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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 ($\lambda_1$, $\lambda_2$, $\lambda_3$) 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, $\lambda_1$) 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