analysis is possible but at the same time the interpretations of the results is limited to a rather general level, like the direction of change. A next step would thus be the quantification of change using ROI analysis, which would quantify the FA change further by allowing researchers to calculate standardized effect sizes. Using effect sizes would also enable to include moderators, such as scanner type or symptom severity of PTSD. For this next step several prerequisites will be needed concerning study design and methodology of diffusion tensor imaging studies in patients with PTSD (for a summary see Appendix Table A2).

First, four key study design-specific considerations are proposed to enhance the explanatory power of future studies. The average sample size should be increased per group to ensure enough statistical power to be able to perform statistical tests including methods for bias corrections. A meta-analysis of all meta-analyses ($n = 46$) published between 2006 and 2009 found a median statistical power of 8% across 461 individual neuroimaging studies (Button et al., 2013). The relative bias of research findings in the field of neuroscience was found to be negatively related to the statistical power of studies, indicating that higher power improves the validity of the results. Importantly, studies should aim to have at least two matched control groups, including healthy participants without any traumatic experiences and healthy participants with trauma experiences. As mentioned previously, a second control group is essential to draw conclusions about whether structural WM changes arise due to neuroplastic changes after traumatic experience or whether these WM changes are also associated with symptoms of PTSD or may even be a pre-existing vulnerability factor. An important goal of future studies should be to clearly define target groups including subgroups within underage and adult patients with PTSD. We propose four target groups of patients suffering from PTSD, which are clearly understudied up to this point: b) children with traumatic experience in childhood, b) adolescents with traumatic experience in childhood; c) adolescents with traumatic experience in adolescence; d) adults with traumatic experience in childhood. In a recent survey of almost 6500 adolescent-parent pairs (aged 13–17 years), McLaughlin et al. (2013) found that 61.8% of the adolescents experienced a lifetime potential traumatic experience. The lifetime prevalence of developing PTSD in the group of adolescents according to the DSM-IV criteria was 4.7% with a significantly higher prevalence for females with 7.3% in comparison to males with 2.2%. In this context, it will become even more important to take into account moderators such as sex or comorbid disorders in underage but also adult populations suffering from PTSD. In the same line of argumentation, clearly stated inclusion and exclusion criteria are essential for increasing the validity with which group differences in FA values are associated with clinical symptoms of PTSD. Clearly stated criteria also make it possible to later compare more refined groups of studies in a meta-analysis.

Second, several methodological considerations are proposed to ensure high quality of data. Although the majority of studies reported basic demographic information including gender ratio, age or race, this information is crucial for replication and comparison between studies and should be clearly stated. Furthermore, the assessment of clinical disorders should include at least one common scale for the assessment of PTSD and at least one for common comorbid disorders such as depression, anxiety disorder and substance misuse. Breslau et al. (2000) found that the risk to develop depression was increased in adults with PTSD in comparison to trauma exposed adults without PTSD. The neural mechanisms of PTSD and depression might overlap and are important to take into account when investigating correlations between clinical assessments and changes in FA. In addition, a variety of clinical disorders were found to have comorbid PTSD including disorders such as schizophrenia, bipolar disorder or borderline personality disorder (Mueser et al., 1998). In these cases, PTSD might not be the primary outcome of structural changes in WM but rather an additional factor in the eq. A clear assessment of comorbid disorders is needed to understand these relations between disorders. In addition, the chronicity of PTSD might influence structural long-term changes and should be assessed and included in the analysis as covariate. Finally, the type of traumatic event experienced varies dramatically related to age and sex (McLaughlin et al., 2013; Mueser et al., 1998) and may influence the characteristics and severity of PTSD symptoms. A list of the type and number of traumatic experiences to which participants were exposed to should be included.

Third, we raise some methodological considerations concerning the acquisition, the pre-processing, the analyses and the reporting of DTI data. Since DTI is a rather novel technique in the field of neuroscience, the past ten years have seen a development towards a more standardized manner of acquiring and handling diffusion data. The heterogeneity in the results presented in this review can partly be explained by the variance in DTI methods applied, in the protocols used for acquiring the data as well as scanner type and field strength. For data acquisition and data pre-processing we recommend to follow the guidelines suggested by Jones et al. (2013). In the case of data analysis, two approaches are most common in DTI: whole brain and region of interest analyses. As mentioned previously, studies using whole brain analysis in research on patients with PTSD have the advantage to be included in meta-analyses because the limited number of studies using ROIs, at least in adult-onset with PTSD, focus on different regions, which made a meaningful comparison across studies difficult at the point in time of this review. In children with PTSD, the picture is reversed with almost all studies using region of interest analysis on different segments of the corpus callosum. Finally, the interpretation and reporting of DTI in PTSD has to be done with great caution. Studies should include the coordinates of foci of significant changes in FA as well as the cluster size and peak values. Several studies could not be included in the meta-analysis due to missing data. For the interpretation of DTI data and specifically FA, we again refer to the excellent list of “do's” and “don'ts” in the overview article by Jones et al. (2013). Up to date, many articles interpret changes in FA in the context of PTSD as changes in ‘white matter integrity’. The FA value, however, varies across the brain and can be low in areas where, for example, fibers cross. In their review, Zatorre et al. (2012) mention at least three processes, which can lead to an increase in FA: fiber organization, myelin formation and myelin remodelling. Furthermore, changes in glial cells, myelin context or the permeability of membranes might also contribute to changes in FA (Sampaio-Baptista and Johansen-Berg, 2017). In addition, stochastic errors, model simplifications or given anatomical structures like crossing fibers or changes in packing density (Jones et al., 2013) can influence the results. Overall, fractional anisotropy has a high sensitivity and a low specificity for the above mentioned anatomical properties to which it is often associated. For future research, it would be necessary to compare changes in FA to changes in GM or functional connectivity (Zatorre et al., 2012) in PTSD patients and the appropriate controls. Furthermore, a wide range of DTI acquisition procedures is in use in combination with various software packages for DTI pre-processing and data analysis. The high heterogeneity in findings for FA differences between studies in individuals with PTSD in comparison to healthy control subjects or subjects with trauma experience might therefore be partly the result of the high number of existing procedures to measure, pre-process and analyse data based on DTI. Methodological variability based on type of scanner, magnetic field strength, measurement parameters or pre-processing steps like motion correction are potential moderators influencing the magnitude and direction of FA change. Also, there is no theoretical framework explaining or predicting white matter changes in PTSD in specific areas or fiber tracts. Since PTSD is not explicitly impacting on WM, a theory why and where changes in WM should occur, is needed.

6.2. Limitations

Several limitations apply to our systematic review. First, despite the increased number of studies published in the past five years on WM alterations in adult-onset PTSD, only a limited number of studies could be included. The majority comprised a sample size of 15–20 individuals with PTSD in comparison to only one control group, either trauma-exposed or healthy controls. Only one study in adult-onset PTSD and one study in childhood-PTSD had a larger sample size of over 75 participants and only one study in each of these two subgroups compared PTSD patients to two control groups. Second, the heterogeneity of the WM tracts identified as well as the direction of change, with some studies reporting an increase and others a decrease in FA, allow only a preliminary interpretation of the results. Another explanatory factor to be taken into account in the future are methodological differences in software and scanner types used as well as diverse methodological approaches to assessment and analysis. A final note on GingerAle, which was originally designed for summarizing results of changes in GM. By applying the same technique to changes in white matter taken from DTI two problems arise: the analysis space and error distribution are different. In addition, studies using tract based spatial statistics (TBSS) with individual skeletons should be treated differently than DWI analysis, which they are currently not. To encounter these problems ne toolboxes and software packages are urgently needed with the growing number of studies focusing on structural changes in white matter.

7. Conclusions and future directions

This review provides novel conclusions on WM changes in individuals with underage-onset PTSD and traumatic experience in childhood, adult-onset PTSD with traumatic experience in childhood and adult-onset PTSD with traumatic experience in adulthood. The studies reported revealed some patterns of changes in WM integrity including the CC, ACC, PCC, SLF and SFG/MFG. In the group of adult-patients with traumatic experience in adulthood, changes in FA were found in the cingulum, most prominently with decreases in the ACC and increases in the PCC, the SLF and frontal tracts associated with the SFG and MFG. These findings are in line with recent psychobiological models of PTSD focusing on brain networks such as a context learning and memory, salience processing, emotional control and executive functions. In the group of children with PTSD and adults with PTSD after traumatic experience in childhood, almost exclusively changes in the corpus callosum are reported, particularly in the anterior and posterior midbody, the isthmus and the splenium. Although most of the studies included found significant correlations between PTSD symptom scales and their reported WM alterations, future studies should focus on specific symptoms like intrusions or overgeneralization as well as effects of WM changes on functional connectivity. This would allow for easier identification of mechanisms behind clusters of symptoms, enhance a mechanism-oriented approach to psychopathology, and help to embed findings into a larger theoretical framework. We suggest that future studies on WM in underage and adult populations suffering from PTSD should focus on more specifically selected groups of participants, including adolescent populations and adults with PTSD and trauma experience in childhood. Furthermore, future studies will have to take into account covariates such as demographic data (e.g. age, gender), the assessment of clinical factors (e.g. comorbidity, type of trauma experience, PTSD chronicity) as well as methodological considerations (e.g. acquisition and pre-processing of DTI data). Finally, whereas the assessment of structural changes in WM due to the experience of traumatic events and the development of PTSD is highly valuable, a theoretical foundation is needed putting possible alterations in FA in association with symptom clusters of PTSD or functional network changes.

Appendix A

Table 1

PTSD vs. HC — **Adults with PTSD (trauma in adulthood)** — **PTSD vs. TC**

Region	WB	ROI	↑	↓
cingulum [1 (l. ant.); 9 (rostral ant., subgenual ant., dorsal ant.)]	x	x	x	x
frontal gyrus [15 (sup. and orbital); 18 (l. sup.)]	x	x	x	x
occipital gyrus [15 (r. inf.)]	x			x
temporal gyrus [15 (sup.)]	x			x

Region	WB	ROI	↑	↓
angular gyrus [14 (post.)]	x			x
cingulum [3 (r.); 4 (bil. post.); 6, 7 (dorsal, hippocampal); 8 (l. ant.); 14 (ant.); 15 (r. ant.); 17 (r. post.); 19 (l. and r. post.)]	x	x	x	x
forceps mayor [11 (l.)]	x		x	
forceps minor [6]	x			x
fornix [7]		x	x	
fronto-occipital fasciculus [6 (inf. and sup.)]	x	x		x
frontal gyrus [11 (l. sup. and middle); 14 (precentral & prefrontal); 15 (medial, gyrus rectus); 16 (commisural tract connecting sup. and middle)]	x		x	x
hippocampus [17 (body)]	x	x		x
internal capsule [14 (post.)]	x			x
longitudinal fasciculus [4 (l. sup.); 6 (sup.); 12 (inf)]	x			x
midbrain [15 (r.)]	x			x
middle temporal gyrus [15 (r.); 19 (l.)]	x		x	x
parietal sub-gyrus [19 (r.)]	x		x	
precuneus [19 (r.)]	x		x	
stria terminalis [7]		x	x	
thalamic radiation [6 (ant.)]	x			x

Table 2

PTSD vs. HC — **Adults with PTSD (trauma in childhood)** — **PTSD vs. TC**

Region	WB	ROI	↑	↓	→
Corpus callosum [20; 21 (genu, ant. mid-body, mid-body, isthmus)]		x		x	x

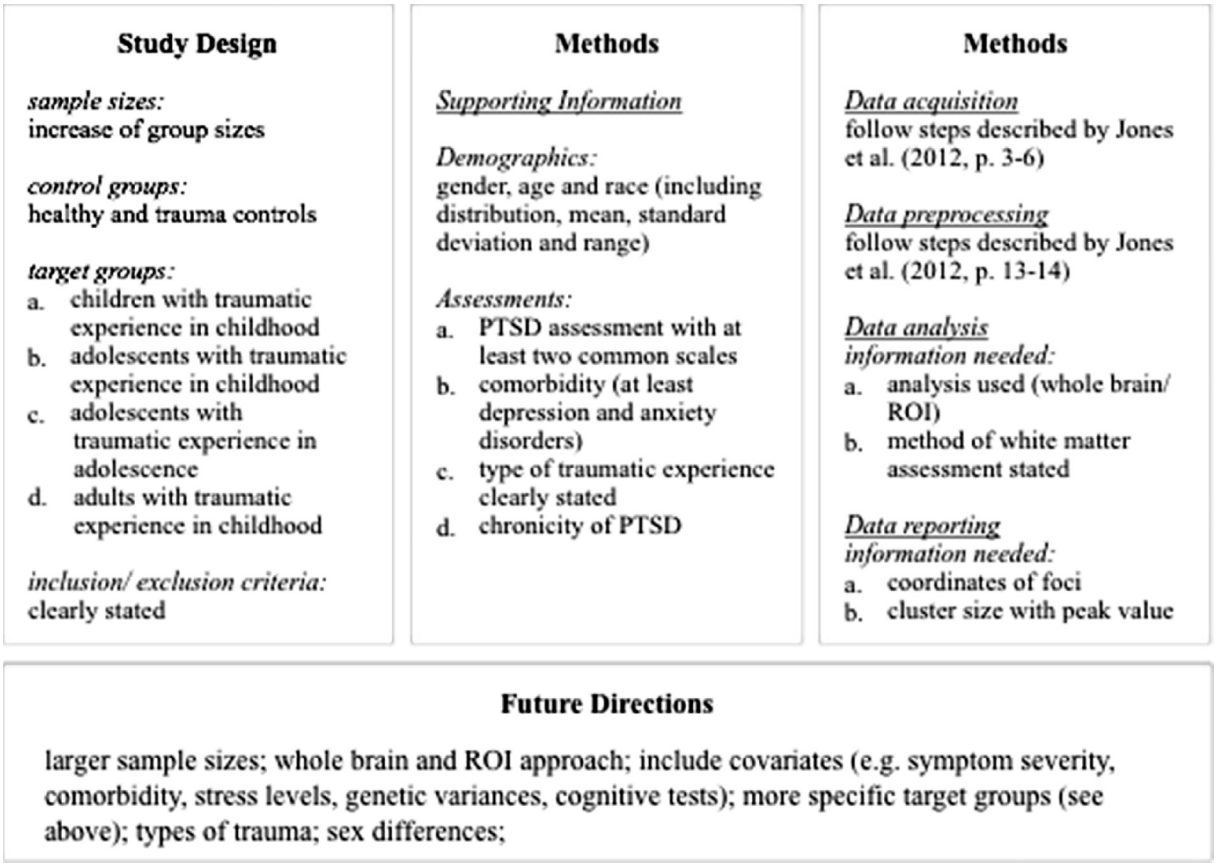
Table 3

PTSD vs. HC — **Children with PTSD (trauma in childhood)** — **PTSD vs. TC**

Region	WB	ROI	↑	↓	→
Corpus callosum – rostrum [30]		x		x	
Corpus callosum – genu [22]		x		x	
Corpus callosum – ant. midbody [22; 23; 24; 26; 30]		x		x	
Corpus callosum – post. midbody [22; 23; 24; 26; 30]		x		x	
Corpus callosum – isthmus [22; 23; 24; 30]		x		x	
Corpus callosum – splenium [22; 23; 24; 29 (l.); 30]	x	x		x	
Prefrontal cortex [28]		x			x

Region	WB	ROI	↑	↓	→
Corpus callosum – total [25]		x			x

A1. These tables summarize all the regions mentioned in the reviewed studies in which a significant change in FA was found between adult patients with PTSD after traumatic experience in adulthood and healthy control patients (HC; left table) or trauma control patients (TC; right table). The tables are subdivided in three groups: a) adults with PTSD and traumatic experience in adulthood, b) adults with PTSD and traumatic experience in childhood and c) children with PTSD and traumatic experience in childhood. The *first column* of each tables indicates the white matter tract or more global region in which a significant change in FA was reported. The *second* and *third column* show, if the change in this specific tract or region was found after using a whole brain analysis (WB) or setting a region of interest (ROI). The arrows indicate if a significant increase (upwards pointing) or decrease (downwards pointing) was found or if no significant change (rightwards pointing) was reported for the specific region. (ant. - anterior; bil. - bilateral; inf. - inferior; l. - left; post. - posterior; r. - right; sup. – superior)



A2. Considerations for future DTI studies with PTSD patients concerning study design and methodology

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