Structural and functional brain alterations in psychiatric patients with dissociative experiences: A systematic review of magnetic resonance imaging studies

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ABSTRACT

Introduction: There is currently no general agreement on how to best conceptualize dissociative symptoms and whether they share similar neural underpinnings across dissociative disorders. Neuroimaging data could help elucidate these questions.

Objectives: The objective of this review is to summarize empirical evidence for neural aberrations observed in patients suffering from dissociative symptoms.

Methods: A systematic literature review was conducted including patient cohorts diagnosed with primary dissociative disorders, post-traumatic stress disorder (PTSD), or borderline personality disorder.

Results: Results from MRI studies reporting structural (gray matter and white matter) and functional (during resting-state and task-related activation) brain aberrations were extracted and integrated. In total, 33 articles were included of which 10 pertained to voxel-based morphology, 2 to diffusion tensor imaging, 10 to resting-state fMRI, and 11 to task-related fMRI. Overall findings indicated aberrations spread across diverse brain regions, especially in the temporal and frontal cortices. Patients with dissociative identity disorder and with dissociative PTSD showed more overlap in brain activation than each group showed with depersonalization/derealization disorder.

Conclusion: In conjunction, the results indicate that dissociative processing cannot be localized to a few distinctive brain regions but rather corresponds to differential neural signatures depending on the symptom constellation.

1. Introduction

Dissociation is a heterogeneous, transdiagnostic phenomenon defined as a loss of integration in essential functions including memory, consciousness, perception, motor control, or identity (American Psychiatric Association, 2013). Dissociative symptoms have been reported in a broad range of psychiatric disorders including psychosis, personality disorders, mood and anxiety disorders (Lyssenko et al., 2018). The most prevalent dissociative symptoms across disorders can be clustered as forms of derealization (feeling detached from one's surroundings) or depersonalization (feeling detached from one's self). Among patients without a dissociative disorder, pathological levels of derealization and depersonalization are most prevalent and central in patients suffering from posttraumatic stress disorder (PTSD) and borderline personality disorder (BPD) (Knefel et al., 2016; Scalabrini et al., 2017).

Patients suffering from dissociative disorders might exhibit these symptoms in a very severe form (constituting depersonalization disorder (DPD)) and/or in combination with amnesia, identity confusion, or identity alteration (such as in dissociative identity disorder (DID)). It seems currently unclear whether these symptoms should be conceptualized as forming a dissociative continuum or whether a qualitative differentiation between depersonalization and derealization symptoms on the one hand and amnesia and identity alterations on the other hand is most appropriate (Allen, 2001; Holmes et al., 2005; Putnam, 1997). These conceptual discussions are further complicated by the high diagnostic overlap between PTSD and BDP (Pagura et al., 2010; Sack et al., 2013; Scheiderer et al., 2015) as well as these...
disorders and the dissociative disorders (Bozkurt et al., 2015; Rodewald et al., 2011; Sack et al., 2013; Swart et al., 2020). Convergently, the nosology of BDP and PTSD has recently seen some efforts for differentiation such as the suggestion of dissociative subtypes (see Vermuten and Spiegel, 2014 for BDP and DSM-5 criteria for PTSD) and the introduction of the diagnosis of complex PTSD in the ICD-11 as a disorder category spanning aspects of both disorders.

Severe dissociation is often conceptualized as causally related to traumatic experiences (Dalenberg et al., 2012; Loewenstein, 2018) and is frequently reported in disorders with high prevalence rates of childhood trauma exposure such as BPD (Rafiq et al., 2018; Vonderlin et al., 2018) and the newly introduced complex PTSD category (Jowett et al., 2020; Tian et al., 2020). Meta-analytic evidence indicates that all forms of childhood trauma (including accidental and natural traumatic events) are associated with dissociation severity in patients with severe mental disorders (Rafiq et al., 2018) and that both, abuse and neglect experiences are associated with dissociation severity in the general population and patients with less severe mental disorders, with strongest associations for sexual and physical abuse (Vonderlin et al., 2018). In addition, earlier age of onset, longer duration of abuse, and abuse committed by a parent are associated with significantly higher dissociation scores (Vonderlin et al., 2018). The overwhelming majority of DID patients report such severe forms of childhood trauma (Putnam et al., 1986; Sar et al., 2017; Schultz et al., 1989). Conversely, patients suffering from DPD report low prevalence rates for childhood trauma exposure (Baker et al., 2003; Daniels et al., 2015), i.e. lower than e.g. patients with major depressive disorder (Michal et al., 2016) and instead often report drug-induced symptom onset. Thus, it has been suggested to conceptualize DPD as stemming from a different causal mechanism with disorder-specific neural correlates than the other disorders characterized by prevalent dissociative symptoms (Daniels et al., 2015). Interestingly, DPD patients typically also suffer from persistent depersonalization and/or derealization (Baker et al., 2003; Daniels et al., 2015; Michal et al., 2016), while PTSD and BPD patients mostly report transitory symptoms lasting from a few seconds to a few hours. However, it is currently unclear whether a shared etiology and also shared neural correlates should be assumed for the diverse dissociative symptom profiles observed across disorders, or whether different disorder-specific conceptualizations seem most appropriate. Converging findings of neural alterations across disorders could elucidate this question.

Two seminal neurobiological models have linked dissociation to increased recruitment of regions subserving executive control (Lanius et al., 2010; Sierra and Berrios, 1998) such as the ventromedial prefrontal cortex, anterior cingulate cortex, and inferior frontal gyri resulting in dampened activation of the amygdala. Consequently, many studies have been published which analyzed the functional architecture of the brain using connectivity analyses with the amygdala as their starting point. These studies have implicated very diverse brain regions, including but not limited to frontal regions. Next to the proposed dysfunctional network of fronto-limbic regions, increasing attention has also been paid to altered activation and connectivity of the temporal cortices, especially the temporoparietal junctions. This increased focus was based on new evidence that this region serves as a critical hub for altered processing linked to spontaneously occurring out-of-body experiences during brain stimulation and lesion studies (Blanke et al., 2002, 2005) and dysfunctional body perception in (Sierra et al., 2014). In addition, successful interventions via transcranial magnetic stimulation of this region have been reported for DPD (Christopeit et al., 2014; Jay et al., 2014; Mantovani et al., 2011). However, if and how alterations in temporal regions link to subcortical and prefrontal regions still requires further examination. To our knowledge, no systematic review across dissociative disorders has been published to date and it remains unclear whether the available neuroimaging data on dissociation converge sufficiently to deduce an evidence-based conceptualization of this phenomenon.

1.1. Aims of the study

The current study aims to review the existing magnetic resonance imaging (MRI) studies on neuroanatomical and functional brain changes related to dissociative experiences in patients suffering from PTSD, BPD, or dissociative disorders. Our goal thus is to identify brain regions showing divergent or convergent alterations across different disorder groups characterized by depersonalization, derealization, amnesia, and identity disturbances, which might be able to further the conceptualization of these dissociative symptoms.

2. Methods

Adhering to the PRISMA guidelines for systematic reviews (Moher et al., 2009), a comprehensive search was conducted of several databases, including PubMed, ScienceDirect, Scopus, and Web of Knowledge for studies published between February 1990 and September 2019. The search was performed using the following MESH terms, free text, and keywords: (Dissociative Disorders OR Dissociative Identity Disorder OR Dissociation OR Dissociative AND Magnetic Resonance Imaging).

Inclusion criteria were (1) original articles on (2) patients with PTSD, BPD, or dissociative disorders as listed in the DSM-5 (i.e. including DPD), (3) diagnosed based on either Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) or International Statistical Classification of Diseases and Related Health Problems (World Health Organization, 1992), (4) which directly investigated neural alterations associated with the presence of dissociative symptoms in (5) n ≥ 6 adult participants (6) using either structural MRI, resting-state fMRI, or task-related fMRI. Only studies including (7) either a healthy control group or a clinical control group with the same disorder were considered. Research based on exclusively healthy subjects or with a purely correlational design was excluded. We opted to include BPD in the current review as most of the dissociative symptoms observed in these patients can be classified as either depersonalization or derealization symptoms. In addition, its dynamic nosology and high comorbidity with both PTSD and the dissociative disorders indicates no clear-cut distinction. Conversely, we opted to exclude studies limited to patients suffering from conversion (or functional neurological) disorder (Brown et al., 2007) as this disorder is mainly characterized by qualitatively different, somatoform symptoms. These symptoms are not assessed comprehensively by the diagnostic instruments used in most of the available publications focusing on PTSD, BDP, and the other dissociative disorders. Convergingly, current conceptualizations of its neurobiology point towards different key neural mechanisms (Edwards et al., 2013).

Studies based purely on a correlational approach were excluded for two reasons - to prevent the inclusion of results driven by variance in the low severity range of dissociation and because assessment tools used to measure symptom severity cover different sets of (somatoform) symptoms and thus introduce bias that cannot be controlled for in such a review. We opted to include studies with a small sample size as some dissociative disorders are notoriously difficult to study. However, in order to account for the increased risk introduced by low statistical power, studies with adequate sample sizes of n ≥ 20 (Button et al., 2013; Thirion et al., 2007) will be given additional weight in this review.

All studies presenting neuroimaging analyses for MRI data collected in dissociative patients were reviewed. The identified abstracts were independently screened by two reviewers. Extracted data included age, gender, number of subjects, comorbid disorders, diagnostic strategy, neuroimaging methods, and the contrast between patient’s activation or volume as compared to the control group.

After the removal of duplicates, 1902 unique publications were...
inspected of which 1808 studies were excluded based on their titles as they did not refer to clinical populations studied for the presence of dissociative disorders, did not present original data, or were not published in English. In total, 94 potentially eligible studies were thus identified. Out of these, 61 articles were subsequently excluded due to the lack of either a healthy control group, reported contrasts between PTSD or BPD patients with and without dissociative symptoms, or official diagnoses based on either DSM or ICD. Of the remaining 33 studies, 12 analyzed structural brain alterations (10 using voxel-based morphometry (VBM), and two using diffusion-tensor imaging (DTI)), 11 were task-related fMRI studies, and 10 were resting-state fMRI studies. In total, data from at least 414 patients with dissociative symptoms (150 in VBM, 90 in resting-state fMRI, 147 in task-related fMRI, and 38 in DTI), 252 PTSD or BPD patients without dissociation (70 in VBM, 151 in resting-state fMRI, and 31 in task-related fMRI), and 436 healthy subjects (160 in VBM, 102 in resting-state fMRI, 151 in task-related fMRI, and 38 in DTI) was found eligible for the current review. Due to the at times unclear overlap of samples, we assume this to be a conservative estimate of how many unique patients were included in the review. The PRISMA flow chart diagram in Fig. 1 displays the selection and exclusion process of studies.

3. Results

3.1. Results of structural brain alterations

The majority of the structural studies focused on patients with a primary dissociative disorder; only four studies assessed volume changes in PTSD or BPD patients (see Tables 1 and 2). In addition, most studies analyzed brain volume or cortical thickness, and only two studies analyzed group difference in white matter integrity. In the following sections, the main findings will be summarized per diagnosis.

3.1.1. Depersonalization/derealization disorder (DPD)

Three studies investigated structural changes in DPD patients. Sierra and colleagues (Sierra et al., 2014) compared DPD patients (n = 20) to healthy controls (n = 21) and found decreased cortical thickness in the right middle temporal gyrus. A different group (Daniels et al., 2015) analyzed gray matter volume in DPD patients (n = 25) compared to matched healthy controls (n = 23) and reported reduced volume in the right caudate, thalamus, and occipital gyri as well as increased volume in the right postcentral and superior temporal gyrus and left superior frontal gyrus in the DPD group. For the same sample, the authors also reported alterations in white matter structural connectivity (Sierk et al., 2018), with lower white matter integrity in the left temporal and right temporoparietal regions in the DPD group.

3.1.2. Dissociative identity disorder (DID)

Six studies (with partly overlapping samples) investigated structural changes in DID patients and reported overall alterations in the temporal lobes (inferior, middle, superior, and fusiform gyri), the frontal (superior frontal, precentral and cingulate gyri) lobes, as well as the insulae and amygdalae. A recent publication by Reinders et al. (2019) indicated widespread gray matter volume reductions in frontal and temporal regions in female DID patients (n = 32) including the patients published on by Chalavi et al. (2015a, 2015b) reviewed below as
<table>
<thead>
<tr>
<th>Type of neuroimaging</th>
<th>Primary disorder</th>
<th>Year</th>
<th>Author</th>
<th>Sample sizes for clinical group/healthy control group/non-dissociative subtype</th>
<th>Number of female subjects in clinical group/healthy control group/non-dissociative subtype</th>
<th>Age of patients/controls/non-dissociative subtype (Mean ± S. D)</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural MRI</td>
<td>DPD</td>
<td>2015</td>
<td>Daniels et al.</td>
<td>25/23/- 18/18/-</td>
<td>31.69 ± 8.09/29.96 ± 7.99/ 32.56 ± 8.43</td>
<td>SCID-D and clinical diagnosis by DSM-IV and ICD-10 criteria and SDQ-5 (cut-off 7)</td>
<td></td>
</tr>
<tr>
<td>Structural MRI</td>
<td>DPD</td>
<td>2014</td>
<td>Sierra et al.</td>
<td>20/21/- 4/12/- 35.75 ± 11.5/27.2 ± 5.6/-</td>
<td>DDP S ≥70 and clinical diagnosis by ICD-10 criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural MRI</td>
<td>DID</td>
<td>2019</td>
<td>Reinders et al.</td>
<td>32/43/- 32/43/- 43.56 ± 9.34/42.28 ± 11.57/</td>
<td>SCID-D, SCID-D (cut-off 25) and SDQ-5 (cut-off 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural MRI</td>
<td>DID</td>
<td>2018</td>
<td>Reinders et al.</td>
<td>32/43/- 32/43/- 43.56 ± 9.34/42.28 ± 11.57/</td>
<td>SCID-D, SCID-D (cut-off 25) and SDQ-5 (cut-off 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural MRI</td>
<td>PTSD</td>
<td>2016</td>
<td>Daniels et al.</td>
<td>15/-/44 10/-/18 38 ± 12.5/-/38 ± 11.7</td>
<td>SCID for DSM-IV, CAPS PTSD + D = PTSD patients scoring ≥4 (frequency + intensity) on CAPS depersonalization or derealization symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural MRI</td>
<td>PTSD, DID</td>
<td>2015</td>
<td>Chalavi et al.</td>
<td>17/28/16 17/28/16 43.82 ± 9.85/41.75 ± 12.29/40.75 ± 12.05</td>
<td>SCID-D, DES (cut-off 25) and SDQ-5 (cut-off 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural MRI</td>
<td>BPD</td>
<td>2007</td>
<td>Irle et al.</td>
<td>30/25/- 30/25/- 31 ± 6/33 ± 7/-</td>
<td>SCID-D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTI</td>
<td>DPD</td>
<td>2018</td>
<td>Sierk et al.</td>
<td>23/23/- 18/18/- 30.61 ± 7.31/29.96 ± 7.99/-</td>
<td>SCID-D and clinical diagnosis by ICD-10 criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTI</td>
<td>DD NOS</td>
<td>2015</td>
<td>Basmacı Kandemir et al.</td>
<td>15/15/- 14/14/- 27.40/27.47 ± 7.99/-</td>
<td>DDP S ≥70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting-state fMRI</td>
<td>PTSD</td>
<td>2015</td>
<td>Nicholson et al.</td>
<td>13/40/36 11/29/26 37 ± 12.7/23.3 ± 11.4/37 ± 12.9</td>
<td>CAPS for DSM-IV, PTSD patients scoring ≥2 on both frequency and intensity for the CAPS depersonalization or derealization symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting-state fMRI</td>
<td>PTSD</td>
<td>2018</td>
<td>Rabellino et al.</td>
<td>37/47/65 29/32/49 40.38 ± 13.69/33.81 ± 11.8/37.58 ± 11.75</td>
<td>CAPS for DSM-IV, PTSD patients scoring ≥2 on both frequency and intensity for the CAPS depersonalization or derealization symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting-state fMRI</td>
<td>PTSD</td>
<td>2019</td>
<td>Nicholson et al.</td>
<td>49/51/81 38/34/46 40 ± 13.5/34.2 ± 11.9/37.72 ± 11.79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting-state fMRI</td>
<td>PTSD</td>
<td>2017</td>
<td>Harricharan et al.</td>
<td>37/40/60 33/36/35 41.12 ± 13.7/35 ± 11.6/37.8 ± 11.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting-state fMRI</td>
<td>PTSD</td>
<td>2016</td>
<td>Harricharan et al.</td>
<td>37/40/60 33/36/35 41.12 ± 13.7/35 ± 11.6/37.8 ± 11.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task-related fMRI</td>
<td>DPD</td>
<td>2016</td>
<td>Lemmi et al.</td>
<td>9/12/- 4/5/- 35.11 ± 2.34/27.25 ± 1.95/-</td>
<td>CDS ≥70 and clinical diagnosis by ICD-10 criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task-related fMRI</td>
<td>DPD</td>
<td>2016</td>
<td>Medford et al.</td>
<td>14/25/- 3/11/- 33.7 ± 8.9/29.8 ± 5.68/-</td>
<td>CDS ≥70 and clinical diagnosis by ICD-10 criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task-related fMRI</td>
<td>DPD</td>
<td>2014</td>
<td>Ketay et al.</td>
<td>9/10/- Data not available 33.2 ± 11.8/31.9 ± 11.8</td>
<td>SCID-D (Controls: also scoring &lt;10 on DES)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Type of neuroimaging</th>
<th>Primary disorder</th>
<th>Sample size of clinical group</th>
<th>Healthy control group</th>
<th>Number of female subjects</th>
<th>Age of patients/controls/none dissociative subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task-related fMRI DPD 2006</td>
<td>Depersonalization Disorder</td>
<td>10/12/15</td>
<td>10/12/15</td>
<td>36.1 ± 3.2</td>
<td>SCID-1 and IPDE, No Significant Difference between clinical group and healthy control group</td>
</tr>
<tr>
<td>Task-related fMRI DPD 2006</td>
<td>Dissociative Disorder Not Otherwise Specified</td>
<td>11/15/-</td>
<td>11/15/-</td>
<td>43.3 ± 9.1</td>
<td>SCID-D, Significant Difference between clinical group and healthy control group</td>
</tr>
<tr>
<td>Task-related fMRI DID, DD-NOS 2007</td>
<td>Dissociative Disorder Not Otherwise Specified</td>
<td>14/14/-</td>
<td>14/14/-</td>
<td>35 ± 8</td>
<td>SCID-D, Significant Difference between clinical group and healthy control group</td>
</tr>
<tr>
<td>Task-related fMRI PTSD 2008</td>
<td>Post-traumatic Stress Disorder</td>
<td>17/18/12</td>
<td>17/18/12</td>
<td>27.41 ± 6.20</td>
<td>SCID-I and IPDE, Score of ≥ 1.5 on the Dissociation Stress Scale 4 after script compared to baseline was defined as inclusion criterion for the BPD_D group</td>
</tr>
<tr>
<td>Task-related fMRI BPD 2015</td>
<td>Borderline Personality Disorder</td>
<td>18/19/19</td>
<td>18/19/19</td>
<td>27.61 ± 5.95</td>
<td>SCID-I and IPDE, Significant Difference between clinical group and healthy control group</td>
</tr>
</tbody>
</table>

**Note.**

Primary Disorder: BPD = Borderline Personality Disorder, DD-NOS = Dissociative Disorder Not Otherwise Specified, DID = Dissociative Identity Disorder, PTSD = Post-traumatic Stress Disorder. Diagnostic Criteria: CADSS = Clinician-Administered Dissociative States Scale, CAPS = Clinician-Administered PTSD Scale, CDS = Cambridge Depersonalization Scale, DDIS = Dissociative Disorder Interview Schedule, IPDE = International Personality Disorder Examination, DES = Dissociative Experiences Scale, SCID-D = Structured Clinical Interview for DSM-IV Dissociative Disorders, SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders, SDQ-5 = The 5-item Somatoform Dissociation Questionnaire.
prefrontal gyrus, cingulate, and insula (Ketay et al., 2014; Lemche et al., 2007, 2016; Medford et al., 2006, 2016; Weniger et al., 2013). A study by Lemche et al. (2016) tested the neural correlates of inhibitory capacity via a combined Stroop/negative priming task. They found greater activation of the dorsomedial prefrontal cortex and posterior cingulate cortex in DPD patients during the Stroop task (n = 16) as compared to healthy controls (n = 12). Medford et al. (2016) examined brain activity in response to emotive visual stimuli in DPD patients (n = 14) as compared to healthy controls (n = 25). The patient group exhibited lower activity in the secondary visual cortex as well as increased activation in dorsolateral prefrontal cortex and anterior cingulate cortex. Related research (Lemche et al., 2007) demonstrated that DPD patients (n = 9) showed decreased BOLD signals in hypothalamus and amygdala during the processing of happy and sad facial expressions compared to healthy subjects (n = 12). However, DPD patients (n = 9) also exhibited a greater activation than healthy controls (n = 10) in response to viewing their own faces vs. that of a stranger in the frontal cortices (anterior cingulate cortex, bilateral medial prefrontal cortex, and left middle frontal gyri) (Ketay et al., 2014). Another study (Medford et al., 2006) indicated lower activation in bilateral frontal areas, bilateral precuneus, and cerebellum during target word recognition task in DPD patients (n = 10) than healthy controls (n = 12).

### 3.2.2. Dissociative identity disorder

Weniger et al. (2013) compared brain activity patterns in response to a virtual maze task in female patients (n = 14) with a diagnosis of primary DID or dissociative amnesia, but without comorbid PTSD, to healthy subjects (n = 14). Patients depicted reduced activity in the cingulate, insular, and inferior parietal cortex and adjacent part of the superior temporal cortex. Elzinga et al. (2007) demonstrated that a verbal working memory task elicited stronger activation of the left anterior prefrontal cortex, dorsolateral prefrontal cortex, and parietal cortex in DPD patients (n = 16) as compared to healthy controls (n = 16). Schlumpf and coworkers (Schlumpf et al., 2013) compared reactions to subliminal angry and neutral faces in DID patients (n = 11, also included in the study by Reinders et al. (2018, 2019) reviewed above) to those in trained actors (n = 15). Patients exhibited more activation of the precentral gyrus during the processing of angry faces

### Table 2

Summary Results

<table>
<thead>
<tr>
<th>Amygdala</th>
<th>Hippo-campus</th>
<th>Insula</th>
<th>Cingulate Cortex</th>
<th>Frontal Cortex</th>
<th>Parietal Cortex</th>
<th>Temporal Cortex</th>
<th>Occipital Cortex</th>
<th>Brain Stem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural MRI</td>
<td>DPD</td>
<td>&amp; (WM)</td>
<td>↓ (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ superior PFC</td>
<td>↓ inferior PFC</td>
</tr>
<tr>
<td>PTSD</td>
<td>↓</td>
<td>↑ anterior PFC (WM)</td>
<td>↓ postcentral (RH)</td>
<td>↓ superior PFC</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ middle PFC (WM)</td>
<td>↓ middle PFC</td>
<td>↓ inferior PFC</td>
</tr>
<tr>
<td>Functional MRI</td>
<td>PTSD</td>
<td>↑ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
</tr>
<tr>
<td>BPD</td>
<td>↓</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
<td>↓ anterior PFC (WM)</td>
</tr>
<tr>
<td>Functional Connectivity</td>
<td>PTSD</td>
<td>↑ (sub)</td>
<td>↑ (sub)</td>
<td>↑ (sub)</td>
<td>↑ (sub)</td>
<td>↑ (sub)</td>
<td>↑ (sub)</td>
<td>↑ (sub)</td>
</tr>
<tr>
<td>BPD</td>
<td>↑ (sub)</td>
<td>↑ (sub)</td>
<td>↑ (sub)</td>
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<td>↑ (sub)</td>
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</tr>
</tbody>
</table>

Note. Each arrow corresponds to findings extracted from a single study (DID = Dissociative Identity Disorder; DPD = Depersonalization/Derealization Disorder; PTSD = Post-traumatic Stress Disorder; BPD = Borderline Personality Disorder; LH = left hemisphere; RH = right hemisphere; PFC = prefrontal cortex; FG = frontal gyrus; dl = dorsolateral; dm = dorsomedial; v = ventral; vm = ventromedial; rTPJ = right temporoparietal junction; V2 = secondary visual cortex; SC = superior colliculi; VC = vestibular cortex; ST = stria terminalis; THA = thalamus, AMY = amygdala; PAG = periaqueductal gray; rs = resting-state fMRI; WM = white matter; supra = supraliminal processing of fearful stimuli; sub = subliminal processing of fearful stimuli).

- Structural alterations in white matter were derived from the anatomical T1 scan in the DID study, and diffusion tensor imaging (DTI) in the DPD study.
and of the brain stem and lingual gyrus during the processing of neutral faces.

3.2.3. Post-traumatic stress disorder

A study by Felmingham et al. (2008) examined brain activation in response to supra- and subliminal presentations of fearful facial expressions in PTSD patients. Patients with elevated dissociative symptoms (n = 12) exhibited greater activation of the ventral prefrontal cortex and reduced activation of the dorsomedial prefrontal cortex during the conscious (supraliminal) processing of fearful faces compared to non-dissociative PTSD group (n = 11). Conversely, the same group had greater activation of the bilateral amygdalae and insulae as well as the left thalamus during nonconscious (subliminal) processing of fear stimuli.

3.2.4. Borderline personality disorder

Winter and coworkers (2015) used an emotional Stroop task to investigate emotional inhibitory functioning in BPD. Patients who first underwent dissociation induction (n = 19) showed decreased neural activity in the fusiform gyrus and parietal cortices, and increased activity in the left dorsolateral and inferior frontal gyri as compared to BPD patients without induced state dissociation (n = 19) (Winter et al., 2015). Using the same paradigm, the same group showed that BPD patients who underwent a dissociation induction (n = 17) exhibited lower activation in the bilateral amygdalae and lingual gyri, left cuneus, and posterior cingulate during an emotional working memory task compared to BPD patients (n = 12) without dissociation induction (Krause-Utz et al., 2018).

3.3. Results of resting-state fMRI studies focused on activation differences

One study investigated brain activation during the resting-state as a pattern classifier in PTSD patients. PTSD patients with dissociative symptoms (n = 49) showed greater activation of the cerebellum, the right vmPFC, orbitofrontal cortex, and frontal pole, while PTSD patients without dissociative symptoms (n = 81) showed greater activation of postcentral and precentral gyri, globus pallidus, thalamus, putamen, and the left amygdala/parahippocampal gyrus region (Nicholson et al., 2019).

3.4. Results of functional connectivity studies

Most of the functional connectivity studies were conducted in PTSD patients during the resting state and stem from just one research group. Six publications largely used the same patient sample (Harricharan et al., 2016; Nicholson et al., 2015, 2016; Olive et al., 2018; Rabellino et al., 2018a; Terpou et al., 2018) and the recruitment information for the remaining three publications suggests at least some overlap with this sample (Harricharan et al., 2017; Nicholson et al., 2017, 2019b; Nicholson et al., 2019c; Nicholson et al., 2019d). According to their analyses, dissociative PTSD patients (n = 37) as compared to non-dissociative PTSD patients (n = 65) were characterized by increased functional connectivity between the cerebellum and the ventromedial prefrontal and orbito-frontal cortex (Rabellino et al., 2018b) and showed reduced connectivity between the right supramarginal gyrus and the pulvinar (thalamic region) than non-dissociative patients (Terpou et al., 2018).

Reduced functional connectivity between the left superior colliculus and the right dorsolateral prefrontal cortex as well as increased connectivity between the right superior colliculus and the right temporoparietal junction was reported for dissociative (n = 41) vs. non-dissociative (n = 67) PTSD patients (Olive et al., 2018), while reduced functional connectivity between the brainstem and the parieto-insular vestibular cortex and the dorsolateral prefrontal cortex distinguished dissociative patients (n = 41) from both non-dissociative patients (n = 60) and healthy controls (n = 40) (Harricharan et al., 2017). In addition, enhanced functional connectivity between the right and left bed nucleus of the stria terminals with the left cuneus, calcarine cortex, and lingual gyrus as well as between the left bed nucleus and the right dorsal anterior insula and right frontal operculum were reported in dissociative (n = 41) as compared to non-dissociative (n = 70) PTSD patients (Rabellino et al., 2018a).

Nicholson and coworkers (2017) compared PTSD patients with (n = 41) and without (n = 62) dissociative symptoms and showed that dissociative patients exhibited predominant top-down connectivity between the ventromedial prefrontal cortex to the amygdala and periaqueductal gray, and from the amygdala to the periaqueductal gray. The same authors (Nicholson et al., 2016) further suggested that dissociative PTSD (n = 17) is characterized by increased connectivity between subregions of the insula to the left basolateral amygdala and that the amygdala displayed increased connectivity with middle and medial frontal gyri (Nicholson et al., 2015) as compared to non-dissociative PTSD (n = 44). In addition, PTSD patients with dissociative symptoms (n = 37) exhibited greater functional connectivity between the periaqueductal gray and the right tempoparietal junction, the right rolandic operculum, the left fusiform gyrus and cerebellum than non-dissociative PTSD patients (n = 60) (Harricharan et al., 2016). Using the pattern classification approach mentioned above, Nicholson and colleagues (Nicholson et al., 2019) also reported a significant interaction between PTSD group and functional connectivity between the amygdala and adjacent regions on the one hand and frontal and parietal regions on the other hand, but did not specify which group showed greater connectivity between these structures.

One study (Krause-Utz et al., 2018) focused on BPD indicated that patients who underwent a dissociation induction (n = 17) showed reduced amygdala functional connectivity with the left fusiform gyrus and increased functional connectivity with the left inferior parietal lobule, the right middle occipital gyrus, and the right middle/superior temporal gyrus as compared to BPD patients without dissociation induction (n = 12).

4. Discussion

To our knowledge, this is the first systematic review that investigated brain aberrations in patients with dissociative symptoms. The current review identified 33 studies comprising data of structural MRI, task-related fMRI, and resting-state fMRI research in over 400 patients with dissociative symptoms. Specifically, neuroimaging findings in patients with a primary dissociative disorder, PTSD patients with dissociative symptoms, and BPD patients with dissociative symptoms will be discussed in the following section. Overall results indicate that dissociation may be related to alterations spread across temporal and frontal cortices as well as the limbic system and brainstem.

4.1. Aberrations in subcortical regions

Volume reductions in the bilateral amygdalae gray matter (Vermetten et al., 2006) and the adjacent white matter (Reinders et al., 2019) have been reported in DID patients. However, these alterations could be primarily related to comorbid PTSD and therefore may not be disorder-specific for DID as there is some evidence for smaller amygdala volumes in adults with PTSD (mixed, with and without dissociative symptoms) as compared to both trauma-exposed and non-exposed healthy subjects from meta-analytical and data pooling studies (Karl et al., 2006; Logue et al., 2018). The only two studies directly comparing DID patients with comorbid PTSD to patients suffering only from PTSD (Chalavi et al., 2015a, 2015b) did indicate larger volumes in putamen and pallidum in the PTSD-only group and smaller hippocampal volume in both the PTSD-only group and the comorbid PTSD-DID group compared to a healthy control group, but no volume alterations in the amygdalae. Remarkably, no structural alterations of the amygdalae were reported for DPD patients (Daniels et al., 2015; Sierra et al., 2006).
et al., 2014). While replication research is highly warranted, the extracted findings suggest that decreased amygdala volume as present in PTSD with and without comorbid DID could be due to (severe) trauma-exposure itself.

Meanwhile, a functional MRI investigation with supraliminal and subliminal presentation of fearful stimuli (Felmingham et al., 2008) indicated differential activation patterns in PTSD with and without dissociation. While conscious processing lead to increased recruitment of frontal regions, non-conscious processing resulted in increased amygdala activation for the dissociative group. This might suggest that the amygdala plays a crucial role in early threat detection and initiates pathological emotion modulation mechanisms underlying PTSD (Andrewes and Jenkins, 2019; Nicholson et al., 2015).

Regarding the functional connectivity of the amygdala, several studies have indicated alterations in PTSD patients with dissociation symptoms (Nicholson et al., 2015, 2016, 2017bibNicholson_et_al_2015 bibNicholson_et_al_2016). However, these studies all showed altered communication with divergent brain regions (i.e. middle and medial prefrontal regions (Nicholson et al., 2015), the ventromedial prefrontal gyrus and the periaqueductal gray (Nicholson et al., 2017), and the insula (Nicholson et al., 2016) and thus still await replication. A recent review (Andrewes and Jenkins, 2019) detailing how two separate regulatory neurocircuits are likely subserving the adaptive regulation of amygdala activation is well in line with the reviewed alterations observed across several disorders with dissociative symptoms.

The bilateral insula indicated reductions in cortical thickness (Reinders et al., 2018), increases in the adjacent white matter (Reinders et al., 2019) as well as dampened task-related activity (Weniger et al., 2013) in patients with mixed dissociative disorders. In DPD, the insula showed increased resting-state activity (Medford et al., 2016). In dissociative PTSD patients, increased functional connectivity was observed with the striatopallidal terminals (Rabellino et al., 2018a). As the insula is involved in functions associated with many aspects of consciousness and awareness such as bodily arousal, pain perception, olfaction, and somatotopic representations (Craig, 2009, 2013; Pitman et al., 2012), neural alterations at this region could potentially correspond to the disrupted multisensory integration of sensory signals encountered in dissociation.

4.2. Alterations in the cingulate gyri

The cingulate encompasses many functionally diverse subregions, subserving processes ranging from emotion regulation in the anterior cingulate (Andrewes and Jenkins, 2019) to self-processing, familiarity and memory formation in the posterior part (Laird et al., 2009; Leech and Sharp, 2014; Vogt and Laureys, 2005; Vogt et al., 2006). DID patients depicted structural alterations in the bilateral (Reinders et al., 2019) or right (Reinders et al., 2018) anterior cingulate gyrus. DPD patients exhibited greater activation of the anterior cingulate during self-related processing (Ketay et al., 2014) and of the posterior cingulate during the Stroop task (Lemche et al., 2016). Following a dissociation induction, BPD patients showed reduced activation of the posterior cingulate during a working memory task (Krause-Utz et al., 2018). These heterogeneous findings are in line with the fact that many different mental disorders have been associated with aberrant activation and connectivity in cingulate subregions (Whitfield-Gabrieli and Ford, 2012). Identifying which specific processes are causally related to the experience of dissociative disorders will thus require precisely targeted experimental designs. The studies reviewed here certainly do not yet allow any firm conclusions to be drawn in this respect.

4.3. Alterations in frontal gyri

As can be seen in Table 2, different brain regions in the frontal lobes exhibited alterations, but these were not very consistent across studies or disorders. DPD patients were reported to exhibit volume increases in the bilateral medial superior frontal gyrus (Daniels et al., 2015) as well as decreased cortical thickness in the bilateral superior frontal gyri (Sierra et al., 2014). The left middle frontal gyrus showed greater responding during cognitive processing (Lemche et al., 2016) and in response to a self vs. strange face task (Ketay et al., 2014). DID patients, in turn, were characterized by reduced bilateral gray matter volume in dispersed frontal cortex regions (Reinders et al., 2018, 2018b bibReinders_et_al_2018bibReinders_et_al_2019), but also increased white matter integrity (Reinders et al., 2019). During task-related fMRI, increased activation was found of the left anterior prefrontal cortex and dorsolateral prefrontal cortex during a verbal working memory task for DID patients (Elzinga et al., 2007). Elevated activation in frontal regions was also observed in PTSD patients with dissociative symptoms during the resting state (Nicholson et al., 2019) and during the conscious processing of fear stimuli (Felmingham et al., 2008). BDP patients with acute dissociative symptoms exhibited increased activation of the left inferior frontal gyrus in reaction to negative words (Winter et al., 2015). Taken together, the findings of increased frontal activity may suggest tentative support for medial-frontal hyper activation. However, generalizations should be made with caution due to differences in the employed paradigms and control groups.

The reviewed studies analyzing functional connectivity differences between PTSD patients with and without dissociative symptoms reported group differences in connectivity with different frontal cortex regions, but showed little overlap across studies (Harricharan et al., 2016, 2017; Nicholson et al., 2015, 2017, 2019; Olive et al., 2018; Rabellino et al., 2018a, 2018b; Terpou et al., 2018). One study (Nicholson et al., 2017) found evidence for predominant top-down connectivity between the ventromedial prefrontal cortex and the amygdala in the dissociative group. No other brain region is as functionally specialized as the frontal cortex, with several regions involved in distinct aspects of emotion regulation (Andrewes and Jenkins, 2019), response inhibition (Zhang et al., 2017), attention allocation (Riedel et al., 2018), and self-processing (Mak et al., 2017). However, which specific role these diverse frontal regions play in dissociative processing can currently not be discerned. Two influential theoretical models (Lanius et al., 2010; Sierra and Berrios, 1998) assume a direct causal involvement in emotional numbing and depersonalization/derealization via amygdala, but the reviewed studies did not identify converging results across disorders that would support this assumption. Further investigations, ideally using experimental manipulation such as via transcranial magnetic stimulation, might help elucidate this issue.

4.4. Alterations in temporal gyri

In DPD, lower cortical thickness was reported for the right middle temporal region (Sierra et al., 2014) and greater gray matter volume in the right superior temporal gyrus (Daniels et al., 2015). In addition, lower white matter integrity in the left temporal and right temporoparietal junction was found (Sierra et al., 2018). DPD patients showed increased activation during cognitive processing in the left angular gyrus (Lemche et al., 2016). Decreased activation of the left superior temporal gyrus during a virtual maze task was reported in patients with either primary DID or dissociative amnesia, of which the majority also was diagnosed with comorbid DPD and BDP (Weniger et al., 2013). In comparison, DID patients exhibited dispersed gray matter volume reductions including in bilateral temporal and fusiform gyri (Reinders et al., 2019), reduced cortical surface area in temporal regions and reduced cortical thickness in the left angular gyrus (Reinders et al., 2018) and greater activation of the fusiform gyrus during the processing of neutral faces (Schlumpf et al., 2013). In PTSD, greater gray matter volume in fusiform gyr as well as less volume in the right inferior temporal gyrus was reported in patients with dissociative symptoms (Daniels et al., 2016). In addition, lower functional connectivity between the cerebellum and the temporoparietal junction was
identified (Rabellino et al., 2018b) as well as increased connectivity between the right temporoparietal junction and the right superior colliculus (Olive et al., 2018) as well as the periaqueductal gray (Harricharan et al., 2016). Relatedly, BPD patients who had undergone a dissociation induction displayed decreased neural activation of the left fusiform gyrus during the processing during the Stroop task (Winter et al., 2015) as compared to patients who did not undergo dissociation induction. Furthermore, BPD patients with experimentally elicited dissociative symptoms showed lower functional connectivity between the left fusiform gyrus and the amygdala as compared BPD patients without dissociation induction (Krause-Utz et al., 2018).

In conjunction, both structural and functional aberrations were observed in the fusiform gyrus across disorders, with the notable exception of DPD. The fusiform gyri are known to be involved in face processing (Sabatinelli et al., 2011), visual imagery (Pidgeon et al., 2016) as well as cognitive forms of emotion regulation (Dorfel et al., 2014).

Alterations were also reported for the temporoparietal junctions including both angular gyri. In DPD and DID, both structural and functional aberrations were reported for this region, while PTSD showed altered functional connectivity with the cerebellum, the periaqueductal gray, and the superior colliculus. There is growing evidence that the temporal cortex, especially the temporoparietal junction, is a relevant region for multisensory integration, embodiment, and self-other distinction (Eddy, 2016). In light of the limited empirical basis, one can only speculate that the observed alterations in this region across dissociative disorders as well as PTSD are related depersonalization/derealization symptoms. As such, experiences of detachment (e.g. out-of-body experiences, decreased sense of agency) could be partially steered by integration deficits located at the temporal cortex.

4.5. Alterations in other regions

Aberrations in the occipital lobes were reported less frequently. The superior occipital gyri exhibited volume reductions in DID (Reinders et al., 2019). Convergently, DPD patients also showed lower gray matter volume in the right middle and superior occipital gyri (Daniels et al., 2015). In addition, lower activation of the left middle occipital gyrus was reported in patients with mixed dissociative disorders with a high prevalence of comorbid BPD and BDP (Weniger et al., 2013). The left lingual gyrus exhibited lower cortical thickness in DPD patients (Sierra et al., 2014), lower activation during an emotional working memory task in BPD (Krause-Utz et al., 2018), and greater functional connectivity with the bed nucleus of the stria terminals in PTSD (Rabellino et al., 2018a).

The brain stem is notoriously difficult to analyze with MRI, but several studies reported significant group differences. Dissociative PTSD patients were characterized by reduced functional connectivity between the brainstem and the parieto-insular vestibular cortex and the dorsolateral prefrontal cortex (Harricharan et al., 2017), as well as increased connectivity between the right temporoparietal junction and the right superior colliculus (Olive et al., 2018) as well as the periaqueductal gray (Harricharan et al., 2016). Nicholson and coworkers (2017) showed that dissociative patients exhibited predominant top-down connectivity between the ventromedial prefrontal cortex to the amygdala and periaqueductal gray, and from the amygdala to the periaqueductal gray.

The cerebellum also showed divergent aberrations across disorders. In DPD, it displayed greater activation during an emotional memory task (Medford et al., 2006). Dissociative PTSD patients were characterized by increased functional connectivity between the cerebellum and the ventromedial prefrontal and orbito-frontal cortex (Rabellino et al., 2018b) and with the periaqueductal gray (Harricharan et al., 2016).

4.6. Limitations

The current review has several limitations. We opted to restrict the scope of this review in several ways, most notably by excluding studies focused on conversion disorder or employing a purely correlational design. This might have introduced bias as studies investigating somatoform dissociation, i.e. presumably a related but distinguishable set of symptoms, were not included. Future research is strongly encouraged to review and expand on the potential differences and similarities present in conversion disorder compared to other dissociative disorders and to aim to distill the neurobiological correlates of those dissociative symptoms assessed comparatively by the different instruments employed to measure symptom severity. Furthermore, studies using alternative methods to investigate neural alterations, e.g. EEG, SPECT, PET, were excluded. Future reviews and meta-analyses are encouraged to include and compare results derived from distinct methodologies across the complete range of disorders linked to pathological dissociative expression.

Concerning the reviewed studies, interpretations of the above-mentioned findings are limited by following methodological shortcomings: First, most research on DID investigated brain alterations in patients with comorbid PTSD. As such, it remains unclear whether the observed alterations are pathognomonic to DID. It is recommended that future DID research should either include a control group of PTSD patients without dissociation (Reinders et al., 2019) or include PTSD symptom severity as covariate in their analyses. Second, differences in trauma type (interpersonal vs. natural and accidental trauma) were not considered in most PTSD studies. Third, no conclusions on developmental influences can be drawn as the age at onset of the disorder was often not considered. It remains unclear whether the observed neurobiological aberrations predated the onset of symptoms or whether they are a result of dissociative processing over time and development. Such insight might be gained by studying patients with a recent onset of symptoms or by covarying for time since symptom onset. Most studies did neither assess nor control for childhood trauma in their analyses although an extensive body of literature has presented robust associations between early life adversity, e.g. childhood maltreatment, and neural alterations (McCroy et al., 2011), and childhood trauma and dissociative responding in adulthood (Rafiq et al., 2018; Vonderlin et al., 2018). Future neuroimaging research is strongly encouraged to include childhood trauma as covariate in their models to reliably assess the unique variance explained by the (dissociative) symptomatology.

Fourth, a general interpretation of the task-related fMRI studies reviewed in the current study should be viewed with caution as the variety of employed experimental tasks makes direct comparison of the elicited brain activations difficult. Fifth, many analyses reviewed by the current study are underpowered due to small samples, which limits their reliability and thus also their validity (Button et al., 2013). Group comparisons with a minimum n = 20 subjects per group are strongly encouraged to obtain reliable results in (functional) neuroimaging research (Thirion et al., 2007). Most, but not all, DPD studies failed to meet this quality criterion. At last, it should be noted that all findings reported on functional connectivity in PTSD stem from the same research group large overlap in sample composition and two of the five reviewed studies on DID patients were based on the two combined samples used in the remaining three papers. Such sample overlap might increase the risk of bias and calls for independent replication. In conjunction, this illustrates that neuroimaging research on dissociative symptoms is still rare and requires a more global representation.

To conclude, there is some converging, albeit preliminary empirical evidence for neural aberrations in the frontal and temporal cortices, amygdalae, and insulae in patient populations characterized by dissociative symptoms. DPD patients exhibited diverging patterns in brain structure and activity as compared to DID, providing tentative support either for the differentiation between detachment and compartmentalization (Allen, 2001; Holmes et al., 2005; Putnam, 1997) or for
differential antecedents for these disorders. However, the reviewed studies merely reported observed group differences at one time point, but cannot ascertain whether these are a prerequisite for or a result of dissociative processing. More neuroimaging research on dissociation including careful screening for symptom severity, comorbidity, and childhood trauma is warranted.

Declaration of competing interest

The authors do not report any conflicts of interests.

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Appendix A  Supplementary data

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