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A Review of the Relation Between Dissociation, Memory, Executive Functioning and Social Cognition in Military Members and Civilians with Neuropsychiatric Conditions

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ABSTRACT

Dissociative experiences, involving altered states of consciousness, have long been understood as a consequence or response to traumatic experiences, where a reduced level of consciousness may aid in survival during and after a traumatic event. Indeed, the dissociative subtype of post-traumatic stress disorder (PTSD-DS) was added recently to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Dissociative symptoms are present across a host of neuropsychiatric conditions, including PTSD, psychotic spectrum illnesses, anxiety and mood disorders. Transdiagnostically, the presence of dissociative symptoms is associated with a greater illness burden and reduced treatment outcomes. Critically, dissociative symptoms are related to impaired performance on measures of attention, executive functioning, memory, and social cognition and may contribute to the widespread cognitive dysfunction observed across psychiatric illnesses. Despite this knowledge, the relation between dissociative symptoms and reduced cognitive function remains poorly understood. Here, we review the evidence linking dissociative symptoms to cognitive dysfunction across neuropsychiatric disorders. In addition, we explore two potential neurobiological mechanisms that may underlie the relation between dissociative symptoms and cognitive dysfunction in trauma-related neuropsychiatric conditions. Specifically, we hypothesize that: 1) functional sensory deafferentation at the level of the thalamus, as observed in the defence cascade model of dissociation, may underlie reduced attention and arousal leading to progressive cognitive dysfunction and; 2) altered functional connectivity between key brain networks implicated in cognitive functioning may represent a critical neurobiological mechanism linking dissociative symptoms and cognitive dysfunction in patients with PTSD-DS and transdiagnostically.

1. Introduction

Dissociation refers to a disturbance in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behaviour (APA, 2013). Whereas some theoretical frameworks describe dissociative experiences as involving a division within the sense of self (van der Hart et al.,

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2004; 2006), others highlight altered states of consciousness surrounding dissociative experiences (Cardeña and Carlson, 2011; Frewen and Lanius, 2015; Holmes et al., 2005; Putnam, 1997; Spiegel, 1997; Spiegel et al., 2013; Steele et al., 2009). Core symptoms of dissociation include disengagement (not paying attention or "spacing out"), emotional constriction, memory disturbances, depersonalization (feeling outside of and as if you do not belong to your own body), derealization (feeling as though things around you are not real) and identity dissociation (Briere et al., 2005; Dell and Lawson, 2009; Lanius et al., 2012; Spiegel et al., 2013). Dissociative experiences have been conceptualized as lying on a continuum from normal integration of consciousness, followed by depersonalization/derealization, through to identity fragmentation (Bernstein and Putnam, 1986; Bremner and Marmar, 1998; Spiegel, 1997). One recent theory suggests that dissociative experiences may be separated into two distinct forms, involving detachment (e.g., altered states of consciousness) and compartmentalization (e.g., inability to control deliberately processes such as memory) (Holmes et al., 2005). Other researchers have noted the distinction between altered states of consciousness and structural dissociation (e.g., divisions in personality), while noting that the two may co-occur in trauma-related disorders (Steele et al., 2009). Regardless of theoretical orientation, trauma has long been recognized as an antecedent to dissociative symptoms, where in the early 20th century Pierre Janet first described dissociation as the most direct defence against overwhelming traumatic experiences (Janet, 1901). Indeed, the trauma model of dissociation suggests that dissociation is a psychobiological response to threat or danger that allows an organism to engage in automized behaviour, enhancing analgesia, depersonalization, and removal of oneself from traumatic or catastrophic experiences with the aim of enhancing survival during and after the event (Dalenberg et al., 2012). Accordingly, dissociation allows for psychological escape when physical escape is not possible (Putnam, 1997). In addition to their association with traumatic life events, dissociative symptoms are frequently associated with disrupted development of attachment relationships (Dutra et al., 2009; Liotti, 2006, 2004; Schore, 2002, 2009).

Dissociation is associated classically with trauma-related disorders following both civilian and military trauma exposure, including borderline personality disorder (BPD) (Bremner, 2005; Meares, 2012; Vermetten and Spiegel, 2014; Winter et al., 2015), dissociative disorders (Brand et al., 2012; Dell and O'Neil, 2009; Spiegel et al., 2013; van der Hart et al., 2006) and post-traumatic stress disorder (PTSD) (Bremner and Brett, 1997; Dalenberg and Carlson, 2012; Ginzburg et al., 2006; Lanius et al., 2010, 2012; Stein et al., 2013; Wolf et al., 2012a, 2012b). In response to recent work indicating that a subset of approximately 15 – 30% of patients with PTSD present with symptoms of depersonalization and derealization (Armour et al., 2014; Blevins et al., 2014; Frewen et al., 2015; Lanius et al., 2010, 2012; Putnam et al., 1996; Spiegel et al., 2013; Steuwe et al., 2012; Tsai et al., 2015; Wolf et al., 2012a, 2012b), the recently revised Diagnostic and Statistical Manual of Mental Disorders (DSM-5) now includes a dissociative subtype of PTSD (PTSD-DS). Notably, dissociative symptomatology can also be present in syndromes less frequently associated with trauma including major depressive disorder (MDD) (Bob et al., 2008; Molina-Serrano et al., 2008; Mula et al., 2007; Sar et al., 2013; Parlar et al., 2016), anxiety disorders (Ball et al., 1997; Marquez et al., 2001; Mula et al., 2007; Sierra et al., 2012), obsessive compulsive disorder (OCD) (Belli, 2014; Belli et al., 2012; Rufer et al., 2006a; Semiz et al., 2014; Watson et al., 2004), bipolar disorder (Hariri et al., 2015; Mula et al., 2009; Oedegaard et al., 2008), alcohol and drug abuse and dependence (Evren et al., 2011, 2008, 2007; Tamar-Gurol et al., 2008) and schizophrenia (Haugen and Castillo, 1999; Holowka et al., 2003; Sar et al., 2010; Spitzer et al., 1997; Yu et al., 2010). Taken together, the widespread appearance of dissociative symptoms suggests high rates of trauma exposure across neuropsychiatric conditions and points to the need for careful assessment of dissociation as a transdiagnostic psychiatric symptom.

Given that dissociation is associated with a disrupted integration of consciousness, memory, and behaviour, involving symptom clusters of memory disturbance and disengagement, it follows that individuals who experience dissociative symptoms would experience disruptions in cognitive function, affecting memory, attention, and executive functioning. This observation is in line with widespread reports of cognitive dysfunction across psychiatric disorders associated with dissociative symptoms, including schizophrenia (Millan et al., 2012; Wykes et al., 2011), MDD (Marazziti et al., 2010; Millan et al., 2012; Rock et al., 2014), bipolar disorder (Lee et al., 2014; Millan et al., 2012), OCD (Shin et al., 2014), and both civilian and combat-related PTSD (Aupperle et al., 2012; Millan et al., 2012; Polak et al., 2012; Scott et al., 2014). Notably, although the results of one systematic review pointed towards greater cognitive dysfunction among individuals with combat-related as compared to civilian PTSD (Polak et al., 2012), a recent quantitative meta-analysis reported no differences in severity of cognitive dysfunction across trauma etiologies (Scott et al., 2014). Critically, poor cognitive functioning is thought to contribute to the development and maintenance of these disorders, where, for example, executive dysfunction impacts negatively on response to pharmacological and non-pharmacological treatments for psychiatric disorders including mood disorders and PTSD (Dunkin et al., 2000; Polak et al., 2012; Wild and Gur, 2008) (but see Walter et al. (2010)). Here, the ability to engage in and successfully complete treatment relies heavily on higher-order cognitive processes. Indeed, leading treatment interventions for affective disorders, including PTSD and depression (e.g. cognitive behavioural therapy), rely heavily upon cognitive processing resources (e.g. working memory; attention) that are impacted negatively by these conditions.

A growing body of evidence points towards a relation between dissociative symptoms, including altered states of consciousness and identity fragmentation, and cognitive dysfunction in trauma-related psychiatric conditions. Specifically, dissociative symptoms have been linked to reduced attention, executive functioning, and memory performance in healthy individuals (Amrhein et al., 2008; Bergouignan et al., 2014; Brewin et al., 2013; Bruce et al., 2007; Freyd et al., 1998; Olsen and Beck, 2012), trauma-exposed individuals from general (Cromer et al., 2006) and military populations (Morgan et al., 2006), and in military and civilian psychiatric samples, including individuals with PTSD (Chae et al., 2011; De Bellis et al., 2013; DePrince et al., 2009; Kaplow et al., 2008; Minshew and D'Andrea, 2015; Rivera-Vélez et al., 2014; Roca et al., 2006; Twamley et al., 2009), BPD (Haaland and Landrø, 2009; Winter et al., 2015), MDD (Parlar et al., 2016), DID (Dorahy et al., 2006, 2005, 2002), and DPD (Guralnik et al., 2007, 2000). The nature of the relation between dissociation and cognitive dysfunction, however, remains poorly elucidated.

Our primary objective was therefore to review emerging evidence supporting the link between dissociative symptoms and cognitive dysfunction among healthy individuals and military and civilian samples with trauma-related neuropsychiatric conditions. In addition to surveying the results of studies involving participants with civilian *or* military-related PTSD, we examine findings across the broad range of psychiatric conditions that are associated with dissociative symptoms. Here, we begin by reviewing the evidence for PTSD-DS, as well as for considering dissociation as a transdiagnostic feature across psychiatric conditions. The evidence linking dissociation to cognitive dysfunction is then identified. We next introduce a neurobiological model of dissociation that

provides a partial explanation for the emergence of cognitive dysfunction in patients with dissociation. A secondary aim of this review is to propose a model linking dissociation and cognitive dysfunction to alterations in connectivity among three key brain networks, the default mode network (DMN), central executive network (CEN), and salience network (SN) that are consistently reported altered in psychiatric disorders. Accordingly, we propose a model where alterations among these key brain networks proposed to underlie psychopathology across psychiatric disorders (Menon, 2011) contribute to reduced cognitive functioning in individuals who experience high levels of dissociation. Specifically, reduced coupling between the networks responsible for orienting individuals to internal and external stimuli (SN), executive control ((CEN), and self-referential processing (DMN) may be a key neurobiological mechanism by which dissociation and cognitive dysfunction are linked. We also examine the role of brainstem regions, including the PAG, in an attempt to elucidate the relation between functional connectivity between neural regions involved in defensive responses and basic emotional processing and those implicated in higher emotional and cognitive brain networks.

2. Evidence for the dissociative subtype of PTSD

Over the past decade, a significant body of research has emerged pointing towards a dissociative subtype of PTSD, leading to the recent addition of this subtype to the DSM 5 (APA, 2013). Early work, including that of Putnam et al. (1996), indicated that a subset of individuals with PTSD experienced chronically higher levels of dissociation (see also Ginzburg et al., 2006). Building on this seminal work, Lanius et al. (2010) proposed a neurobiological model of PTSD-DS, characterized primarily by symptoms of derealization, depersonalization, and tonic hypoarousal that contrasted with the more typical symptoms of re-experiencing and hyperarousal that feature predominately in the majority of cases of PTSD. Subsequent latent class and confirmatory factor analyses have indicated that approximately 15–30% of individuals with PTSD experience symptoms of depersonalization and derealization that are consistent with the dissociative subtype (Armour et al., 2014; Bennett et al., 2015; Blevins et al., 2014; Frewen et al., 2015; Spiegel et al., 2013; Steuwe et al., 2012; Tsai et al., 2015; Wolf et al., 2012a, 2012b) Critically, increased disease severity (e.g., elevated risk of 12-month suicidality), earlier age of onset, and poorer functional outcomes have been reported in this subtype (Stein et al., 2013). Indeed, dissociative symptoms are associated with elevated rates of suicidal ideation, self-harm and multiple suicide attempts, with multiple suicide attempts significantly associated with dissociative status even after controlling for diagnoses such as PTSD and BPD (Foote et al., 2008).

2.1. Impact of dissociative symptoms on treatment response

Dissociative symptoms also appear predictive of treatment response. In a recent study, levels of dissociation present at baseline assessment following an acute trauma were the only significant predictor of treatment response at one and three months follow-up (Price et al., 2014). Indeed, among individuals with BPD, pre-treatment dissociative symptomatology predicted reduced symptom improvement following treatment with dialectical behavioural therapy (Kleindienst et al., 2011). In addition, a recent study indicated that whereas more frequent experiences of depersonalization and derealization were associated with non-response to treatment with eye movement desensitization reprocessing therapy, symptoms of avoidance, hyperarousal, and intrusion were not (Bae et al., 2016). These findings may be a consequence of detachment and avoidance, symptoms related to PTSD-DS, and associated reductions in cognitive and affective processing of trauma in its aftermath. Interestingly, Sar (2015) has proposed the concept of a “dissociative depression” where recovery from the dissociative aspects of the illness is associated with relief of depressive symptoms. This putative subtype of depression is thought to be treatment resistant, and is associated with an earlier onset, increased suicidality, and more frequent somatic complaints. Interestingly, a recent study investigating the efficacy of exposure therapy compared with present-centred therapy for female veterans and active duty members of the military with PTSD found a small but significant difference in treatment response (collapsed across treatment types) between those with versus without PTSD-DS. Here, individuals with the non-dissociative subtype of PTSD showed a 10 point greater improvement in CAPS score compared to individuals with PTSD-DS. However, the authors questioned the clinical significance of this difference and raised doubts that PTSD-DS is a contraindication for the use of exposure therapy in the treatment of PTSD (Wolf et al., 2015; see also Cloitre et al., 2012; Resick et al., 2012). Similar reports that dissociative symptoms do not impact negatively on treatment outcome have been made elsewhere (Hagenaars et al., 2010; Speckens et al., 2006). Importantly, in the Wolf et al. (2015), Hagenaars et al. (2010), and Speckens et al. (2006) studies, the authors focused on measures of trait dissociation, rather than state dissociation experienced at the time of treatment sessions, where trait dissociation refers to the tendency of the individual to dissociate over time, and state dissociation refers to acute dissociative experiences. Indeed, it is measures of state dissociation that have shown to interrupt emotional learning in individuals with BPD, a form of learning crucial for effective engagement in cognitive behavioural therapies (Ebner-Priemer et al., 2009). As such, future studies will be necessary to examine the effects of state dissociation directly before and *during* treatment sessions on treatment outcome.

2.2. Dissociative symptomatology and immune system functioning

Neurobiological studies of PTSD-DS continue to underscore the observation that depersonalization and derealization represent distinct responses from re-experiencing/hyperarousal reactivity in persons with PTSD (Lanius et al., 2010, 2012, 2006; Nicholson et al., 2015). Specifically, whereas reliving responses are thought to be mediated by a failure of prefrontal inhibition or top-down control of limbic regions, depersonalization and derealization responses are thought to be mediated by increased prefrontal inhibition of limbic regions. These findings are mirrored in the reactivity of the hypothalamic-pituitary-adrenal axis (HPA axis) among individuals with PTSD. Specifically, roughly half of female PTSD patients exposed to a Trier Social Stress Test (TSST) were classified as HPA-axis non-responders in that they did not exhibit an expected increase in cortisol levels in response to the TSST. Critically, HPA-axis non-responders also showed significantly higher levels of trauma-related dissociative symptoms as compared to PTSD HPA-axis responders. These findings represent the first empirical evidence of differences in HPA-axis reactivity among individuals with PTSD in relation to dissociative symptomatology (Zaba et al., 2015). Recent work by Quevedo et al. (2012) reported a flattening of the cortisol awakening response among pre- or early-pubertal youth who had been institutionalized (e.g., orphanages) early in life that was no longer apparent when mid-late pubertal post-institutionalized youth were tested. These findings are of interest given the well-established role of early childhood adverse experiences and disrupted attachment in the development of dissociative psychopathology (Carlson et al., 2009), while also suggesting that pre-pubertal alterations in HPA-axis function may be re-programmed through puberty (Quevedo

et al., 2012). By contrast, increased salivary cortisol in response to exposure to trauma-related material was noted in a sample of individuals with PTSD who had been raped and who described coping strategies including emotional shut-down and immobilization responses (processes that have been linked to dissociation) as compared to those with PTSD who had not been raped but had equivalent symptom severity (Gola et al., 2012). Additional research will be required to determine the directionality of the relation between cortisol and dissociative symptoms among individuals with PTSD. Notably, immune responses, including markers of inflammation, have also been implicated in PTSD (Passos et al., 2015).

Interestingly, among individuals with depression, higher levels of traumatic stress-related symptoms and somatoform dissociation have been related to higher levels of interleukin-6 (Bob et al., 2010). Similarly, among individuals with unipolar depression, tumour necrosis factor alpha has been related to dissociation, but not to depressive or PTSD symptoms (Bizik et al., 2011). Moreover, in a recent meta-analysis, multiple inflammatory biomarkers, including interleukin-6, tumour necrosis factor-alpha, and c-reactive protein, were associated with trauma exposure among a heterogeneous psychiatric sample (although dissociation was not investigated as a factor here) (Tursich et al., 2014). Critically, both elevated cortisol (Brown et al., 2013; Lara et al., 2013) and increased inflammatory markers (Bermejo et al., 2008; Guerreiro et al., 2007; Patanella et al., 2010; Peng et al., 2013; Yaffe et al., 2003) have been related to cognitive dysfunction in healthy controls and patient populations, highlighting another potential link between dissociative processes and cognitive dysfunction.

2.3. Neuroimaging and dissociative symptomatology

Recent work has begun to elucidate differences in functional connectivity within and between intrinsic connectivity networks (ICNs) in relation to dissociative symptomatology among individuals with PTSD. ICNs refer to brain networks made up of brain regions that are temporally and functionally connected. Three key ICNs, the central executive network (CEN), salience network (SN), and the defaultmode network (DMN), have been implicated in psychiatric disorders as well as in understanding higher cognitive function (Menon, 2011). The CEN consists of two main nodes, the dorsolateral prefrontal cortex (dlPFC) and the posterior parietal cortex (PPC), and is involved in the active maintenance and manipulation of information in working memory and executive functioning (Habas et al., 2009; Koechlin and Hyafil, 2007; Koechlin and Summerfield, 2007; Miller and Cohen, 2001; Petrides, 2005; Seeley et al., 2007). The SN is anchored by the dorsal anterior cingulate cortex (dACC) and the anterior insular cortex (AI), and is important for the detection, integration, and filtering of internal and external stimuli (Dosenbach et al., 2007; Lovero et al., 2009; Seeley et al., 2007; Sridharan et al., 2008). Finally, the DMN is comprised of cortical midline structures and the lateral parietal lobes, with anchors in the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC). In contrast to the CEN, the DMN is generally deactivated during cognitive tasks and is involved further in self-related processes, autobiographical memory, and social cognition (Amodio and Frith, 2006; Buckner et al., 2008; Greicius et al., 2003; Qin and Northoff, 2011; Raichle et al., 2001; Spreng et al., 2009).

Importantly, higher levels of dissociative symptoms were associated with greater connectivity of the dlPFC with the DMN among women with PTSD as a result of early life trauma (Bluhm et al., 2009), suggesting inappropriate recruitment of CEN brain regions to the DMN. Moreover, reduced connectivity between DMN regions (e.g., dorsal anterior and posterior DMN regions and ventromedial PFC and right perigenual ACC with DMN) as well as between the CEN and ventral anterior DMN, was associated with depersonalization/derealization symptoms among individuals with PTSD related to childhood trauma, suggesting reduced synchrony between and within brain networks. Recent work investing functional connectivity of ICNs during supra- and sub-liminal threat processing revealed increased functional connectivity of the ventrolateral PFC with the CEN as a function of dissociative subtype status among individuals with PTSD (Rabellino et al., 2015). Further research has identified heightened insular connectivity of the left basolateral amygdala complex among individuals with PTSD-DS compared to individuals with PTSD without the dissociative subtype, where higher symptoms of depersonalization and derealization were predictive of increased insular connectivity with the left basolateral amygdala (Nicholson et al., 2016), suggesting increased connectivity within the SN. Here, the authors posit that the basolateral amygdala may attenuate the activity of the anterior insula via GABA-ergic connections, leading to reduced arousal and interoceptive awareness, alertness, and emotional processing as seen in PTSD-DS (Nicholson et al., 2016).

In addition, Daniels et al., (2016) reported recently that patients with the PTSD-DS exhibited increased gray matter volume in the right precentral gyrus, a brain region involved in fear-related motor neurocircuitry (Williams et al., 2001). Daniels et al. (2016) also noted that increased volume in the right middle frontal gyrus, a region shown previously to contribute to downregulation of emotional arousal (Dorfel et al., 2014) was positively correlated with dissociative symptoms. Finally, compared to individuals with PTSD without the dissociative subtype, individuals with PTSD-DS show greater connectivity of the amygdala to prefrontal regions involved in emotion regulation (i.e., the bilateral basolateral amygdala (BLA) and left centromedial amygdalar (CMA) regions with the middle frontal gyrus and bilateral CMA with the medial frontal gyrus) and with regions involved in proprioception, consciousness, and awareness (i.e., the left BLA with the superior parietal lobe and cerebellar culmen and the left CMA to the dorsal posterior cingulate and precuneus) (Nicholson et al., 2015). These findings, along with those described above by Nicholson et al. (2016), indicate that altered connectivity of the amydala complex may be related to the distinct symptom and neurobiological profile of PTSD-DS. Thus, emerging work indicates that functional connectivity within and between ICNs may differentiate individuals with PTSD-DS from those with PTSD without the dissociative subtype. Taken together, the empirical evidence reviewed here favours recognition of PTSD-DS at the symptom, neurobiological, endocrine and immunological levels.

2.4. Dissociation transdiagnostically

2.4.1. Dissociation in anxiety disorders

Although a large body of evidence supports the relation between dissociative symptomatology and trauma-related disorders (Dalenberg and Carlson, 2012; Gershuny and Thayer, 1999; Lanius et al., 2012; Spiegel, 1984; Spiegel et al., 2013; Stein et al., 2013; Vermetten and Spiegel, 2014; Vermetten et al., 2007; Winter et al., 2015) there is also significant evidence of dissociation across a host of other psychiatric conditions that are less often considered trauma-related. Dissociative symptoms, specifically depersonalization/derealization, occur transdiagnostically, rather than representing disease-specific processes. For example, among anxiety disorders, symptoms of depersonalization are commonly experienced in in panic disorderand agoraphobia, and have been reported in social phobia (Mula et al., 2007). Interestingly, among a sample of individuals with panic disorder and other anxiety disorders (social phobia; generalized anxiety disorder; OCD; specific phobia), individuals who experienced symptoms of depersonalization had higher rates of comorbid depression and personality

disorder symptoms (Ball et al., 1997) Further, individuals with panic disorder and higher levels of depersonalization exhibited poorer functional outcomes and greater illness severity (Marquez et al., 2001). Similarly, both panic disorder and social phobia are frequently comorbid with depersonalization disorder (Simeon et al., 2003). Moreover, among individuals with bipolar I and II disorder, symptoms of depersonalization are associated with comorbid panic disorder (Mula et al., 2009). Additional studies reveal that dissociative symptoms are present in OCD and are correlated with increased disease severity (Belli et al., 2012; Rufer et al., 2006a), treatment non-compliance and reduced treatment effectiveness (Rufer et al., 2006b; Semiz et al., 2014). Belli et al. (2012) reported further that approximately 14% of a sample of individuals with OCD met criteria for a comorbid dissociative disorder. Indeed, it has been proposed that dissociative symptoms may constitute a specific subtype of OCD, where symptoms of checking and obsessive intrusions are the main features of the disorder (Watson et al., 2004).

2.4.2. Dissociation in mood disorders

Although less empirical work supports a relation between dissociative symptomatology and depression, depersonalization in MDD has been linked tentatively to a longer duration of depressive symptoms and a reduction in treatment efficacy (Nuller, 1982). In addition, a recent study reported that dissociative symptoms were present in individuals with both MDD and bipolar type II disorder, with higher levels of symptoms observed in patients with bipolar type II disorder (particularly on one item measuring identity fragmentation) and in patients who reported a cyclothymic temperament (Oedegaard et al., 2008). Similarly, in a recent factor analysis, Hariri et al., (2015) reported that approximately 20% of individuals with a bipolar disorder experience dissociative symptoms, including identity fragmentation, amnesia and depersonalization/derealization symptoms. Whereas all symptom dimensions were associated with an earlier age of illness onset, amnesia and depersonalization/derealization symptoms were associated with a longer illness duration. Finally, overall dissociative symptoms were associated with the presence of childhood trauma (Hariri et al., 2015).

Interestingly, in a recent study, 4.1% of women in a community sample were found to have a current major depressive episode involving a comorbid dissociative disorder (termed dissociative depression) that was associated with higher levels of suicidality and childhood sexual abuse than observed in non-dissociative depressed women (Sar et al., 2013). Recent work from our group has indicated that levels of dissociative symptoms are higher in trauma-exposed individuals with a primary diagnosis of MDD than in healthy controls (Parlar et al., 2016). Indeed, dissociative symptoms have been linked theoretically to the restricted range of emotional experience seen in depression (e.g., anhedonia), particularly given that emotional constriction has been identified as a facet of dissociative experiences (Briere et al., 2005). Finally, traumatic experiences are highly prevalent in mood and anxiety disorders, where in a recent sample of 2000 persons with mood and anxiety disorders, 91.2% of reported having experienced a potentially traumatic or bothersome life event (Spinhoven et al., 2014).

2.4.3. Dissociation in alcohol and substance disorders

Similarly, studies in alcohol and drug abuse/dependency populations report the presence of comorbid dissociative symptoms in these conditions (Evren et al., 2011, 2008, 2007; Tamar-Gurol et al., 2008). Specifically, among a sample of drug-dependent individuals, 26% had a comorbid dissociative disorder, predicted by past suicide attempts and childhood emotional abuse (Tamar-Gurol et al., 2008). One additional study reported that among individuals with alcohol use disorders, approximately 9% had a comorbid dissociative disorder (Evren et al., 2007). In a pattern similar to that reported in mood disorders, dissociative pathology has been associated with increased suicidality and past suicide attempts, childhood emotional and sexual abuse and neglect, self-harm behaviours, and increased severity of anxiety, depression and alcoholism-related symptoms (Evren et al., 2008, 2007).

2.4.4. Dissociation in psychotic-spectrum illness

Symptoms of dissociation also emerge in psychotic-spectrum illness, and voice hearing is increasingly recognized within the symptomatology of dissociative experiences. For example, in a sample of individuals with schizophrenia, approximately 15% were diagnosed with a comorbid dissociative disorder (Yu et al., 2010). The authors of this study and of the above studies in OCD populations acknowledge that exposure to traumatic experiences may contribute to the emergence of dissociative symptoms in OCD and schizophrenia (Belli, 2014; Belli et al., 2012; Rufer et al., 2006b; Semiz et al., 2014; Yu et al., 2010). It is also important to note the association between early psychological trauma histories and voice hearing where a recent review suggested that voice hearing in individuals with trauma-related disorders does not differ significantly from that observed in individuals with schizophrenia (Longden et al., 2012). Moreover, individuals with dissociative disorders were more likely to experience hearing voices before reaching the age of 18 and were more likely to experience hearing both child and adult voices in comparison to individuals with psychotic-spectrum disorders, who generally report hearing adult voices exclusively (Dorahy et al., 2009). Finally, in a sample of individuals with chronic PTSD, approximately half reported experiencing auditory hallucinations (AH); these individuals also experienced higher levels of pathological dissociation in comparison to participants who did not experience AH (Anketell et al., 2010). Indeed, a recent meta-analysis has confirmed a strong relation between voice hearing and the presence of dissociative symptoms (Pilton et al., 2015). Future research will be required, however, to disentangle the clinical and neurobiological factors that differentiate voice hearing associated with dissociative symptomatology and voice hearing related to psychotic disorders.

3. Evidence for the relation between dissociation and neuropsychological functioning

3.1. Dissociation and neuropsychological functioning in the general population

Table 1 provides a summary of research articles surveyed here that have examined the relation between dissociative symptoms and cognitive function indexed by cognitive domain and psychiatric condition. Dissociative tendencies are not isolated to psychiatric disorders but are also present in the general population (albeit to a lesser extent) (Kihlstrom et al., 1994; Ross et al., 1991). Here, a large body of evidence supports the relation between the presence of dissociative experiences and decrements in neuropsychological functioning. Both chronic dissociation and state dissociation have been associated with reduced performance on measures of attention, executive functioning, and memory (Amrhein et al., 2008; Brewin et al., 2013; Bruce et al., 2007; Giesbrecht et al., 2004; Olsen and Beck, 2012). In studies differentiating healthy individuals by levels of dissociative symptoms, or the extent to which individuals have dissociative experiences in their day-to-day lives, individuals higher in dissociation performed worse on tasks assessing executive functioning (Amrhein et al., 2008; Giesbrecht et al., 2004), divided attention (Olsen and Beck, 2012), verbal memory (Amrhein et al., 2008; Devilly et al., 2007),

episodic memory (Olsen and Beck, 2012) and working memory (Amrhein et al., 2008). Similarly, higher levels of dissociation are associated with worse performance on executive functioning tasks (Freyd et al., 1998), and are associated with greater self-reported difficulties in executive function (Bruce et al., 2007).

In contrast, a smaller number of studies have suggested that dissociative traits may enhance neuropsychological functioning among healthy individuals. For example, in two studies from the same group, individuals who scored higher in dissociation performed better on measures of verbal working memory span and on a n-back task (De Ruiter et al., 2004; Veltman et al., 2005). The authors of these studies suggest that dissociative tendencies may confer a unique information processing style that contributes to this enhanced performance. Similarly, DePrince and Freyd (2004, 2001) described a directed forgetting task where participants were instructed to attend to some words and forget others; under divided attention conditions, individuals higher in dissociation recalled fewer to-be-remembered trauma-related words but *more* to-be-remembered neutral words when asked to recall all presented words (DePrince and Freyd, 2004, 2001). Moreover, Deprince and Freyd (1999) reported that whereas high dissociators showed greater interference in a selective attention condition of the Stroop task compared to low dissociators, the opposite pattern held for a divided attention condition of the Stroop task (although this finding did not reach significance). These findings were not replicated in subsequent studies, however (Devilly et al., 2007; Giesbrecht and Merckelbach, 2009). Notably, in a recent study investigating state-based dissociation in healthy controls where dissociation was induced using a mirror-gazing protocol, higher levels of dissociation were associated with a shorter digit span (working memory) and greater deterioration in story recall following a delay (Brewin et al., 2013).

3.2. Dissociation and episodic memory in the general population

Dissociative responses may instantiate further symptoms of dissociative amnesia through episodic memory deficits associated with symptoms of depersonalization and derealization. The encoding of experiences in long-term memory requires a “sense of bodily self”, where events are experienced from the perspective of one's own body (Bergouignan et al., 2014). Accordingly, dissociative “out-of-body” experiences may interrupt the encoding and integration of environmental details into episodic memory. Indeed, in a recent key study of healthy individuals, participants underwent induction of out-of-body and in-body experiences while engaging in a simulated social interaction involving enactment of real-life events with an actor. One week later, participants showed significantly less episodic recall of events encoded during the out-of-body condition as compared to in-body experiences, including reduced spatial and temporal recall (Bergouignan et al., 2014). In a separate sample, the same authors reported contrasting patterns of recruitment of the left posterior hippocampus, with differential activation during retreival of out-of-body events as compared to in-body events experienced two weeks previously. Specifically, for in-body events, participants showed strong activation of the left posterior hippocampus during initial retrieval trials, with progressively less recruitment of this region for further trials. By contrast for out-of-body events, reduced initial recruitment of the left posterior hippocampus was observed, with *increasing* recruitment over further trials (e.g., following reproduction of the event). These findings demonstrate the necessity of sensory integration from an embodied perspective, or the experiencing of life events from within one's own body (rather than from an observer persepctive as seen in depersonalization), in the encoding of episodic or autobiographical memories, a process likely to be disrupted by dissociative processes both at the behavioural and neural level. Critically, these findings are consistent with evidence of disrupted episodic and autobiographical memory among individuals with high levels of pathological dissociation (e.g., Chae et al., 2011; Roca et al., 2006).

3.3. Dissociation and neuropsychological functioning among individuals exposed to trauma

The association between dissociation and cognitive performance has also been supported in studies of patients with trauma-related disorders and among trauma-exposed individuals. Here, pathological dissociation has been linked to neurocognitive vulnerabilities or impairments across various conditions. In one recent study of adults with PTSD stemming from childhood sexual abuse, impaired performance on indices of verbal and visual memory was strongly correlated with higher levels of dissociation (Rivera-Vélez et al., 2014). Similarly, among children with PTSD due to abuse or neglect, higher levels of dissociation were associated with worse performance on measures of attention (De Bellis et al., 2013). Among a community sample of children both dissociative symptoms and familial trauma-exposure status accounted for *unique* proportions of the variance in a model predicting executive functioning performance that also included, anxiety, socioeconomic status, and possible traumatic brain injury (DePrince et al., 2009). Moreover, among a sample of foster children, higher levels of trait dissociation were related to worse performance on measures of response inhibition and auditory attention (Cromer et al., 2006). In addition, Chae et al. (2011) reported that among traumatized children, trauma symptoms were associated with reduced accuracy on an interview measuring recall for a play activity that had occurred three days prior *only* among those who were identified as high dissociators. Another recent study indicated that the presence of dissociative symptoms immediately following disclosure of sexual abuse by children predicted parent-reported attentional dysfunction, as measured 8–36 months later. Here, PTSD symptoms were only indirectly related to attention dysfunction through their relation to dissociation (Kaplow et al., 2008). These findings are of particular relevance given that dissociation is understood as a psychobiological response to threat and danger that occurs in both children and adults (Dalenberg et al., 2012). Accordingly, disruptions in cognitive function as a result of dissociative symptoms arising from early traumatic experiences may continue to have detrimental impacts on the lives of impacted individuals through key developmental periods well into adulthood, as demonstrated by Rivera-Vélez et al.'s (2014) study . By contrast, in a study investigating neuropsychological dysfunction following a recent trauma, peritraumatic dissociation (dissociation that occurred *during* the event) was not associated with impaired performance on tasks assessing visuospatial memory and attention among individuals with high levels of PTSD symptoms (Brandes et al., 2002). Notably, these cognitive impairments were no longer significant when depressive symptoms were controlled for, a finding that may be accounted for by high collinearity (i.e., symptom overlap) between depressive and PTSD symptoms.

The impact of dissociation on cognitive functioning has also been examined in members of the military and in women who have experienced intimate partner violence (IPV). Specifically, recent work among active military personnel who were asked to complete a visual memory task under stressful conditions (i.e., after a mock interrogation in a mock prisoner of war camp) demonstrated that baseline state dissociation, state dissociation induced during a stressful task, and history of traumatic stress predicted reduced performance on the visual memory task (Morgan et al., 2006). Similarly, among veterans with PTSD, those with a comorbid dissociative disorder demonstrated greater deficits on

measures of attention, executive function, autobiographical memory, and verbal memory than those with PTSD alone (Roca et al., 2006). Finally, in studies of women with PTSD as a result of IPV or treatment-seeking women exposed to IPV, those with more severe dissociative symptoms performed worse on a task of reasoning (Twamley et al., 2009), and on a measure of explicit verbal memory for threat-related (but not trauma-related) stimuli (Minshew and D'Andrea, 2015).

Dissociative symptoms have been linked further to neuropsychological dysfunction in other trauma-related disorders, including BPD and dissociative disorders. For example, among individuals with BPD, pathological dissociation was associated with reduced functioning on measures of attention, verbal memory, working memory, and executive functioning relative to healthy control performance. Conversely, relative to healthy controls, individuals with BPD without pathological dissociation showed impairment on measures of executive functioning only (Haaland and Landrø, 2009) (but see Cloitre et al. (1996)). In a pattern similar to that found in healthy populations, state dissociation among individuals with BPD (induced using script-driven imagery of an autobiographical memory) was associated with reduced inhibitory control for emotional stimuli and a trend toward reduced verbal memory performance when compared to performance among individuals with BPD who did not undergo dissociation induction and who performed similarly to healthy controls (Winter et al., 2015). Similarly, Guralnik et al. (2007) found that higher levels of dissociative symptoms among individuals with depersonalization disorder were associated with slowed processing speed and heightened distractibility. Previous work from this group also revealed that lower levels of performance on measures of visuospatial functioning and verbal memory predicted DPD status (Guralnik et al., 2000). Similarly, reduced cognitive inhibition and slower processing speed has also been reported in individuals with DID in response to emotionally negative contexts (Dorahy et al., 2006, 2005, 2002). Finally, work from our group has identified a relation between dissociative symptoms (depersonalization and derealization) and cognitive performance in trauma-exposed individuals with MDD, where higher levels of derealization were related to worse performance on tasks measuring verbal and visual recollective memory and higher levels of depersonalization were associated with worse performance on tasks measuring cognitive flexibilityand sustained attention (Parlar et al., 2016).

3.4. Episodic memory in dissociative identity disorder

Recent work has pointed to the presence of autobiographical memory disturbance among individuals with DID, a disorder where an individual's sense of self is experienced as fragmented or divided into different "parts". For example, in one model, "emotional parts" (EPs) that have access to traumatic memories are differentiated from "apparently normal parts" (ANPs) that inhibit or avoid access to traumatic memories and thus enable daily life functioning (also referred to as the "trauma identity state" (TIS) and "neutral identity state" (NIS), respectively) (van der Hart et al., 2006', 2004). In comparison to the TIS, the NIS is thought to act as a protective state, avoiding access or response to traumatic memories (Reinders et al., 2006), a process that may render the NIS amnesic for these memories. Indeed, inter-identity amnesia is a clinical hallmark of DID (Bryant, 1995; Elzinga et al., 2003; Schlumpf et al., 2014; Reinders et al., 2012), yet mixed findings are reported in the literature when this association is investigated objectively. For example, in a directed forgetting experiment involving patients with DID who were able to alternate between identity states yet have no conscious awareness between states, Elzinga et al. (2003) reported intact cued recall of stimuli that were encoded in the same identity state as was present at encoding (e.g., no directed forgetting effect with participants recalling equal number of to-be-remembered and to-be-forgotten stimuli), but impaired cued recall when participants were in a different, amnestic, identity state than was present at encoding (e.g., directed forgetting effect with participants recalling fewer to-be-forgotten stimuli compared to-be-remembered stimuli). Conversely, other studies report a transfer of information between identity states, for both explicit verbal memory (Huntjens et al., 2007) and implicit procedural (Huntjens et al., 2005a) and recognition memory (Huntjens et al., 2012) assessments. Notably, two studies failed to find differences in memory transfer between identity states in DID patients and control participants simulating DID-like amnesia, rendering interpretation of these findings unequivocal (Huntjens et al., 2006, 2005b). Notably, a recent study reported reduced autobiographical memory specificity for emotionally-valenced events (i.e., overgeneral memory consisting of primarily semantic associates, extended memories (memories for extended time periods rather than specific events) and categorical memories (memories referring to a whole class of events)) similar to that seen in PTSD (Ono et al., 2016) among individuals with DID, regardless of their identity state (Huntjens et al., 2014) (but see also Barlow, 2011).

Recent studies have identified further differential patterns of psychobiological response to trauma-related memories when in a trauma identity state as compared to a neutral identity state. For example, Reinders et al. (2006) reported increased activation of brain areas involved in somatosensory processes and negative emotional states (e.g., insular cortex) when the trauma identity state was presented with a traumatic memory script as compared to a neutral memory script; no such difference was reported for the neutral identity state. Similarly, Reinders et al. (2014) reported differential patterns of brain activation in response to trauma-related script-driven imagery as compared to neutral scripts. Here, as compared to the trauma identity state, the neutral identity state showed increased activation of the prefrontal cortex in response to trauma scripts as compared to neutral scripts, and greater activation in posterior association areas, and hippocampal gyri in response to trauma scripts (demonstrating emotional overmodulation). By contrast, the trauma identity state showed increased activation of the amygdala and insula in response to trauma scripts as compared to neutral scripts, and greater dorsal striatum activation in response to trauma scripts when compared with the neutral identity state (emotional undermodulation) (Reinders et al., 2014). Notably, this pattern of brain activity is similar to that seen in patients with the PTSD-DS during presentation of trauma-related scripts (Lanius et al., 2010, 2012, 2006).

3.5. Preliminary work supporting the relation between neuropsychological function and dissociative symptoms in military trauma exposed individuals

Unpublished work from our group links further the presence of dissociative symptoms to cognitive dysfunction in military samples. We recruited twenty military-combat-exposed males through operational stress injury referrals made by military providers. Diagnosis of PTSD and symptom severity were determined using the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995). Fourteen participants had a current diagnosis of PTSD related to military trauma, three were in remission from PTSD, and three had no current or past diagnosis of PTSD and were considered resilient. Participants also completed self-report measures of depression, anxiety, and dissociative symptoms, as well as childhood trauma history. The Repeatable Battery of the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998) was used to determine participants' neuropsychological status,

measuring Immediate Memory (short-term memory), Visuospatial/Constructional, Language, Attention, and Delayed Memory.

Whereas no significant correlations were found between RBANS scores and CAPS, nor with the self-report indices of depression, anxiety, or childhood trauma history, the immediate memory subscale of the RBANS was significantly correlated with severity of dissociative symptoms, specifically, Multiscale Dissociation Inventory (MDI) (Briere, 2002) total scores ($\rho = -0.48$, $P = 0.031$), and scores on the disengagement ($\rho = -0.60$, $P = 0.006$), derealization/depersonalization ($\rho = -0.56$, $P = 0.01$), and memory impairment ($\rho = -0.47$, $P = 0.036$) subscales (see Table 2). These results indicate that higher levels of dissociative symptomalogy are associated with worse performance on a measure of short-term verbal memory. Critically, other factors, such as illness severity and level of trauma exposure putatively associated with cognitive dysfunction following trauma exposure showed no such relation. Taken together, these data suggest that dissociation contributes to impaired memory performance in military-trauma exposed populations.

3.6. Dissociative symptomatology and social cognition

Social cognition, involving the ability to use, encode, and store information about others that we gain from social interactions (Brothers, 1990; Adolphs, 2001), is disrupted across a host of psychiatric conditions, including schizophrenia (Savla et al., 2013), mood disorders (Cusi et al., 2010, 2011, 2013, 2012a, 2012b; McKinnon et al., 2010), borderline personality disorder (Domes et al., 2009), and PTSD (Nazarov et al., 2014, 2015; Parlar et al., 2014; Steuwe et al., 2015) Critically, alterations in social cognitive functions relying upon the joint contribution of cognitive and affective processing resources (McKinnon and Moscovitch, 2007; McKinnon et al., 2007) known to be disrupted in neuropsychiatric illness may contribute to the impairments in interpersonal functioning (e.g., relations with family and friends) seen in these conditions.

Recent work indicates that dissociation may contribute to deficits in social cognition among individuals with PTSD and schizophrenia. Specifically, in a recent study of women with PTSD stemming from childhood abuse, we found impaired performance on a theory of mind (ToM) task tapping the ability to identify kinship interactions (e.g., who is the parent and who is the child) and requiring participants to take the perspectives of others and understand their emotions, intentions, and behaviours. Critically, the degree of ToM impairment in this sample was also related to the severity of dissociative symptoms present, including disengagement, memory disturbance and identity dissociation (Nazarov et al., 2014). In the same study, slower response time on the Reading the Eyes in the Mind Task, a ToM task where participants are asked to discriminate complex emotions depicted through the eyes, was associated with heightened symptoms of dissociation, including disengagement, memory disturbance and identity dissociation (Nazarov et al., 2014). Similarly, in a related study involving the same sample, we found that reduced ability to recognize emotions conveyed through speech was associated with heightened symptoms of dissociation and greater severity of childhood abuse (Nazarov et al., 2015). These findings are consistent with a recent study among individuals with schizophrenia and schizoaffective disorder where dissociative symptoms were the strongest predictor of performance on an emotion recognition task, over and above the impact of positive and negative symptoms of schizophrenia, cognitive symptoms, symptoms of PTSD, and the impact of social desirability bias (Renard et al., 2012).

Interestingly, an individual's response to socially complex scenarios may vary with their dissociative state. Here, Frewen and Lanius (2015) describe the case of a male patient with high levels of dissociative symptoms who had experienced childhood sexual, physical, and emotional trauma. Interestingly, his responses to complex moral reasoning dilemmas, including whether or not a prescribed course of action was ethical and what course of action he might choose in response to the dilemma, varied radically from one week to the next. Moreover, on a task where he was required to interpret a social scenario, he reported amnesia for his response from the previous week upon being queried again at a second session (in line with inter-identity amnesia as discussed in Section 3.1). Notably, we did not find a relation between dissociation and moral reasoning performance in a sample of women with PTSD stemming from childhood abuse (Nazarov et al., submitted for publication). Nonetheless, this case study suggests that an individual's responses to social cognitive tasks may vary depending on the dissociative state present. Future work will be required to confirm this hypothesis.

3.7. Interim summary: neuropsychological function and dissociation

Table 1 provides a summary of studies that have examined the relation between dissociative symptoms and cognitive function indexed by cognitive domain and psychiatric condition. Among healthy controls, trauma-exposed individuals, and in trauma-related psychiatric populations both chronic and state dissociation have been associated with reduced performance in a wide variety of cognitive domains, including attention, executive functioning, working memory, immediate and delayed verbal and visual memory, autobiographical, and episodic memory. Although there is conflicting evidence from a number of studies suggesting enhanced cognitive performance among individuals higher in dissociation, these findings are constrained to indices of working memory and verbal memory performance (Cloitre et al., 1996; De Ruiter et al., 2004; Elzinga et al., 2007, 2000; Veltman et al., 2005). Here, it has been suggested that an enhanced ability to elaborate coupled with the ability to divide attention between multiple streams of information may improve working memory in highly dissociative individuals (De Ruiter et al., 2004; Elzinga et al., 2000). Taken together, however, the evidence in favour of the association between neuropsychological dysfunction and dissociative symptoms or traits among healthy controls and civilian or military trauma-related psychiatric populations appears stronger than that suggesting that dissociation confers a beneficial effect on neuropsychological functioning. Moreover, recent provocative work from our group has identified dissociation as the single clinical correlate of neuropsychological functioning (short-term memory) in a small sample of individuals exposed to military trauma.

Episodic memory also appears affected by dissociation, specifically among individuals with the most severe dissociative disorder, DID. Here, it has been suggested that trauma identity states are privy to trauma-related memories that their “normal” identity counterparts are not (Bryant, 1995; Elzinga et al., 2003; Reinders et al., 2012; Schlumpf et al., 2014). Although reports are mixed as to whether these subjective memory impairments hold when tested objectively (Elzinga et al., 2003; Huntjens et al., 2012, 2006, 2005a, 2005b), differences in psychophysiological and neural functioning between states when processing traumatic or emotional stimuli (e.g., Reinders et al., 2006, 2014) support the authenticity of DID patients’ subjective reports of autobiographical memory deficits. Moreover, these patients showovergeneral recall of autobiographical memories regardless of their identity state (Huntjens et al., 2014).

Importantly, the impact of dissociation on neuropsychological functioning does not appear limited to purely cognitive domains, but also extends to social cognition. Specifically, recent work from our group has identified a relation between reduced functioning

Table 1
Summary of studies examining the relation between dissociative symptoms and cognitive functioning separated by cognitive domain and psychiatric condition. Positive results denote studies supporting the relation between dissociative symptoms and cognitive dysfunction. Whereas negative results denote studies that do not support such a relation, mixed results provide some support for this relation.

Population	Study	*N*	Cognitive Domains	Positive Negative or Mixed Results	Relevant findings
Healthy Controls	Amrhein et al., 2008	17 High Dissociators, 17 Low Dissociators	VM, WM, EF	Positive	Poorer performance on measures of VM (story recall) and WM and increased perseveration among high dissociators.
	Bergouignan et al., 2014	32 HC	EM	Positive	Significantly reduced recall of episodic events encoded in an induced out-of-body condition compared to a within-body condition.
	Brewin et al., 2013	60 HC in study 1; 40 HC in study 2	VM, WM, Att, time perception	Positive	Participants who underwent experimentally induced dissociation had greater deterioration in VM between immediate and delayed recall in study 2 and worse performance on a digit span test (WM) in study 1 compared to participants who didn't undergo dissociation induction. State dissociation correlated negatively with an assessment of time perception and digit span in study 1 and delayed VM in study 2.
	Bruce et al., 2007	65 HC	WM, EF	Positive	Individuals with higher trait dissociation reported significantly more EF difficulties; no objective differences were found
	DePrince and Freyd, 1999	54 High Dissociators, 54 Low Dissociators	VM, EF	Mixed	Following a divided attention condition of the emotional Stroop task, high dissociators recalled more neutral and fewer emotional words as compared to low dissociators. High dissociators showed greater interference in a selective attention condition of the Stroop task compared to low dissociators. The opposite pattern held for a divided attention condition of the Stroop task (although this did not reach significance).
	DePrince and Freyd, 2001	28 High Dissociators, 28 Low Dissociators	VM	Mixed	In a divided attention directed forgetting task, high dissociators recalled fewer to be remembered trauma-related words and more neutral words compared to low dissociators, who showed the opposite pattern
	de Ruiter et al., 2004	119 HC	WM	Negative	High dissociative students had higher WM span than medium or low dissociative students.
	Devilly et al., 2007	23 Low Dissociators, 14 High Dissociators in study 1; 20 Low Dissociators, 17 High Dissociators in study 2	VM	Positive	No significant interaction effects between high and low dissociators were found on a directed forgetting task in either a divided or selective attentioncondition in regard to stimulus type (trauma vs. neutral words) in either study. Lower overall word recall and increased commission errors on a recognition task was noted in high dissociators compared to low dissociators in study 1 but not study 2
	Freyd et al., 1998	40 High Dissociators, 40 Low Dissociators	EF	Positive	High dissociators showed increased interference on a task of response inhibition (Stroop) in comparison to low dissociators
	Giesbrecht et al., 2004	185 HC	EF	Positive	Disruptions in EF were related to higher trait dissociation
	Giesbrecht and Merckelbach, 2009	22 High Dissociators, 24 Low Dissociators in study 1; 38 High Dissociators, 28 Low Dissociaters in study 2	VM, EF	Positive	No significant differences emerged between groups on verbal recall tasks, all participants recalled more emotional than neutral words in a directed forgetting task in experiment 2. High dissociators showed a trendtoward longer response times on an emotional stroop task under divided and selective attention conditions and for both trauma and neutral words compared to low dissociators in study 1.
	Olsen and Beck, 2012	27 High Dissociators, 27 Low Dissociators	DA, IM, EM	Positive	Using stimuli presented in a trauma film and a neutral film, high dissociators demonstrated reduced scores on a DA task during the trauma film, reduced IM for trauma-related stimuli, and greater EM detail for neutral stimuli but lower EM detail for trauma stimuli in comparison to low dissociators
	Veltman et al., 2005	11 High Dissociators, 10 Low Dissociators	WM	Negative	High dissociators performed significantly better on WM tasks
Trauma-Exposed	Cromer et al., 2006	24 Foster-care Children	EF, Att	Positive	Significant relation between dissociation and response inhibition and attention tasks among children in foster care
	DePrince et al., 2009	110 Children	IQ, WM, EF, Att	Positive	Guardian reported dissociative symptoms and familial trauma exposure status accounted for unique proportions of the variance in the prediction of EF, while socioeconomic status and dissociation made unique contributions in the prediction of IQ.
	DePrince and Freyd, 2004	21 High Dissociators; 24 Low Dissociators	VM	Mixed	High dissociators had significantly more trauma exposure than low dissociators.In a directed forgetting task, high dissociators recalled fewer trauma-related and more neutral to-be-remembered words compared to low dissociators under divided attention conditions. High dissociatiors recognized more neutral and fewer trauma to-be-forgotten words under divided attention conditions than low dissociators.

	Morgan et al., 2006	184 Military Personnel	VSM	Positive	Baseline and stress-induced dissociation and history of traumatic stress predicted performance on a VSM task under stressful conditions
PTSD	Chae et al., 2011	322 Abused Children	IQ, Lang, VM, VSM, EM	Positive	Trauma symptoms were associated with reduced EM (e.g., higher suggestibility) among children reporting high levels of dissociative symptomatology, but not those reporting low levels of dissociative symptomatology
	De Bellis et al., 2013	38 maltreated children, 60 maltreated+PTSD, 104 HC	Att, Lang, VS, VM, VSM, EF	Positive	Dissociative symptoms were negatively correlated with Att scores among maltreated children with and without PTSD.
	Kaplow et al., 2008	156 (56 at follow up) Abused Children	Att	Positive	Sexually abused children who reported dissociative symptoms upon disclosure of abuse demonstrated higher parent-reported attentional problems 8–36 months later
	Minshew and D'Andrea, 2015	27 PTSD	IM, VM	Positive	Higher dissociative symptoms were related to reduced explicit recall of threat-related (but not trauma-related) word stimuli
	Rivera-Vélez et al., 2014	12 PTSD, 12 HC	VM, WM, EF, Att	Positive	Dissociative symptoms negatively correlated with VM and VSM measures
	Roca et al., 2006	10 PTSD+dissociative disorder, 17 PTSD only	IQ, Att, VM, VSM, EF, AM	Positive	Greater deficits on measures of Att, AM, EF, and VM in PTSD+dissociative disorder group compared to PTSD only group
	Twamley et al., 2009	55 PTSD, 20 HC	EF, VS, VM	Positive	Among the PTSD group, those with greater levels of dissociative symptoms performed worse on a reasoning task (EF).
	Brandes et al., 2002	14 PTSD, 14 Trauma-exposed control	WM, EM, Att, VSM	Negative	Group differences in performance on measure of VSM and Att remained significant after controlling for peri-traumatic dissociation.
MDD	Parlar et al., 2016	23 MDD, 20 HC	VSM, VM, PS, EF, Att	Positive	Among a sample of trauma exposed individuals with MDD, higher levels of derealization symptoms were associated with reduced VSM and VM and higher levels of depersonalization symptoms were associated with reduced performance on a measure of PS and EF and a measure of sustained attention.
BPD	Cloitre et al., 1996	24 BPD + childhood abuse, 24 BPD only, 24 HC	VM	Negative	Dissociative symptomatology was positively correlated with recall for "to-be-remembered" words in a directed forgetting task.
	Haaland and Landrø, 2009	10 BPD + pathological dissociation, 20 BPD no pathological dissociation, 30 HC	Att, WM, EF, VM, VSM, IQ	Positive	BPD+pathological dissociation was related to worse performance on measures of Att, VM, WM, VSM, IQ, and EF compared to controls. BPD without pathological dissociation performed worse only on measures of EF compared with controls. The BPD+dissociation group showed worse performance on IQ, EF, WM, and VM than BPD without dissociation. Significant correlation between dissociative symptoms and Att and VM scores in the BPD samples were found.
	Winter et al., 2015	37 BPD, 19 HC	EF, VM	Positive	Dissociation induction was associated with reduced EF (inhibitory control) in an emotional Stroop task among BPD patients for emotional stimuli and a trend toward reduced free recall for presented words among the BPD+dissociation induction group compared to the BPD control group (no dissociation induction). The BPD control group performed similarly to controls on both measures.
DID	Elzinga et al., 2007	13 DID, 14 HC	WM	Negative	Smaller decline in WM performance (n-back task) with increased task load in DID patients as compared to HCs.
	Dorahy et al., 2005	11 DID, 11 MDD, 11 HC	EF	Positive	Reduced cognitive inhibition in DID group in an emotionally negative context and a significant correlation between response speed to negative stimuli and dissociative symptoms was reported
	Dorahy et al., 2006	12 DID, 12 GAD, 12 HC	EF, Att	Positive	Reduced cognitive inhibition in an anxiety provoking (emotionally negative) context compared to a neutral context in DID group
	Dorahy et al., 2002	20 DID, 20 HC, 20 MDD	EF	Positive	An absence of cognitive inhibition (negative priming effect) in a DID and in the psychiatric comparison group (MDD) was noted. Slowed response time was noted in the DID group compared to the HC group. A second study, with a subsample from the first study confirmed the findings of study 1 and reported slowed response time in the DID group compared to both the HC and MDD groups.. Dissociative symptomatology was associated with reduced cognitive inhibition in the second study.
DPD	Guralnik et al., 2000	15 DPD, 15 HC	IQ, VM, VSM, EF, VS, Att	Positive	DPD patients performed worse on measures of VM, VSM, VS, and Att as compared to HCs. VS and VM functioning predicted membership in the DPD group. DPD patients demonstrated greater recall for emotional words presented in an emotional Stroop task than HC, where DPD patients did not display greater interference effects.
	Guralnik et al., 2007	21 DPD, 17 HC	IQ, PS, VM, VSM, WM, Att	Positive	Dissociative symptoms in the DPD group were negatively correlated with IQ, PS, and selective attention scores. The DPD group performed worse on measures of PS, immediate VM and immediate VSM as compared to HCs
Dissociative Disorder	Elzinga et al., 2000	18 Low Dissociator HC, 17 High Dissociator HC in study 1; 20 High Dissociator HC, 23 Low Dissociator HC, 14 Dissociative	VM	Negative	Study 1: No significant difference between groups on directed forgetting. Study 2: Patients and high dissociative controls completed more stem words with target words in a word

Table 1 (*continued*)

Population	Study	*N*	Cognitive Domains	Positive Negative or Mixed Results	Relevant findings
(Not Specified)	Disorder patients in study 2				completion memory test following a directed forgetting task compared to low dissociative controls. High dissociative controls and patients showed less directed forgetting than low dissociative controls (i.e., an inability to purposefully forget target words), particularly for sex-related words.

HC = Healthy Controls; PTSD = Post-traumatic Stress Disorder; MDD = Major Depressive Disorder; BPD = Borderline Personality Disorder, DID = Dissociative Identity Disorder, DPD = Depersonalization Disorder, GAD = Generalized Anxiety Disorder.
IQ = Intelligence.
VM = Verbal Memory.
WM = Working Memory.
EM = Episodic Memory.
AM = Autobiographical Memory.
IM = Implicit Memory.
VSM = Visuospatial Memory.
VS = Visuospatial Functioning.
EF = Executive Function; including response inhibition, perseveration, rule learning.
PS = Processing Speed.
Lang = Language.
Att = Attention.
DA = Divided Attention.

on measures of prosody and theory of mind and higher levels of dissociative symptomatology among women with PTSD (Nazarov et al., 2015, 2014). These findings are similar to those reported among individuals with schizophrenia-spectrum disorders (Renard et al., 2012). Poor social or interpersonal functioning is a hallmark of many psychiatric disorders, including PTSD (Charuvastra and Cloitre, 2008; Lanius et al., 2011; Olatunji et al., 2007), mood disorders (Romera et al., 2010; Wells et al., 1989), and schizophrenia (Couture, 2006; Fett et al., 2011) and is associated with reduced treatment efficacy (Sotsky et al., 1991). As such, identifying factors related to deficits in social cognition may help to target treatment approaches related to interpersonal and social functioning, thereby improving functional outcomes.

A number of authors suggest that dissociation contributes to reduced cognitive functioning as the result of its interference with the integration of perceptual and other forms of incoming information (e.g., Kaplow et al., 2008). For example, Dorahy (2006) has described a *dissociative processing style* associated with a learned strategy for dealing with perceived or actual threat. Here, individuals may redirect awareness away from threatening stimuli or fail to integrate multiple streams of encoded information following a traumatic event. Although this processing style may be protective in the face of a traumatic event or during its aftermath, it may become maladaptive if adopted as a general processing strategy, thus leading to reductions in neuropsychological function among individuals who experience high levels of dissociation. Indeed, cognitive functions (e.g., cognitive control) and dissociation may depend on shared processing resources, thus competing for these resources when simultaneously activated, and leading to the disruption of cognitive operations (e.g., attention, memory). Despite this apparent link between dissociation and reduced neuropsychological functioning, the biological underpinnings of this relation remain largely unexplored.

Importantly, the majority of studies reviewed here focus on *trait* dissociation rather than *state* dissociation. Critically, measures of trait dissociation demonstrate good test-retest reliability (Bernstein and Putnam, 1986; Dell, 2006; Dubester and Braun, 1995). Given that dissociative states are transient, however, one might expect cognitive functioning in individuals with these symptoms to change as a function of their dissociative state. Indeed, studies investigating neuropsychological functioning following induction of dissociative states have revealed reduced functioning on measures of executive functioning and verbal memory among BPD patients (Winter et al., 2015), and on measures of episodic memory (Bergouignan et al., 2014) among healthy individuals. Moreover, strikingly different responses to a task assessing moral reasoning in an individual with high levels of dissociative symptomatology from one week to the next were reported by our group, in addition to amnesia for the individual's previous response (Frewen and Lanius, 2015). These results suggest that in addition to the deleterious impact of chronic or trait dissociation on cognitive functioning, state dissociation might also impact negatively on cognitive functioning. As such, future studies should examine neuropsychological functioning as a function of state dissociation.

4. Neurobiological model of dissociation

Neurobiological models linking trauma exposure to the development of dissociation provide one explanatory mechanism for cognitive dysfunction in individuals with dissociation, where the presence of dissociative states in humans exposed to trauma have been linked to more primitive animal defensive responses. Here, the defence cascade model of dissociation proposes that state dissociation occurs on a continuum (Nijenhuis et al., 1998; Schauer

Table 2
Results of correlational analysis between RBANS scores and clinical variables including PTSD symptom severity, anxiety and depressive symptoms, trauma exposure, and dissociation in a sample of military combat-exposed individuals.

Clinical Measure	r or ρ	RBANS total	RBANS immediate memory	RBANS visuospatial/ constructional	RBANS language	RBANS attention	RBANS delayed memory
CAPS (Previous Month)	r	0.13	−0.29	0.36	−0.26	0.21	0.17
BAI	r	0.06	0.001	0.18	−0.27	0.09	0.03
BDI	r	0.26	−0.05	0.35	−0.19	0.38	0.19
CTQ (Total)	ρ	0.14	0.44	−0.02	0.09	−0.14	0.18
MDI (Total)	ρ	−0.11	**−0.48***	0.07	−0.01	0.20	−0.23
Disengagement	ρ	−0.13	**−0.60****	0.17	−0.11	0.17	−0.23
Depersonalization/ Derealization	ρ	−0.23	**−0.56***	−0.03	−0.06	0.12	−0.33
Emotional Constriction	ρ	−0.06	−0.28	−0.02	0.11	0.15	−0.11
Memory Impairment	ρ	−0.05	**−0.47***	0.19	0.08	0.16	−0.21
Identity Dissociation	ρ	−0.23	−0.29	−0.22	−0.36	−0.01	−0.16

* $P < 0.05$.
** $P < 0.01$.

and Elbert, 2010). Such phylogenetically old states of arousal are mediated by a common neural pathway involving the periaqueductal gray (PAG), hypothalamus, amygdala, and sympathetic and vagal nuclei (Kozlowska et al., 2015; Lanius et al., 2014) (see Figs. 1 and 2). In this model, initial responses to confrontation with threat are thought to be accompanied by an orienting response characterized by bradycardia and inhibition of the startle response (Schauer and Elbert, 2010). Importantly, threat-related stimuli are first processed via the superior colliculus (through direct projection from the retina), a midbrain structure closely linked to the periaqueductal gray (PAG) (see below), that plays a crucial role in spatial attention, orienting and target selection prior to processing at the cortical level (Lanius et al., 2014; Merker, 2007; Panskepp, 1998). Flight or fight follows, characterized by prolonged discharge of the sympathetic division of the autonomic nervous system, leading to a generalized sympathetic response including increased heart rate and vasoconstriction of peripheral blood vessels (Schauer and Elbert, 2010), as well as activation of the adrenal medulla to release catecholamines (e.g., noradrenaline amplifying the sympathetic response (Porges, 2011)). Concomitant activation of the lateral PAG via direct projection from the amygdala and limbic forebrain activates motor patterns of fight or flight (Carrive, 1993; Keay and Bandler, 2001; Kozlowska et al., 2015; LeDoux et al., 1988; Rizvi et al., 1991). At the same time, cortical loops in the basal ganglia and cerebellum are activated to modulate basic motor patterns consistent with context and defence strategies (Kozlowska et al., 2015; Lanius et al., 2014). Notably, the fight or flight response involves non-opioid (endocannabinoid-mediated) analgesia evoked by the lateral PAG (Keay and Bandler, 2001; Kozlowska et al., 2015). Critically, in cases where the organism determines it has little to no chance of survival, unresponsive immobility or death feigning may occur in an attempt to decrease predator interest, which may lead to tonic or collapsed immobility (Kozlowska et al., 2015; Schauer and Elbert, 2010). This type of response is initiated through tonic immobility, where activation of tactile sensory, proprioceptive and visceral afferents are coupled with fear (i.e., when an animal is struggling with a predator). Here, higher-order judgment is not involved, but rather, these processes rely on phylogenetically old regions of the brain (such as the ventrolateral (VLPAG)) and occur in organisms without a highly developed cerebral cortex, such as insects and birds (Gallup and Rager, 1996). The VLPAG receives signals from muscle and visceral tissues via the dorsal horn of the spinal cord and the parabrachial and vagal sensory nuclei, triggering tonic immobility (Kozlowska et al., 2015). The VLPAG acts as a brake for the lateral PAG, inhibiting fight-or-flight motor patterns. Withdrawal of sympathetic activity and activation of parasympathetic activity occur as the organism becomes increasingly unresponsive to sensory stimulation, including pain, representing the beginning of functional sensory deafferentation at the level of the cortico-sensory pathways (e.g., reduced integration of auditory, visual, proprioceptive, and somatosensory information from the thalamus to cortical sensory processing areas), thereby providing a means of modulating or shutting down overwhelming sensory information, and mimicking death or “death-feigning” ensues (Schauer and Elbert, 2010). Withdrawal of sympathetic activation and increased parasympathetic activation is associated further with vasodilation and a precipitous drop in heart rate and blood pressure, a pattern mimicked in vasovagal syncope (or fainting) (Fenton et al., 2000).

Similarly, the polyvagal theory (Porges, 2011, 2003, 2001) details three response systems related to the autonomic nervous system, where the vagal complex of the parasympathetic nervous system is divided into two branches, the dorsal vagal complex (DVC) and ventral vagal complex (VVC) that work in concert with the sympathetic nervous system, depending on the environmental context. Specifically, the VVC is involved social communication, calming, self-soothing, and bonding, is inhibitory to the sympathetic nervous system and HPA-axis activity via the “vagal brake”, and includes myelinated pathways that originate in the nucleus ambiguous. This system is active when the organism deems the environment to be safe. In contrast, in threatening situations, the vagal brake may be released, leading to discharge of the sympathetic nervous system and initiation of fight or flight patterns. Porges (2011, 2003, 2001) also describes immobilization, or death feigning responses that occur when fight or flight is not an option (e.g., under life-threatening circumstances). These responses are mediated by the DVC, which is the most phylogenetically old system and is comprised of unmeyelinated fibres that originate in the dorsal motor nucleus of the vagus and provide inhibitory input to the sinoatrial node of the heart (the pacemaker).When upregulated, the DVC may lead to immobilization, bradycardia, apnoea and cardiac arrest. Critically, whereas the dorsal motor nucleus is in close communication with the VLPAG, a critical component of immobility or shut-down responses described above, the sympathetic nervous system communicates with the lateral PAG and thus carries out motor patterns of fight or flight (Porges, 2007).

Notably, thalamic pathways may play a central role in shut-down or immobility responses, where they are involved in the relay of sensory information from the periphery to the cerebral cortex (Kandel et al., 2000) and in the regulation of arousal (Schiff, 2008). Accordingly, Schauer and Elbert (2010) suggest that regulation of thalamic activity may allow an organism to shut down peripheral sensory mechanisms in order to enter a state of collapsed immobility. Collapsed immobility is mediated by the same

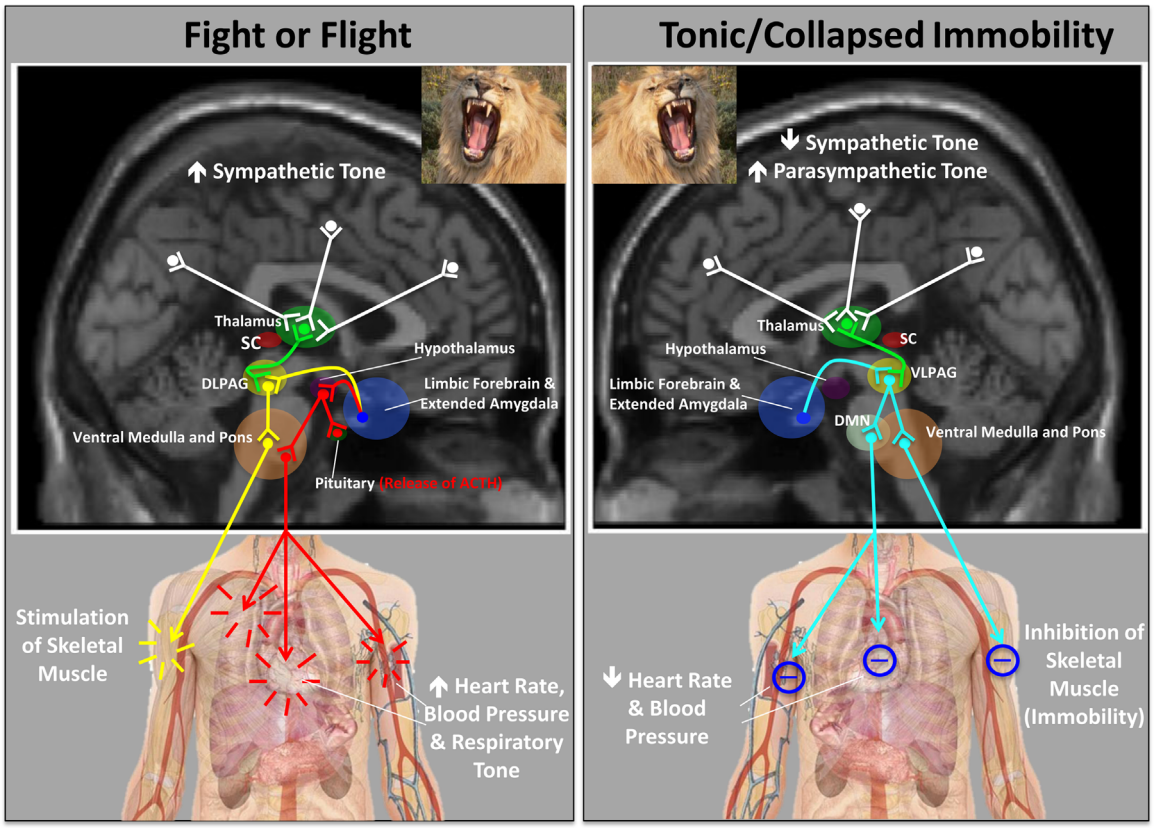

Fig. 1. This figure is based on ideas presented in Kozlowska et al. (2015). Responses to a stressful stimulus (e.g., the tiger) as in animal models are represented here as they might appear in the human brain. Fight or flight response: Information from the limbic forebrain and amygdala mediate somatomotor activation (yellow pathway) via the lateral periaqueductal gray (LPAG) leading to downstream activation of skeletal muscles via premotor centres in the pons and medulla. Autonomic activation (red pathway) via the sympathetic nervous system is mediated by the hypothalamus leading to increased heart rate and vascular resistance via the pons and medulla, while activation of the pituitary causes a release of ACTH and downstream cortisol with concomitant increased sympathetic tone. Tonic/collapsed immobility: Information from the limbic forebrain and amygdala activates the ventrolateral periaqueductal gray (VLPAG), which acts as a break for the LPAG, leading to reduced sympathetic tone. Activation of the vagal pathway from the dorsal motor nucleus (DMN) in the brainstem opposes sympathetic activation. Downstream projections of the VLPAG via the ventral medulla mediate immobility. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

neural networks as tonic immobility, however, para-sympathetically mediated bradycardia leads to hypoxia, disrupting signals from the brain stem that maintain muscle tone and leading to compromised consciousness (Kozlowska et al., 2015). Opioid-mediated analgesia is activated in these states via the PAG and the rostral ventromedial medulla pain circuit (Kozlowska et al., 2015). Finally, in extreme situations, a final stage of response may be mediated by a shut-down of peripheral vagal activity and a vaso-vagal response leading to fainting or flaccid immobility (Schauer and Elbert, 2010) (see Figs. 1 and 2). Notably, although these responses occur during acute stress or trauma exposure, they also continue post-trauma among individuals with trauma-related psychopathology in response to trauma-related cues in the internal or external environment, thus representing learned processes and a continuation of defensive posturing normally observed under threat. Here, Kozlowska et al. (2015) described defensive mind-body states as fixed action patterns that are repeated or reactivated by environmental triggers, including motor patterns, autonomic responses and opioid mediated analgesia (e.g., van der Kolk, 2001).

Accordingly, functional sensory deafferentation mediated by reduced integration of sensory information via the thalamus to the cortex may underlie symptoms of depersonalization and derealization, given that these pathways are central to cohesive perceptual and sensory experiences, and thus embodiment of conscious experience. In the case of individuals with the PTSD-DS, functional sensory deafferentation may be maintained, despite the absence of overt threat. Specifically, Schauer and Elbert (2010) describe re-enactment of defence stages, including tonic and collapsed immobility, in response to internal (e.g., intrusion symptoms) or external environmental trauma cues. Here, associated decrements in attention and arousal would be expected to give rise to progressive cognitive dysfunction and result in diminished availability of cognitive resources. It is important here to consider the role of autonomic arousal in cognition. Stress-cognition relationships have been conceptualized as an inverted u-shaped curve, where increasing levels of arousal are thought to lead to enhanced cognitive performance to some optimal level, after which increased arousal may have deleterious effects on cognition, as in the Yerkes-Dodson Law (Cohen, 2011; Yerkes and Dodson, 1908). More recent conceptualizations integrate dimensions such as task difficulty, cognitive appraisal and individual coping mechanisms into this model (Deffenbacher, 1994). Moreover, recent work has confirmed that acute stress impairs performance on tasks requiring higher-order cognitive resources (e.g., executive functioning) with associated reductions in prefrontal cortex activation (e.g., dlPFC) (Arnsten, 2009). Indeed, high levels of catecholamine release (e.g., dopamine and noradrenaline), which also follow an inverted u-shaped curve in response to stress, appears to lead to reduced neuronal firing in the prefrontal cortex (Arnsten, 2009).

Among individuals with PTSD, the thalamus may also play a key role in the interplay between dissociative symptoms and cognitive functioning where altered thalamic sensory processing is postulated to underlie or enable dissociative symptoms (Krystal et al., 1998; Lanius et al., 2014). Indeed, the thalamus is crucial to the integration of sensory information in the cortex, amygdala, and

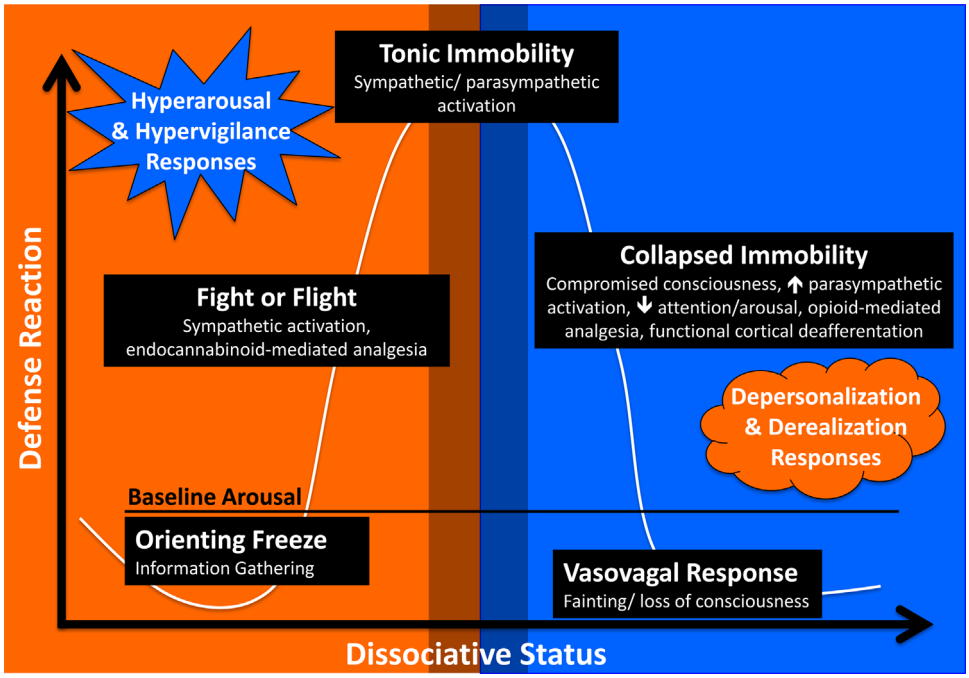

Fig. 2. Adapted with permission *Zeitschrift für Psychologie/Journal of Psychology*2010; Vol. 218(2):109–127, p. 111 ©2010 Hogrefe Publishing, www.hogrefe.com. Illustration of the defence cascade model demonstrating dissociative states occur on a continuum along with the defence reaction adopted by the organism following confrontation by threatening stimuli. During the hyperarousal/hypervigilance stage (marked in orange), an initial orienting freezing response facilitates information gathering (accompanied by bradycardia). This is followed by fight or flight (accompanied by sympathetic activation and endocannabinoid-mediated analgesia) (da Silva et al., 2012; Keay and Bandler, 2001), then tonic immobility, mediated both by sympathetic and parasympathetic activation leading into the dissociative response (dark shaded area in centre of image), when chance of survival is deemed low. On the dissociative side of the continuum (marked in blue), collapsed immobility occurs, consisting of compromised consciousness, increased parasympathetic activation, decreased attention and arousal, decreased muscle tension, and opioid-mediated analgesia (Kozlowska et al., 2015). In extreme situations, a vasovagal response may occur, leading to fainting or loss of consciousness. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

hippocampus (Amaral and Cowan, 1980; Kandel et al., 2000; Krystal et al., 1998; McCormick, 1992; Turner and Herkenham, 1991). Critically, among healthy populations, dissociative states may occur during exposure to very high or very low levels of sensory stimulation (Krystal, 1988; Krystal et al., 1998). Krystal et al. (1998) suggest that the role of the thalamus in trauma-related and possibly dissociative processes is supported by the presence of receptors for neurotransmitters previously implicated in the induction of post-traumatic (e.g., flashbacks) and dissociative symptoms in thalamic networks, including the noradrenergic (Buzsáki et al., 1991; McCormick and Wang, 1991) and glutamatergic receptors (McCormick, 1992). Indeed, whereas responses to trauma have been linked to the noradrenergic system (Bremner et al., 1996a, 1996b; Krystal et al., 1989), ketamine (a glutamate (NMDA) receptor antagonist) has been shown to induce detachment and withdrawal as well as sensory distortions and illusions (Krystal et al., 1994). Krystal et al. (1998) further link alterations in sensory processing via the thalamus and dissociative states with attentional changes, where they cite work reporting alterations in reported locus of attention (e.g., to peripheral sensory stimuli or internal mental processes) among dissociated individuals (Carlson and Putnam, 1989). Taken together, Krystal et al. (1998) hypothesize that extensive activation of monoamine systems under conditions or stress (e.g., dissociation) may lead to interference with, rather than enhancement of, sensory processing.

4.1. Neuroimaging findings supporting neurobiological model of dissociation

More recent work has indicates that individuals with hyperarousal and flashback/reliving show less activation of the thalamus as compared to those with depersonalization/derealization responses during responses to trauma scripts (Lanius et al., 2006). As such, the nature of the relation between thalamic activity and dissociative symptomatology remains an important focus of future research. Notably, in keeping with this model, D'Andrea et al. (2013) recently described two patterns of psychophysiological response to startle probes among trauma-exposed individuals with PTSD symptomatology. Specifically, participants who reported state dissociation after startle, had a PTSD diagnosis, and varied exposure to trauma, showed initial reduced heart rate acceleration and reduced skin conductance (that remained low throughout the task), while also exhibiting decreasing heart rate deceleration with concomitant increasing heart rate acceleration as the task progressed. Conversely, participants who did not meet criteria for PTSD, had lower trauma exposure (e.g., later in life, single trauma) and who did not demonstrate state dissociation in response to startle showed decreased heart rate acceleration and skin conductance as the task continued along with stable heart rate deceleration. D'Andrea et al. (2013) postulate that the response pattern seen in the high-trauma, dissociative group-represents activation of a shut-down of defensive responses, where the individual engages in passive immobilization and withdrawal of resources. These findings are consistent with previous reports of an absence of heart-rate increase in response to traumatic scripts among patients with PTSD and comorbid dissociative symptoms (Lanius et al., 2002), and of depressed skin conductance and heart rate when recalling a trauma among rape victims high in peri-traumatic dissociation (Griffin et al., 1997). Moreover, in a recent study, Sack et al. (2012) reported reduced heart-rate reactivity and attenuated reductions in parasympathetic cardiac activity in response to a trauma script among individuals reporting high levels of acute dissociative symptoms as compared

to those reporting low dissociative symptoms. Finally, in a large scale study including 1461 military veterans, a logistic regression model for predicting current PTSD status that included baseline heart rate, heart rate in response to trauma-related audio-visual cues, and electromyogram and skin conductance response to trauma scripts was successful in identifying two thirds of participants (Keane et al., 1998). Here, it is possible that the remaining one third of participants with PTSD were not characterized by heightened physiological arousal in response to trauma stimuli, a pattern similar to that seen in PTSD-DS. Finally, heightened parasympathetic activity, as seen in tonic and collapsed immobility, may be associated with reduced sensory perception, where among healthy males, higher pain sensitivity was associated with *lower* parasympathetic activity (Koenig et al., 2015). Further work is required to determine whether heightened parasympathetic activity is associated with reduced sensory perception among healthy individuals.

Among individuals with PTSD, neurobiological evidence points to differing patterns of neural activation among individuals who exhibit hyperarousal or re-experiencing reactivity (similar to the "fight or flight" response (see Figs. 1 and 2)) in comparison to those who experience dissociative symptomatology (similar to unresponsive immobility, as above) (Bremner, 1999; Lanius et al., 2010, 2012, 2006, 2002). Specifically, functional neuroimaging studies indicate that individuals who reported re-experiencing a traumatic memory in response to script provocation with concomitant psychophysiological hyperarousal exhibit reduced activation in the medial prefrontal and rostral anterior cingulate cortex, accompanied by increased amygdala reactivity. These reliving responses are therefore thought to be mediated by a failure of prefrontal inhibition or top-down control of limbic regions. By contrast, individuals who reported symptoms of depersonalization and derealization (without concomittant psychophysiological hypoarousal) showed increased activation in the rostral anterior cingulate cortex and the medial prefrontal cortex, suggesting that depersonalization/derealization responses are mediated by midline prefrontal inhibition of the limbic regions (Frewen and Lanius, 2006; Lanius et al., 2010, 2012).

4.2. Opioid-mediated contributions to neurobiological model of dissociation

As noted by Kozlowska et al. (2015), dissociative responses (i.e., tonic collapsed immobility (see Figs. 1 and 2)) are associated with opioid-mediated analgesia via the PAG and ventromedial medulla pain circuit, where opioids are involved in triggering immobility (Fanselow, 1986; Makino et al., 2000), suppressing vocal responses to threat (Lanius et al., 2014), and down-regulation of the hypothalamic mediated sympathetic responses to stress (Drolet et al., 2001). Opioid receptors are present in high volumes in the thalamus (Henriksen and Willoch, 2008), and opioids have been linked to sensory perception, including pain and non-pain related somatosensory perception (Mueller et al., 2010) and physiological arousal, two key roles of thalamic nuclei. Accordingly, we posit that opioid-mediated alterations in thalamic activity may underlie, in part, the altered sensory integration and arousal levels associated with states of collapsed immobility and dissociative symptoms. Indeed, stressful situations elicit the release of endogenous opioids, as is seen in stress-induced analgesia (van der Kolk et al., 1989) and endogenous opioid secretion following exposure to trauma-related stimuli has been reported among individuals with PTSD, whose self-reported responses included emotional blunting (van der Kolk, 2001). Further, a study measuring endogenous β-endorphin secretion in the cerebrospinal fluid of combat veterans with PTSD reported significantly higher levels of β-endorphin in the PTSD group compared with controls and a *negative* correlation between β-endorphin levels and PTSD intrusion and avoidant symptoms (Baker et al., 1997). Although not assessed in this study, the inverse relation between intrusion and avoidant symptoms and plasma β-endorphin levels may be related to an opioid-mediated vulnerability to dissociative states. Moreover, exposure to trauma-related stimuli induces a naloxone (opioid antagonist) reversible increase in pain threshold among individuals with PTSD (Pitman et al., 1990). Finally, a handful of studies report successful reductions in dissociative symptoms, including depersonalization, following treatment with opioid-receptor antagonists (e.g., naloxone and naltrexone) among individuals with depersonalization disorder (Nuller et al., 2001; Simeon and Knutelska, 2005), and BPD (Bohus et al., 1999; Schmahl et al., 2012; but see Philipsen et al., 2004). Future work should aim to identify whether stress-induced analgesia or the presence of endogenous opioids among individuals with PTSD is related specifically to symptoms associated with the dissociative subtype, including depersonalization and derealization. Moreover, additional study is required to determine whether reductions in pain sensitivity, as seen in highly dissociative individuals (Bekrater-Bodmann et al., 2015; Ludascher et al., 2007; Schmahl et al., 2014), are subserved by the endogenous opioid system.

Opioid receptors are present throughout the cortex and limbic system (Le Merrer et al., 2009) and opioids have been implicated in memory disturbance in the animal literature (Itoh et al., 1994; Ma et al., 2007; Ukai et al., 1997; Zhu et al., 2011). Specifically, treatment with opioid agonists have been reported to interfere with acquisition (Spain and Newsom, 1991; Zhu et al., 2011) and retrieval (Zhu et al., 2011) of spatial memories, and to disrupt working memory (Itoh et al., 1994), avoidance learning (Aguilar et al., 1998; Ukai et al., 1997; Zarrindast and Rezayof, 2004), and spatial recognition memory (Ma et al., 2007). Importantly, opioid receptor antagonists appear to reverse the effects of opioid agonists (Ukai et al., 1997; Zhu et al., 2011), and even facilitate memory performance (Canli et al., 1990; Gallagher et al., 1983). These findings are mirrored in human populations, where treatment with naltrexone (opioid receptor antagonist) improved recognition memory following stress induction by physiologically arousing stimuli as compared to a matched placebo condition (KatzenPerez et al., 2001). Among individuals receiving opioid treatment for pain management in cancer, opioid use has also been associated with reduced performance on measures of reaction time, attention, and episodic memory, related to initial dosing or dose increases (Kurita et al., 2009; Lawlor, 2002). Similar findings have been reported among individuals with chronic pain, where those using opioid-analgesics for pain management showed greater impairment on tests of spatial memory, cognitive flexibility, and working memory (Schiltenwolf et al., 2014) (but see Hojsted et al. (2012)).

Critically, not only do opioids interfere with memory acquisition and retrieval, but they also interfere with hippocampal neurogenesis, where chronic administration of morphine leads to reduced hippocampal neurogenesis and cell proliferation (Eisch et al., 2000; Kahn et al., 2005; Mandyam et al., 2004). By contrast, mice who were knocked out for the mu opioid receptor showed *enhanced* neurogenesis as evidenced by increased number of hippocampal progenitor cells and increased volume and neuron number in the dentate gyrus (Harburg et al., 2007). These findings were mirrored in a recent study among individuals with PTSD with and without comorbid DID, where the authors reported smaller global and subfield hippocampal volume among the PTSD-DID group and smaller subfield hippocampal volume correlated with dissociative symptoms in both PTSD groups (Chalavi et al., 2015) (but see Nardo et al., 2013). Moreover, a study by Liberzon et al. (2007) revealed alterations in central mu-opioid receptor binding following psychological trauma, where men with combat-

related PTSD and combat-trauma-exposed men without PTSD demonstrated lower mu-opioid receptor binding in the extended amygdala/ventral pallidum, thalamus, nucleus accumbens, insula, dorsal ACC, and mPFC, but higher mu-opioid receptor binding in the oribitofrontal cortex (with even higher binding among trauma-exposed controls) and subgenual ACC relative to controls. In addition, the PTSD group showed reduced binding in the rostral ACC relative to both control groups. Critically, the up-regulation of mu-opioid receptors in the orbitofrontal cortex as a function of military trauma exposure may contribute to the effects of endogenous opioids on cognitive functioning among individuals with PTSD-DS. Future work should aim to identify differences in opioid receptor availability and binding in individuals with PTSD-DS as compared to those with PTSD.

Taken together, functional sensory deafferentation at the level of the cortico-sensory pathways may contribute further to patterns of cognitive dysfunction in patients with high levels of dissociation. Here, the development and maintenance of functional sensory deafferentation may limit access to cortical processing resources including those required for memory encoding and retrieval, attention and executive functioning. Moreover, poor integration of sensory experiences would be expected to contribute further to deficits in most aspects of cognitive functioning where sensory input is requisite to the majority of cognitive control operations. Concomitant activation of the endogenous opioid system during states of thalamic-mediated sensory deafferentation and collapsed immobility or dissociation may further compromise cognitive functioning through opioid-mediated memory disturbances and reduced neurogenesis and neuroplasticity (see Fig. 3).

4.3. *Altered brain connectivity among trauma exposed populations: a potential link between dissociative status and cognitive dysfunction*

As outlined above, emerging evidence points to a link between dissociative symptoms and alterations in resting-state functional connectivity within and between these neural networks and other brain regions among trauma-related psychiatric populations. For example, among women with PTSD as a result of early life trauma, higher levels of dissociation were associated with increased connectivity of the dlPFC (a main node of the CEN) with the DMN (Bluhm et al., 2009). In addition, in women with BPD and a history of trauma, increased levels of dissociative symptoms were associated with increased functional connectivity of the amygdala (which has been associated with the SN (Seeley et al., 2007)) with the dlPFC (Krause-Utz et al., 2014a). An additional study of the same population revealed that higher levels of state dissociation were associated with increased connectivity of the amygdala with the right ACC, right thalamus, and left insula when confronted with negative stimuli in an emotional working memory task where prolonged reaction times were also observed (Krause-Utz et al., 2014b). A related study showed increased activity in limbic brain regions, including the amygdala, hippocampus, insula, and ACC during performance on the same task, however, higher levels of state dissociation present at the beginning of the experiment correlated negatively with activation in the amygdala, hippocampus, ACC, and insula, suggesting reduced emotional responding among individuals experiencing dissociation (Krause-Utz et al., 2012). In another study investigating functional connectivity of the DMN in women with BPD, women who scored higher on a measure of trait dissociation showed attenuated fMRI signal decrease in the DMN in response to a “painful” stimulus during a functional imaging task where participants were instructed to rate the severity of pain (Kluetsch et al., 2012). The authors of this study suggest that a reduced ability to down-regulate DMN activity during task performance may contribute to the poor attentional and inhibitory control observed in this population.

Interestingly, a related study identified distinct connectivity profiles for specific symptom profiles of PTSD. Specifically, in women with chronic PTSD as a result of childhood maltreatment, higher severity of hyperarousal was associated with reduced connectivity within the salience network. In addition, increased severity of dissociative symptoms (specifically, depersonalization and derealization) was associated with reduced connectivity of the right perigenual ACC and the ventromedial prefrontal cortex with the DMN and reduced connectivity between the dorsal anterior and posterior regions of the DMN and between the CEN and ventral anterior DMN (Tursich et al., 2015). Rabellino et al. (2015) also examined functional connectivity of ICNs during supra- and sub-liminal threat processing among individuals with PTSD and PTSD-DS (Rabellino et al., 2015). Here, the authors reported altered functional connectivity within the CEN, particularly, increased functional connectivity of the vlPFC with the CEN in PTSD-DS as compared to individuals with PTSD without the dissociative subtype. The authors speculate that this hyperconnectivity within the CEN may contribute to the increased top-down inhibition of limbic regions seen in PTSD-DS (Frewen and Lanius, 2006; Lanius et al., 2010, 2012). Finally, in unpublished preliminary work from our group, we found anterior insular uncoupling with the right CEN as a function of increasing levels of dissociation, including depersonalization and derealization, as measured by the well-validated MDI.

The limited but provocative evidence for the impact of dissociative symptomatology on functional connectivity in ICNs sheds light on potential neural mechanisms underlying the association between dissociation and cognitive dysfunction. Specifically, the three aforementioned ICNs are linked inextricably to higher-order cognitive processes (Menon, 2011), and alterations in these networks as a function of dissociative symptomatology would be expected to impact negatively on cognitive functioning in these populations. For example, inappropriate recruitment of regions associated with the network involved in self-referential thinking (DMN) to tasks relying on the CEN, as was reported by Bluhm et al. (2009), may interfere with cognitive function through disruption of the focused activity of the CEN. Increased connectivity of brain regions involved in emotional processing (e.g., the amygdala) with those central to higher-order cognitive processes (e.g., dlPFC) (Krause-Utz et al., 2014a) may also disrupt activity in these regions resulting in cognitive dysfunction (e.g., in working memory). Moreover, hyperconnectivity within regions associated with the SN (e.g., amygdala with right ACC and left insula) in response to emotionally negative stimuli in association with state dissociation may result in a reduced ability to attend to external cognitive demands in the face of competing emotional stimuli (Krause-Utz et al., 2014b). Critically, hyperconnectivity within the CEN may result in increased top-down inhibition of limbic regions thought to underlie depersonalization/derealization symptoms and reduce the availability of the CEN for use in other cognitively demanding tasks (Rabellino et al., 2015). Finally, our preliminary, unpublished work, points towards uncoupling of the anterior insula with the CEN as underlying, in part, the impact of dissociative symptoms on cognitive dysfunction given the critical role of the anterior insula in coordinating switching between the CEN and DMN (Goulden et al., 2014; Sridharan et al., 2008) and thus engaging appropriate attentional, working memory, and higher cognitive processes.

Indeed, this proposal is supported by work from our group indicating that individuals with PTSD inappropriately recruited task-negative brain networks (e.g., increased functional connectivity within the DMN) during a working memory task, as compared to healthy controls who demonstrated increased functional connectivity of DMN nodes with areas associated with the SN and CEN, suggesting a greater ability to down-regulate the

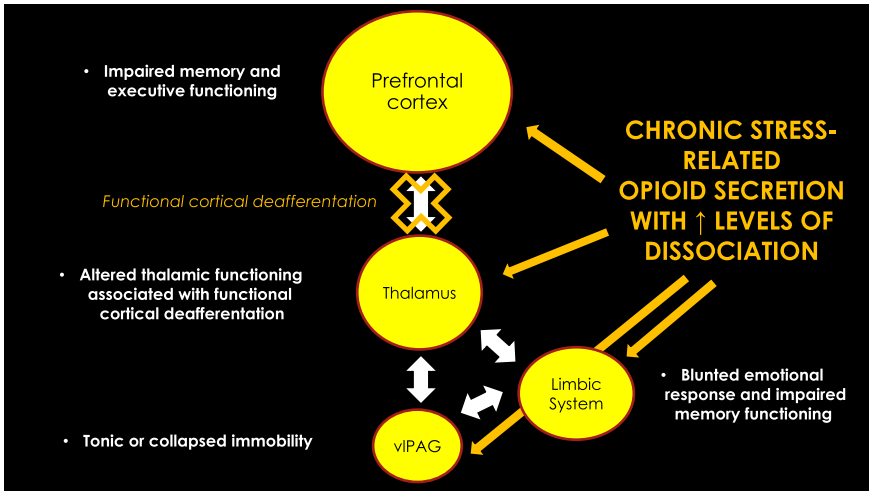

Fig. 3. During states of tonic or collapsed immobility, stress-induced release of endogenous opioids via the periaqueductal gray (PAG) triggers immobility (Fanselow et al., 1986), suppression of vocal responses (Kalin et al., 1998), and down-regulation of the hypothalamic-mediated sympathetic response (e.g., fight or flight) (Drolet et al., 2001). Here, endogenous opioids are postulated to mediate functional cortical deafferentation, given the diffuse distribution of opioid receptors throughout the limbic system, thalamus, and prefrontal cortex (Le Merrer et al., 2009), and their influence on sensory perception (Mueller et al., 2010), arousal, memory (e.g., Zhu et al., 2011) and executive functioning (Kurita et al., 2009; Lawlor, 2002). Specifically, we hypothesize that endogenous opioids may mediate functional sensory deafferentation via their actions on thalamic nuclei, leading to reduced sensory integration with associated decrements in memory and executive functioning at the level of the prefrontal cortex. Endogeneous opiods are also postulated to be involved in blunted emotional responses and impaired memory functioning via reciprocal projections between the vlPAG and limbic structures, and between thalamic nuclei and limbic structures.

DMN and to activate the CEN and SN during working memory tasks among controls (Daniels et al., 2010). Here, a reduced ability to appropriately recruit task-positive networks (CEN) for tasks requiring working memory may be associated with an inability to switch between the DMN and CEN and thus reduced cognitive capacity. Although Daniels et al. (2010) did not directly assess the relation between these alterations and dissociative symptomatology, these findings coupled with those of Bluhm et al. (2009) suggest that inappropriate recruitment of task-negative brain networks and a potential inability to switch between networks in response to cognitively demanding tasks in association with dissociative symptomatology may be a significant contributor to cognitive dysfunction the populations discussed here. Taken together, aberrant functional connectivity within and between these networks, and reduced ability to appropriately activate task-relevant networks, may be related to reduced cognitive control in association with dissociative symptoms. Future work should aim to confirm the relation of dissociative symptomatology and the ability to switch between task positive, and task negative networks.

5. General discussion and conclusions

Dissociation has been understood as a response to traumatic experiences since the beginning of the 20th century (Janet, 1901), however, its' associations with increased disease severity, poor prognosis, and reduced functional and cognitive outcomes has only begun to be elucidated over the past several decades. More recent work points to a relation between altered patterns of brain activity and connectivity and the presence of dissociative symptoms.

The concept of a PTSD-DS is supported by evidence from studies using latent class and confirmatory factor analysis, where approximately 15–30% of individuals with PTSD can be classified as belonging to a dissociative subtype featuring symptoms of depersonalization and derealization (Armour et al., 2014; Blevins et al., 2014; Frewen et al., 2015; Spiegel et al., 2013; Steuwe et al., 2012; Tsai et al., 2015; Wolf et al., 2012a, 2012b). Evidence of distinct patterns of neural activity (Frewen and Lanius, 2006; Lanius et al., 2010, 2012) and of distinct endocrine (Gola et al., 2012; Zaba et al., 2015) response systems among individuals with PTSD with high levels of dissociative symptomatology provide further evidence for the dissociative subtype. Importantly, dissociation is not a phenomenon linked exclusively to trauma-related disorders, including PTSD, BPD (Meares, 2012; Vermetten and Spiegal, 2014; Winter et al., 2015) and dissociative disorders (Brand et al., 2012). Instead, dissociative symptomatology or comorbid dissociative disorders are observed across numerous psychiatric conditions, including panic disorder, agoraphobia and social phobia (Ball et al., 1997; Marquez et al., 2001; Mula et al., 2007; Simeon et al., 2003), MDD (Nuller, 1982; Parlar et al., 2016), bipolar disorder (Oedegaard et al., 2008), OCD (Belli, 2014; Belli et al., 2012; Rufer et al., 2006a, 2006b), and schizophrenia (Yu et al., 2010). Transdiagnostically, heighted dissociative symptoms are associated with increased disease severity (Belli et al., 2012; Rufer et al., 2006a; Stein et al., 2013), elevated risk of suicidality (Stein et al., 2013), the presence of suicidal ideation and self-harm behaviours (Foote et al., 2008), increased pain threshold, reduced pain perception (related to self-harm behaviours) (Bekrater-Bodmann et al., 2015; Ludascher et al., 2007; Schmahl et al., 2014) poor functional outcomes (Stein et al., 2013), and reduced treatment efficacy (Bae et al., 2016; Kleindienst et al., 2011; Price et al., 2014; Rufer et al., 2006b; Semiz et al., 2014; Spitzer et al., 2007).

In this review, we have identified a significant body of evidence linking dissociative symptomatology to reduced neuropsychological functioning among healthy individuals and individuals suffering from psychiatric conditions. Specifically, evidence linking heightened dissociative symptoms to reduced performance on measures assessing a broad range of cognitive functions including executive functioning, attention, working memory, immediate and delayed verbal and visual memory, autobiographical memory, and episodic memory has been reported among controls and in trauma-related psychiatric populations (Amrhein et al., 2008; Brewin et al., 2013; Bruce et al., 2007; Giesbrecht et al., 2004; Olsen and Beck, 2012) [but see (Cloitre et al., 1996; De Ruiter et al., 2004; Elzinga et al., 2007, 2000; Veltman et al., 2005) and Section 3.3 above for a discussion of conflicting evidence]. Preliminary work from our group, reviewed here, also provides evidence for a link between dissociative symptomatology and poor short-term

memory performance among military trauma-exposed individuals. Differing patterns of episodic memory recall between dissociative states have been reported in individuals with DID (Bryant, 1995; Elzinga et al., 2003; Schlumpf et al., 2014; Reinders et al., 2012), as has overgeneral autobiographical memory recall (Huntjens et al., 2014; Barlow, 2011). Moreover, evidence for the relation between neuropsychological dysfunction and dissociative symptomatology extends beyond purely cognitive domains to the realm of social cognition, where higher levels of dissociation have been related to worse performance on measures of prosody (Nazarov et al., 2015), theory of mind (Nazarov et al., 2014), and emotion recognition (Renard et al., 2012).

Although dissociation may be confused with attention, it is critical to consider dissociation an orthogonal construct, with dissociable neural and behavioural correlates reviewed here. In cases where dissociative processes and cognitive operations compete for shared processing resources and their underlying neural networks, disruption of each may occur, with the evidence reviewed pointing sharply to disruption across multiple cognitive domains. Future work will be required to deconstruct carefully the concept of dissociation to identify specifically those facets of its presentation most likely to be associated with disruption of cognitive performance (see Lanius et al., 2012 and Bryant, 2007 for a discussion). Another critical avenue for future work will be to compare directly the impact of state dissociation at the time of testing to the impact of trait dissociation on cognitive dysfunction, as well as to compare directly heterogeneous samples of trauma-exposed individuals (e.g., military versus civilian trauma). Despite knowledge of a clear relation between dissocaitive symptomatology and cognitive function, however, the neurobiological mechanisms underlying this association remain to be unidentified.

Here, we propose further a neurobiological model linking altered states of arousal, as in the defence cascade model of dissociation (Schauer and Elbert, 2010; Kozlowska et al., 2015), to reduced cognitive functioning among highly dissociative individuals (see Fig. 3). Specifically, we argue that functional sensory deafferentation at the level of cortico-sensory pathways may, in part, underlie cognitive dysfunction among highly dissociative individuals, where reduced integration of sensory experiences, mediated by thalamic relay sites, may interfere with cognitive functioning in these populations. We have also identified the deleterious effect of opioid-mediated analgesia on memory and point to the impact of opiod dysregulation on neurogenesis and neuroplasticity. Future work will be necessary to elucidate further the relation between opioids, cognitive dysfunction, and thalamic sensory integration among individuals with dissociative disorders via prospective, longitudinal methodology.

We present a model linking altered connectivity within, and between, three resting state ICNs crucial for higher-order cognitive processes and consistently linked to psychopathology (Menon, 2011), with dissociative symptomatology in PTSD and other trauma-related disorders. Specifically, we posit that dissociative psychopathology and cognitive dysfunction may be linked through inappropriate recruitment of brain regions associated with task positive networks (CEN) to task negative networks (DMN) (as reported by Bluhm et al. (2009)). Critically, preliminary work from our group has identified insular uncoupling with the CEN and DMN as a function of dissociative symptomatology that we hypothesize to be associated with a reduced ability to switch between task-positive and task-negative networks in response to external demands. Moreover, increased connectivity of emotionally-driven brain regions to nodes of the CEN as a function of dissociative symptomatology (Krause-Utz et al., 2014a) may lead to reduced cognitive capacity. Finally, hyperconnectivity within the SN in response to emotionally negative stimuli (Krause-Utz et al., 2014b) may be related to a reduced ability to attend to external cognitive demands in the face of competing emotional demands leading to impaired cognitive function. Future work will be necessary to determine directly the relation between connectivity within and between these resting state networks, dissociative symptomatology, and cognitive dysfunction in order to confirm these hypotheses. Specifically, it will be critical to investigate the ability of individuals displaying dissociative symptomatology to recruit task-positive networks in cognitively demanding environments and their ability to utilize key nodes of the SN (e.g., the anterior insula) in order to achieve fluid switching.

Further work will also be required to gain an understanding of the longitudinal course of dissociative symptomatology following exposure to trauma, leading up to the development of illness and following individuals through the course of their illness. Here, it remains unknown how dissociative symptoms present longitudinally, and further, how underlying neural, cognitive, and physiological changes may mediate the increased disease severity, treatment resistance, and functional impairment observed among individuals with high levels of dissociative psychopathology. Specifically, prospective, longitudinal studies should investigate the development of cognitive dysfunction among individuals with dissociative psychopathology in relation to the functioning of the CEN, SN, and DMN. Given the association between dissociative symptomatology and reduced treatment efficacy (Bae et al., 2016; Price et al., 2014; Rufer et al., 2006b; Semiz et al., 2014), future work should also focus on identifying treatments aimed specifically at individuals with high levels of dissociative symptoms. It will be of particular importance to investigate the efficacy of treatments aimed at reducing cognitive dysfunction, such as cognitive remediation therapies that have proven effective in other psychiatric populations (Bowie et al., 2013; Deckersbach et al., 2010; Elgamal et al., 2007; Kurtz, 2012; Wykes et al., 2011) but have scarcely been applied to trauma-related psychiatric disorders. It will also be crucial to identify interventions that target simultaneously dissociative symptomatology and cognitive dysfunction and seek to remediate the functioning of large-scale brain networks. As reviewed by our group, these interventions may include cognitive remediation, mindfulness, and neurofeedback-based approaches (Lanius et al., 2015). In addition, it will be important to determine more precisely the impact of dissociation on treatment effectiveness, where conflicting reports have arisen as to the impact of dissociation on treatment (e.g., Bae et al., 2016; Price et al., 2014; Wolf et al., 2015), and other reports where no difference is noted between highly dissociative and low-dissociative individuals. Notably, these studies have focused on the impact of dissociation measured retrospectively, including symptom frequency and severity over the last month, indices that are prone to measurement error and non-specificity. It will be necessary here to determine the impact of *state* dissociation experienced immediately preceding and during therapy. Finally, we have reviewed the transdiagnostic nature of dissociative symptomatology. On balance, it is imperative that clinicians and researchers assess adequately dissociation and consider carefully treatment approaches given the detrimental effects of this symptom profile on disease severity, treatment efficacy and cognitive functioning, with associated decrements in real-world, functional outcomes.

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