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Alterations in the fronto-limbic network and corpus callosum in borderline-personality disorder

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ABSTRACT

Neuroimaging research provides evidence of grey matter changes in the prefrontal-limbic network in borderline personality disorder (BPD), yet research scarcely examines the white matter (WM) within this circuitry. The present study aimed to explore WM in prefrontal-limbic brain networks within BPD. Quantitative diffusion tensor imaging (DTI-MRI) measures of fractional anisotropy (FA) and mean diffusion (MD) were used to analyze the neural pathways in fifteen individuals with BPD (M = 25, SD = 6.76), in comparison to thirteen healthy individuals (M = 27.92, SD = 8.41). Quantitative DTI-MRI measures of FA and MD were evaluated for the cingulum, the fornix, the corpus callosum (CC), the inferior longitudinal fasciculus (ILF), the superior longitudinal fasciculus (SLF) and the uncinate fasciculus (UF). Lower FA values for both the left and the right cingulum, the genu, body, and splenium of the CC, left ILF and right SLF were found in BPD, compared to healthy individuals. MD values were higher for the genu and splenium of the CC in BPD. The findings indicate that a large-scale emotional brain network is affected in BPD with alterations in MD and FA of WM prefrontal-limbic pathways of the heteromodal association cortex involved in emotion processing and emotion regulation.

1. Borderline personality disorder

Borderline personality disorder (BPD) is a complex mental disorder characterized by instability across various life domains with a wide spectrum of characteristic symptoms including affective hyperreactivity, instability of the self-concept, emotional dysfunction, and difficulty in social relationships (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004; Ninomiya et al., 2018; Skodol et al., 2002). The term borderline was introduced in 1953 by R.P. Knight and originated from the idea that some patients can be considered as balancing on the border between neurosis and psychosis. Its official use was finally established in the 1980s to be included among Axis II disorders in the DSM-III with the term ‘Borderline Personality Disorder’. Among the diagnostic criteria indicated in the Diagnostic and Statistical Manual of Mental Disorders, the Fifth Edition (DSM-5) (American Psychiatric Association (APA), 2001), BPD is characterised by a fragile self-structure that is easily disrupted and fragmented under stress, a weak identity, chronic feelings of emptiness and difficulty maintaining enduring intimate relationships. Intimate relationships easily elicit feelings of being misunderstood and even victimized with an enhanced fear of abandonment. BPD is commonly associated with disturbed emotion processing and emotion regulation reflected by rapidly changing, intense, unpredictable and reactive emotions, such as anxiety, anger or depressed feelings. Emotional hyperreactivity in BPD goes often together with different high-risk behaviors and deliberate acts of substance abuse, binge eating, self-harm, suicidal ideation, suicide attempts and high rates of suicide, affecting 1–2% of the general population and 15–20% in psychiatric settings (Lis, Greenfield, Henry, Guilé, & Dougherty, 2007). These behavioural responses occur alongside contexts with intense distress, anger episodes, dysphoria, and
feelings of abandonment (Samuel et al., 2012). Often preceded by an existence consisting of a damaging and traumatizing environment such as those with a lack of nurture, affection and high levels of parental denial, neglect but even massive, repeated or chronic physical, sexual, and emotional abuse before adulthood (Zanarini et al., 2005). As such, adults with BPD often lack the skills needed to handle daily emotional stressful events, maintain stable relationships and to build a strong self-concept and identity, resulting finally in distress intolerance and a variety of problematic behaviors to escape emotions such as by self-harm (Chapman, Specht, & Cellucci, 2005). As these familial, social and societal experiences (Pally, 2002), wires and shapes the human brain, it can readily cause invalidating transgenerational responses from future caregivers who do not teach the child how to adequately regulate one’s own emotions and may exacerbate an individual’s existing vulnerability when handling challenging daily emotional events (Linehan, 1993; Chapman, Dixon-Gordon & Walters, 2011). Also in a society of contingencies in which social and intergenerational problems increase while ties have weakened and unstable family contexts are increasing, ontological unsafety, and anxiety are fed. As a consequence, developmental psychobiological characteristics of this disorder has to be framed in light of pre-existing vulnerability and particularities of developmental influences in childhood, the society, lifestyle and cultural patterns of conduct.

2. Neuronal biomarkers of borderline personality disorder

Despite rapidly growing literature focusing on abnormal developmental, behavioral, societal and neurophysiological constituents in BPD (Carrasco et al., 2012; Krause-Utz et al., 2014; Lischke et al., 2015; Mauchnik & Schmahl, 2010; New et al., 2013; Putnam & Silk, 2005), the developmental psychobiology and the pathogenesis underlying BPD remains complex and not well understood. Emerging techniques enhance insight and clarify disrupted functions such as neural pathways in BPD. Differential fine-grained advances in neuroscience and usage of biological indicators provide innovative opportunities to identify neurobiological underpinnings in BPD (Skodol et al., 2002). Parsing the relationship between BDP and associated neurophysiological circuits may help us further understand the underlying biological mechanisms implicated in this disorder and may help us treat it. Biological markers establishes external validators of diagnostic criteria and provide clues to etiological factors involved in BPD and options for treatment. BPD may be linked to abnormal brain anatomy, but little is known about possible impairments of the white matter microstructure in BPD. As individual variability is encoded neurophysiologically, it is plausible that personality disorders are not only correlated with specific neural regions, but also with white matter correlates (Sprooten et al., 2011). However, research utilizing grey matter and diffusion tensor imaging (DTI) in adult BPD have been inconclusive.

2.1. Grey matter

On the level of grey matter, the most consistent structural imaging finding in adult BPD is a decrease in metabolic activation and volume in the anterior cingulate cortex (ACC), (Hazlett et al., 2005; Minzenberg, Fan, New, Tang, & Siever, 2007; Tebartz van Elst et al., 2003), the hippocampus (Irle, Lange, & Sachse, 2005; Zanetti et al., 2007), and the amygdala (Brambilla et al., 2004; Driessen et al., 2000; Nunes et al., 2009; Schmahl, Vermetten, Elzing, & Bremner, 2003; Tebartz van Elst et al., 2003). A meta-analysis indicated that the amygdala volume in individuals with BPD is smaller than in healthy controls (Nunes et al., 2009). However, other studies found no reduced amygdala volume in BPD (Schmal et al., 2009; Chane, et al., 2008). Other findings include volume reduction in the medial and orbitofrontal cortex (Hazlett et al., 2005; Minzenberg et al., 2007; Tebartz van Elst et al., 2003), which support the assumption of a dysfunctional interplay between limbic and prefrontal brain regions (Krause-Utz et al., 2014; Lischke et al., 2017; Lischke et al., 2015), or a dysfunctional frontolimbic network in BPD. These two assumptions are associated with the following structures: the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), the dorsolateral prefrontal cortex (DLPFC), the hippocampus and the amygdala (New et al., 2013). In line with these structural alterations, a review conducted by Ruocco and Choi-Kain (2013) reported increased functional activity in other limbic structures such as the insula, the left temporal gyrus, and the dorsolateral prefrontal cortex. This frontolimbic network modulates and controls emotion (e.g. fear, anxiety, and anger) and behavioral impulse regulation. Limbic hyperreactivity and reduced enrolment of prefrontal brain regions may produce a link between impaired and distressed emotion processing and characteristics of BPD (Ninomiya et al., 2018). Nevertheless, it remains uncertain whether these functional alterations account also for the structural differences in these regions and vice versa.

2.2. White matter

Despite abundant research on grey matter correlates in BPD, to our knowledge, only a few diffusion- tensor imaging research exists on the white matter (WM) neural pathways of BPD. Little is known about the underlying WM neuronal mechanisms utilized in the processing of emotional material and the regulation of elicited emotions (New et al., 2013; Rüschi et al., 2007; Schmahl & Bremer, 2006; Whalley et al., 2015). Some studies show decreases in FA in both the uncinate fasciculus (UF) and the occipitofrontal fasciculus (OFF) (Carrasco et al., 2012; Grant et al., 2007; Lischke et al., 2015; New et al., 2013). In some other research, such as Grant et al.’s study (2007), higher trace and lower FA values in inferior prefrontal and not in posterior prefrontal regions were found in BPD-self-injurious behavior. Increased MD in the inferior prefrontal WM has been correlated with higher levels of dysfunctional affect regulation, anger-hostility, dissociative symptoms, and general psychopathology. In a study with adolescent and adult individuals with BPD, decreased FA in the ILF, the UF, and the occipitofrontal fasciculi (OFF) was found in adolescents, but not in adults (New et al., 2013). Also, although non-significant, a decreased FA in the fornix has been reported in BPD (Maier-Hein et al., 2014; Gan et al., 2016). Symptoms of harm-avoidance, characterized by excessive worrying, pessimism, shyness and being fearful and doubtful, have been associated with decreased FA and increased MD in cortico-limbic pathways, anterior thalamic radiations, inferior prefrontal-occipital area, and right SLF (Westlye, Bjørnebekk, Grydeland, Fjell, & Wallhovd, 2011). For instance, in a study by Whalley et al. (2015), a significant association between FA in the cingulum and clinical symptoms of anger in BPD has been found. Lischke et al. (2015), on the other hand, only found structural alterations in the UF in BPD. In a more recent study, Lischke et al. (2017) showed a positive correlation between BPD individuals’ suicidal behavior and FA in the splenium and the genu of the CC and a negative correlation between BPD individuals’ suicidal behavior and MD in the splenium of CC. Other research found a lower FA in the genu and body of the CC (Gan et al., 2016). In a study by Rüschi et al. (2007), a thinner isthmus of the CC has been associated with decreased interhemispheric structural connectivity in both the ACC and fiber tracts that pass through the ACC and connect dorsal areas of the ACC in women with BPD (Rüschi et al., 2007). Abnormalities of the CC have also been observed among adult males with antisocial personality disorder (Sundram et al., 2012), while in a study with women with conduct disorder, reduced FA in the body and genu of the CC, has been observed (Lindner et al., 2016).
3. The present study

The present study aims to validate and increase insight into the neural microstructural circuitry and integrity of brain pathways in individuals with BPD compared to healthy individuals. Neurophysiological processes responsible for the differentiation of FA and MD in emotion processing reflect myelin fiber integrity through increases in the quantity and density of axons and enhanced coherence of the measured fiber tract (Le Bihan, 2003). The integrity of connectivity patterns in the limbic and prefrontal pathways are expected to be involved in differences in affective, cognitive processing and emotion- and self-regulatory capacity. Healthy WM structures are hypothesized to be characterized by increases in FA and decreases in MD (Gao et al., 2009), a pattern that emerges with WM myelination, reduced brain water, greater organization of fiber tracts and decreased extra-axonal space during WM development (Huppi & Dubois, 2006).

The intactness of the brain tract supports adaptive processing and healthy emotion regulation and self-regulation. DTI is the only method that allows the simultaneous quantification of WM volume and microstructural integrity within specific tracts in the living human brain (Le Bihan, 2003). It produces MRI-based quantitative maps of microscopic, natural displacements of water molecules that occur in brain tissues as part of the physical diffusion process (Le Bihan, 2003). Because water diffusion in tissues is highly sensitive to differences in the microstructural architecture of cellular membranes, it can reveal microscopic details about the architecture of both normal and diseased tissue (Alexander, Lee, Lazar, & Field, 2007; Le Bihan, 2003). Diffusion anisotropy in WM originates from the organization of this tissue, since bundles of myelinated axonal fibers run in parallel. Diffusion in the direction of the fibers is about three to six times faster than the perpendicular direction (Le Bihan, 2003). MD is characterized by the overall mean-squared displacement of molecules and the overall presence of obstacles to diffusion as well as by the degree of FA or the degree to which molecular displacements vary in space or ellipsoid eccentricity associated with the presence and coherence of oriented structures (Le Bihan, 2003). FA equals the degree of directionality of intravoxel diffusivity (Kollia, 2009) and is thus a highly sensitive biomarker of neuropathology and microstructural architecture.

3.1. Hypotheses

In the present study, the focus lies on the prefrontal-limbic tracts implicated in emotion processing and emotion regulation. It is hypothesized that there are reductions in white microstructural circuitry limbic brain pathways underlying emotion and emotion regulation in individuals with BPD compared to healthy individuals. Functional alterations and decreases in coordinated functioning and weaker WM integrity of the involved pathways are assumed to contribute to the emotional and behavioral vulnerability in BPD. DTI-tractography to obtain FA and MD will be performed in different WM bundles of the major tracts: the cingulum, the fornix, the CC the ILF, the SLF, and the UF. Since dysfunctional affective information processing and emotion regulation are core features of BPD and the cingulum is important for the processing and regulation of emotions (Catheline et al., 2010), altered microstructural integrity by fewer FA, more MD, or both, is expected in the cingulum as part of the prefrontal-limbic pathway. As the genu, body, and splenium of the CC are important in interhemispheric communication, affective processing and the integration of affective, cognitive, motor and sensory information (Carrasco et al., 2012; Salvador et al., 2016; Wang et al., 2008), reduced interhemispheric connectivity in BPD, is expected. As part of the limbic system and an afferent pathway of the hippocampus, connecting it to the septal nuclei and hypothalamic mammillary bodies involved in emotion and motivational processing and learning and memory (Corr, 2006), alterations in the fornix is expected (Aggleton, Vann, & Saunders, 2005; Bernstein et al., 2012; Hescham et al., 2013). Although the exact role of the UF-pathway remains unknown, since this pathway is also supportive in emotion processing, emotion regulation, and memory through its connection to fronto-temporal cortices (Vernace et al., 2010), altered microstructural integrity of the UF is expected. Based on the role of the ILF as mediating the integration of emotional visual signals from the occipital cortex to the parahippocampal gyrus and the amygdala, back to primary visual association areas, less microstructural integrity, also in this pathway is expected (Catani, Howard, Pajevic, & Jones, 2002; Pugliesi et al., 2009; Fischer et al., 2016). Moreover, lower microstructural is expected in the superior longitudinal fasciculus (SLF), the main parietal-prefrontal WM pathway. The inferior parietal lobule supports both working memory functions (Madden, Bennett, & Song, 2009) and motor processes in cognitive control tasks such as task switching, attention and flexible self-regulation.

Taken together, more understanding of the neurobiology and common and distinct neural systems in BPD will provide more insight into some of the crucial underpinnings of BPD, the detection, prevention and treatment of early symptoms and BPD-psychopathology.
The coefficient was above 0.8 for all evaluations. Moreover, unpaired \( t \)-tests with False discovery rate (FDR) correction was utilized to control multiple comparisons for each of the obtained \( p \) values (Storey, 2002), to compare the quantitative DTI- measures of both groups for the different WM structures. Diffusion tensor tractography was performed to mathematically reconstruct the following WM bundles: (1) the cingulum, (2) the fornix, (3) the genu of the CC, (4) the body of the CC, (5) the splenium of the CC, (6) the SLF, (7) the ILF and (8) the UF.

### 4.3. Results

This study aimed to compare the microstructural integrity of limbic pathways between participants with BPD and healthy ones. Typically, in compromised pathways, MD values are higher and FA values lower than in normal WM, presumably owing to axonal degeneration (Beaulieu, Does, Snyder et al., 1996). The present findings show significantly lower FA values for both the left \( p = .004, \text{FDR corrected} \) and the right cingulum \( p = .012, \text{FDR corrected} \), the genu \( p = .004, \text{FDR corrected} \), the body \( p = .004, \text{FDR corrected} \) and the splenium \( p = .004, \text{FDR corrected} \) of the CC, the left ILF \( p = .005, \text{FDR corrected} \) and right SLF \( p = .001, \text{FDR corrected} \) in the BPD group compared to the healthy group. No significant differences in FA values were found in the fornix, the left ILF as well as the right and the left UF. MD values were significantly higher for the genu \( p = .0008, \text{FDR corrected} \), and the splenium \( p = .003, \text{FDR corrected} \) of the CC in the BPD group compared to the healthy group. No significant differences in MD values in the cingulum, the fornix, the ILF, the SLF, the body, and the UF were found (see: Table 1, Fig. 1). For a more detailed description of the bar plots, see Appendix A.

Overall, FA values tended to be significantly higher in the healthy group, whereas MD values tended to be significantly higher in the BPD group. The first hypothesis questioned whether there are differences in FA and MD in the fornix, the cingulum, the genu, the body, and splenium of the CC, the ILF, the UF, as well as the SLF in the group with BPD compared to the healthy group. Our data suggest that motor-prefrontal, limbic – but also corpus callosal structures are altered in BPD (low FA values and high MD values). Results indicate that limbic and emotion-related pathways showed lower FA values and higher MD values in individuals with BPD (see Table 1, Fig. 1). For a more detailed description of the bar plots, see Appendix A.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Borderline group ( (n = 13) )</th>
<th>Healthy group ( (n = 11) )</th>
<th>( p )-Value unpaired ( t )-test FA</th>
<th>( p )-Value unpaired ( t )-test MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Fornix</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean FA (SD)</td>
<td>0.4004 (0.0383)</td>
<td>0.4346 (0.0795)</td>
<td>0.0014 (0.0002)</td>
<td>0.198 (0.085)</td>
</tr>
<tr>
<td>Mean MD (SD)</td>
<td>0.0014 (0.0002)</td>
<td>0.0014 (0.0003)</td>
<td></td>
<td>0.826 (0.262)</td>
</tr>
<tr>
<td>Cingulum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.4800 (0.0478)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0.4611 (0.0325)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean FA (SD)</td>
<td>0.5350 (0.0299)</td>
<td></td>
<td>0.0007 (0.0000)</td>
<td>0.004* (0.010)</td>
</tr>
<tr>
<td>Mean MD (SD)</td>
<td>0.0007 (0.0000)</td>
<td></td>
<td></td>
<td>0.287 (0.116)</td>
</tr>
<tr>
<td>Corpus Callosum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genu</td>
<td>0.5438 (0.0416)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.5865 (0.0315)</td>
<td></td>
<td></td>
<td>0.012* (0.010)</td>
</tr>
<tr>
<td>Right</td>
<td>0.6117 (0.0201)</td>
<td></td>
<td></td>
<td>0.008* (0.008)</td>
</tr>
<tr>
<td>Mean FA (SD)</td>
<td>0.5063 (0.0397)</td>
<td></td>
<td>0.0007 (0.0000)</td>
<td>0.004* (0.007)</td>
</tr>
<tr>
<td>Mean MD (SD)</td>
<td>0.0007 (0.0000)</td>
<td></td>
<td></td>
<td>0.003* (0.011)</td>
</tr>
<tr>
<td>Superior longitudinal fasciculus</td>
<td>0.4647 (0.0161)</td>
<td>0.4895 (0.0227)</td>
<td>0.0008 (0.0000)</td>
<td>0.005* (0.006)</td>
</tr>
<tr>
<td>Inferior longitudinal fasciculus</td>
<td>0.4611 (0.0325)</td>
<td>0.4822 (0.0227)</td>
<td>0.0008 (0.0000)</td>
<td>0.002 (0.006)</td>
</tr>
<tr>
<td>Uncinate fasciculus</td>
<td>0.4089 (0.0342)</td>
<td>0.4209 (0.0191)</td>
<td>0.0008 (0.0000)</td>
<td>0.001 (0.007)</td>
</tr>
<tr>
<td>Left</td>
<td>0.4185 (0.0233)</td>
<td></td>
<td></td>
<td>0.049 (0.030)</td>
</tr>
<tr>
<td>Right</td>
<td>0.3934 (0.0387)</td>
<td></td>
<td></td>
<td>0.747 (0.248)</td>
</tr>
</tbody>
</table>

\*Significant after the FDR correction.
5. Discussion

This study aimed to compare alterations in WM integrity of bottom up limbic pathways between BPD and healthy participants. Typically, in compromised pathways, MD values are higher and FA values are lower than in normal WM, presumably owing to axonal degeneration (Beaulieu, Does, Snyder, & Allen, 1996). In correspondence with our hypotheses, FA values tended to be higher in healthy participants while MD values tended to be significantly higher in BPD participants. These results suggest that healthy participants show more coherent WM-pathways, while BPD show more compromised WM pathways. The present findings show significantly lower FA values for both the left and the right cingulum, the genu, the body, and splenium of the CC, the left ILF and the right SLF in BPD, compared to healthy participants. MD values are significantly higher for the genu and splenium of the CC in BPD, compared to healthy participants. No significant differences in FA values were found in the fornix, the left SLF, the right ILF and the UF and no significant differences in MD values were found in the cingulum, the fornix, the ILF, the SLF, the body CC, and the UF.

5.1. Cingulum

FA values were significantly lower in participants with BPD compared to healthy participants for the left and right cingulum. No significant differences in MD values were found, which is in correspondence with a study of Ninomiya et al. (2018), where the FA of the cingulum in the BPD group has been affected which is inconsistent with Lischke et al. (2015), who did not find structural alterations in the cingulum in BPD. On the other hand, Whalley et al. (2015) found a significant association between FA in the cingulum and clinical symptoms of anger in BPD, relative to healthy individuals. Also, in a study of Lee et al. (2016), symptoms of anger, affective instability and measures of avoidance or abandonment are associated with decreased WM integrity in the cingulum and the fornix in BPD relative to healthy individuals. No significant relationships between FA and measures of childhood trauma have been found. Also in depression, where a history of childhood adversity is present, lower FA was found in the rostral and the dorsal cingulum tracts involved in emotion regulation (Ugwu, Amico, Carballedo, Fagan, & Frodl, 2015). Equally, individuals who present WM abnormalities in the cingulum resulting from post-traumatic stress disorder (PTSD) and/or traumatic brain injury, are more susceptible to develop depression (Isaac et al., 2015). Adolescents at familial risk for major depressive disorder, for instance, showed widespread decreases in FA in the cingulum, the splenium of the CC, the SLF, the UF and the fronto-occipital fasciculi (Huang, Fan, Williamson, & Rao, 2011). Decreased FA was also reported in the right cingulum in adults with ADHD (Konrad et al., 2010; Makris et al., 2008). Based on the functions of the cingulate cortex in various affective processes such as attention to emotional stimuli, emotional awareness and emotion regulation (Phan et al., 2005), the cingulum supports not only affective processing, but also rudimentary affective somatosensory experience of the emotion response that precedes cognitive reflective processing.
giving rise to somatosensory affective level of consciousness or ‘an-oetic consciousness’ (Vandekerckhove & Panksepp, 2011; Vandekerckhove & Panksepp, 2014), and the capacity to acknowledge and approach this anoetic consciousness and emotions in daily life events, or what we termed ‘experiential emotion regulation’ (Vandekerckhove et al., 2012). Experiential emotion regulation is an approach that is effective in the regulation of, and recovery from, emotionally stressful events (Vandekerckhove et al., 2012; Wang et al., 2017). As a result, a lower FA of the cingulum in BPD may contribute to a maladaptive emotion approach, processing capacity, and affective dysfunction in BPD, as well as in psychopathology (Mayberg et al., 2005).

Taken together, significantly lower FA values in the cingulate pathway in BPD, relative to healthy individuals, may interfere with bottom-up somatosensory affective processing and awareness such as anoetic consciousness and acknowledging and approaching one’s own emotions within daily life events, in ways that are effective in the regulation of—and the recovery from—an emotionally painful event. Alterations in microstructural integrity of this pathway in BPD contribute to dysfunctional emotion processing and emotion regulation capacity and is maladaptive to the overall emotional functioning in BPD.

5.2. Corpus callosum

The significant decreased FA and increased MD values in the genu and splenium CC in the BPD-relative to the healthy group is in line with some recent research findings (Carrasco et al., 2012; Lischke et al., 2017; Rüschi et al., 2007). For instance, in a study of Carrasco et al. (2012), a significant decrease of FA in the genu and rostral areas of the CC, as well as in the left and right prefrontal WM fasciculi in BPD, compared with healthy individuals, have been observed. In another study, BPD demonstrated lower FA in the genu and body of the CC, right anterior and superior corona radiate, as well as higher diffusion in the left anterior thalamic radiation (Gan et al., 2018). On the other hand, in still another study on BPD (Zanetti et al., 2007), no abnormalities in CC has been found. Reduced callosal thickness may result from disturbed myelination by reduced FA and enhanced MD and may, therefore, be a structural marker of disturbed interhemispheric structural connectivity (Rüschi et al., 2007). Interestingly, the occurrence of adverse experiences early in life such as neglect and childhood abuse (Teicher et al., 2004) has been linked to CC abnormalities (Paul et al., 2008). Affected MD and FA in the CC has also been found in bipolar disorder which has a close symptomatic overlap with BPD. Related to these findings, a smaller anterior genu CC, predicted higher impulsivity among suicidal bipolar disorder patients (Matsuo et al., 2010). Bipolar disorder and BPD, share some key features in their psychopathology, in particular, emotion processing (e.g. mood lability and impulsive behavior) and emotion dysregulation (Zanetti et al., 2007), which could result in similar WM abnormalities. Also, reduced integrity in anterior and middle CC subregions, encompassing the genu, rostral body and the anterior portion of the mid body of the CC has been found in bipolar disorder (Brambilla & et al., 2003; Brambilla et al., 2004; Wang et al., 2008). As callosal connectivity supports interhemispheric communicatory and the integration of emotional, cognitive, motor, and sensory information (Wang et al., 2008), reduced interhemispheric connectivity in BPD may facilitate an overall vulnerability to less integrated somatosexual emotion processing and emotion regulation enhancing more problems of accessing affective experience, experiential awareness, reading and expressing the own somatosensory affective experience or experiential emotion regulation.

5.3. Inferior longitudinal fasciculus

Significantly decreased FA value in the left ILF has been found in BPD, relative to the healthy individuals, in correspondence with the study of Ninomiya et al. (2018) were lower axial diffusion in BPD has been found in the ILF, the cingulum, and the inferior occipital fasciculus. The findings are also in line with the bilateral tract-specific decrease of FA in ILF in BPD adolescents compared to adolescent controls (New et al., 2013). Other studies found significantly decreased FA in the left ILF in a group of unipolar depressed adults (Versace et al., 2010). Connecting the occipital cortex, the lingula, and the cuneus with the temporal lobe, the fusiform area, the IFL projects to the amygdala (Catani, Jones, Donato, & Flytche, 2003; Pugliesi et al., 2009), mediating the fast transfer of visual signals from the occipital cortex to the parahippocampal gyrus, as well as from the amygdala back to primary visual association areas (Catani et al., 2003; Pugliesi et al., 2009). While approaching the anterior temporal lobe, the fibers of the inferior frontooccipital fasciculus gather together and enter the external capsule dorsally to the uncinate fasciculus fibers (Catani & de Schotten, 2008). Although the mechanism in which the brain integrates visual and emotional information remains not completely understood, this pathway is responsible for transmitting signals back to early visual areas pertaining to the salience of emotionally significant visual stimuli (Ashari et al., 2007; Catani et al., 2003). Decreased FA of this connection may interfere with higher visual-affective integration within emotion processing and emotion identification, as is necessary for instance in emotional facial recognition (Fischer et al., 2016; Philippi, Mehta, Grabowski, Adolphs, & Rudrauf, 2009), a basic element of social cognition. Individuals with BPD do indeed show difficulties in recognizing and interpretation of specific negative emotions in daily life and emotional facial expressions, resulting in misattribution of emotions to faces depicting neutral expressions (Fischer et al., 2016; Philippi et al., 2009). Brain lesions in this area go together with poor object naming ability and semantic processing and recognition of emotions (Mandonnet, Nouet, Gatigol, Capelle, & Dufau, 2007; Shinoura et al., 2010). In line with this finding, individuals with BPD show high levels of alexithymia or a profound deficit in the ability to describe feelings (Gutman & Laporte, 2002).

5.4. Superior longitudinal fasciculus

In the right SLF, significantly lower FA values but not MD values have been observed. To our knowledge, this is the first study where combined decreased FA and increased MD in the SLF were observed in BPD, similar as in other pathologies. A lower FA in the SLF has been also found in intermittent explosive disorder and impulsive aggression (Lee et al., 2016). Latter disorders are similarly characterized by social dysfunction and problematic impulsivity. In ADHD, significantly higher MD in the SLF was reported (Konrad et al., 2010; Pavuluri et al., 2009). Also, in a group of bipolar depressed adults, a decreased FA was found in the left and right SLF (Versace et al., 2010). In other pathologies, results have been inconsistent. For instance, in ADHD (Hamilton et al., 2008; Makris et al., 2008; Wolters et al., 2015), antisocial personality disorder, and conduct disorder, a decreased (Lee et al., 2016) and increased FA in the SLF have been observed (Davenport, Karatekin, White, & Lim, 2010). As the main parietal-prefrontal WM pathway, connecting the supramarginal gyrus (BA 40) with the middle frontal gyrus/dorsolateral prefrontal cortex (Brodmann areas (BA) 9/46) (Petrides & Pandya, 2002), the SLF supports the coordination between corticospinal regions. The inferior parietal and posterior cortex has a role in integrating sensory information from various parts of the body and social cognition (Bzdok et al., 2016), working memory functions (Liston et al., 2006; Madden et al., 2009), and motor processes in cognitive control- and self- and emotion regulation tasks, such as task switching and attention. Executive monitoring may play a functional role in the cognitive control of emotion. Cognitive ‘top-down processing mechanisms,’ such as cognitive information processing, interpretation of the situation in a realistic manner and the tendency to switch attention in stressful, conflicting, and painful emotion information processing streams or between emotions, as well as the ease to flexibly
adapt to changing task demands and social adaptation, are more easily affected in individuals with BPD.

5.5. Uncinate fasciculus

In opposition to the findings of other studies, FA values tended to be lower and MD values tended to be higher in BPD for the UF. However, these differences are not significant (Lischke et al., 2015; New et al., 2013). The UF is a ventral associative bundle that connects the anterior temporal lobe with the medial and lateral orbitofrontal cortex (Catani et al., 2002). As a ventral associative bundle, it connects the anterior temporal lobe, including the amygdala, with the medial and lateral orbitofrontal cortex. Although the UF is considered to belong to the limbic system, its function is poorly understood. This region most likely supports emotion processing, adaptive emotion regulation, and memory by connecting fronto-temporal cortices (Versace et al., 2010).

Higher MD in the UF, for instance, has also been found in attention deficit disorder (Konrad et al., 2010). Since the role of the UF remains unclear and the findings of WM alterations in the UF are inconsistent, further replication and research is necessary.

5.6. Fornix

No significant differences in FA and MD values were found for the fornix. In a study by Maier-Hein et al. (2014), only a non-significant reduction of FA was found in BPD. On the other hand, in a study of Whalley et al. (2015), an association of decreased integrity of the fornix with affective instability and symptoms of avoidance or abandonment was observed. In a study on bipolar disorder, WM disruption was found in limbic structures including the fornix and the mid-posterior cingulate (Barnea-Goraly, Chang, Karchemsky, Howe, & Reiss, 2009). The fornix is the main afferent system of the hippocampus, connecting it to the septal nuclei and hypothalamic mammillary bodies (Aggleton et al., 2005; Bernstein et al., 2012). It constitutes a major inflow and output pathway from the hippocampus and medial temporal lobe (Hescham et al., 2013). While its exact function and importance in the physiology of the brain are still not entirely clear, as part of the limbic system, it is involved in emotion processing and motivation as well as in learning and spatial, episodic and non-declarative memory and executive functions (Corr, 2006; Hamani et al., 2008; Hescham et al., 2013; Lee et al., 2012). Since the present research study also provides explorative results, further research is necessary to provide more clarity about the involvement and role of the fornix in emotion processing and emotion regulation, especially also in psychopathology such as in BPD.

5.7. Limitations of the present study

Despite the importance and strength of the DTI methodology, to meet the limitations, such as the exploratory nature inherent in the present study, future studies should seek to replicate these findings in males and larger mixed-gender sample sizes. The small sample size of this study prevents us from making definitive conclusions. Furthermore, to broaden the translational character of this study, one important direction for future research will be to assess neural pathways in early development and the onset of the symptoms in early development. To provide convergent and divergent validity and specificity of our findings, combined cross-sectional and developmental behavioral and functional imaging studies are required to examine the relationship between white and gray matter in healthy individuals, as well as in those with BPD. The ability to track WM bundles and access detailed anatomical information on WM broadens our investigative ability to uncover disease-related abnormalities. However, even though advances in DTI have enabled us to better study the anatomy involved in human functioning, we still have a poor understanding of the functional role of the various pathways. Similar to previously reported limitations (Maier-Hein et al., 2014), our present study did not include clinical control subjects in the analysis. Although the participants are controlled for comorbidity, previously reported group differences may not necessarily be BPD-specific. The found alterations in the left and the right cingulum, the genu and splenium of the CC, the left ILF and the right SLF in BPD may account for abnormal activity in brain regions implicated in dysfunctional emotion processing and emotion regulation (e.g., the amygdala, the anterior cingulate cortex, and the prefrontal cortex). It thus remains to be determined whether these alterations are BPD-specific (Lischke et al., 2015) or more translational. It is thus important to acknowledge that these findings cannot yield conclusions about the causal influence of altered WM integrity in BPD. Despite mounting evidence suggesting that these negative alterations may indeed increase translational levels of emotional distress due to decreased emotion regulation capacities, further research needs to be conducted to replicate and differentiate these significant findings and their strong consequences as to whether increasing WM integrity in specific limbic WM tracts is associated with BPD or psychopathology in general. In addition to the isolated fronto-limbic disconnectivity hypothesis, the present study suggests that a complementary large-scale brain network of limbic-prefrontal integrity in emotion processing is affected and disrupted in BPD.

6. Conclusion

Overall, the present study demonstrates widespread microstructural alterations in BPD which compromise bottom up limbic pathways and emotion regulation related WM structures in BPD. The present findings indicate less microstructural integrity by the decreased FA in the left and the right cingulum, the genu and splenium of the CC, the left ILF and the right SLF in BPD, in comparison to healthy individuals. Based on the present findings, the variations in how individuals with BPD process daily information and cope with it, consists of how they rely on different pathways of information transfer in different networks. BPD is associated with less microstructural integrity of neural circuits that together modulate ongoing emotional and social processing in the respective brain systems, including the amygdala, the subgenual ACC, the ventromedial PFC, insular areas, and the parietal cortex (Ashtari et al., 2007). Less microstructural integrity of the ILF and the SLF interferes with the ability to cope with stressful emotional life events by automatic lower level cognitive motor expression of emotions and action tendencies, of social self-regulation as well as lower executive control and monitoring of emotion, a phenomenon that explains symptoms of impulsivity and acting out of extreme emotions. In the meanwhile, the decreased structural integrity of the CC may hamper ‘integrated’ affective information processing and the active bottom-up use of affective information contributing to healthy emotion regulation, decision making, and self-regulation.

In another DTI-study by Vandekerckhove (2019) on experiential emotion regulation in healthy individuals, it has been suggested that microstructural integrity of the cingulate pathway relates to bottom-up affective processing; or the capacity of acknowledging, being aware and approaching one’s own affective bodily felt experience in daily life events, as well as emotional expression or experiential emotion regulation. Central to an experiential approach is namely the here-and-now focus, a welcoming and acceptance of affective experience without judgment, for instance by verbalisation or ‘experiential expression’ facilitating the further processing and modulation of negative emotional experiences in the longer term.
In conclusion, these findings of aberrant WM microstructure in limbic tracts confirms our findings of a study on WM microstructural integrity of dispositional experiential emotion regulation (Vandekerckhove, 2019), while extending previous structural and functional neuroimaging data. Understanding underlying microstructural integrity helps us to gain insight into the early precursors of BPD and development of psychopathology in general. The presented results contribute in a timely and innovative way to our understanding of underlying mechanisms and pathways in BPD and contribute to a more general translational understanding of resilience and vulnerability in mental health and psychopathology.

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Declaration of Competing Interest

There is no conflict of interest.

Appendix A

A more detailed description of the bar plots of the Uncinate Fasciculus, Corpus Callosum, Cingulum, Fornix, Superior Longitudinal Fasciculus, and Inferior Longitudinal Fasciculus.

Appendix B. Supplementary material

Supplementary data can be found online at https://doi.org/10.1016/j.bandc.2019.103596.

References


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