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Review article

Stress response in dissociation and conversion disorders: A systematic review

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ABSTRACT

Dissociative disorders (DD) and conversion disorders (CD) are frequent in general and psychiatric populations. Some evidence suggest that the hypothalamic-pituitary axis (HPA) and autonomic nervous system (ANS) are dysregulated in both disorders. We carried out a systematic review of the literature to summarize the existing knowledge on the stress response, via HPA and/or ANS, in patients with DD, CD, or dissociative symptoms. We systematically searched Medline and Web of Science using the Medical Subject Headings related to stress axis, CD, DD, and dissociative symptoms following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Results suggest that in participants without psychiatric history, high cortisol secretion is related to high dissociation scores. Conversely the stress system might be blunted in patients with post-traumatic stress disorder who develop dissociative symptoms. Stress response changes seem to be associated with the emergence and persistence of dissociative and conversion disorders. Hence, monitoring the stress response and examining closely the history of stress exposure in DD and CD should be encouraged in future larger studies.

1. Introduction

Dissociative Disorders (DD) are characterized by a disruption or discontinuity in the normal integration of consciousness, memory, identity, or perception of the environment. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) lists different DD subtypes, such as dissociative identity disorder, amnesia or depersonalization/derealization symptoms, and other specified DD including trance states (American Psychiatric Association, 2013; Spiegel et al., 2011). Conversion Disorders (CD) are defined by the presence of neurological symptoms without identifiable organic origin and include psychogenic non-epileptic seizures (PNES). They are not consistent with neuroanatomical pathways.

CD and DD are frequent in general and clinical populations. CD prevalence ranges from 5 % (American Psychiatric Association, 2013) to 30 % among neurology outpatients (Stone et al., 2009a). DD prevalence is about 10 % in psychiatric settings, and varies between 1.7 % and 18 % in the community (Sar, 2011). Dissociative symptoms are often observed in other psychiatric disorders (Lyssenko et al., 2018), such as post-traumatic stress disorder (PTSD) (Ullah et al., 2018), personality disorders (Ross et al., 2014), and mood disorders (Chatterjee et al., 2018; Montant et al., 2014). Importantly, psychiatric patients with DD or high scores in the Dissociative Experiences Scale (DES) are also more likely to attempt suicide or engage in non-suicidal self-injury compared with patients free from DD (Calati et al., 2017).

Major diagnostic classifications have placed DD and CD into the same disease category (ICD-11) (World Health Organization, 2019) but also as two distinct disorders (DSM-5) (Brown et al., 2007). In DSM-5, CD sits within the larger category "Somatic symptoms and related disorders" which replaced DSM-IV's "Somatoform disorders" and is characterized by the prominence of somatic symptoms associated with significant distress, and excessive thoughts, feelings, or behaviors

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related to them. Despite the diverging classifications, DD and CD seem highly comorbid. A 31 % prevalence of DD evaluated with the Dissociative Experience Scale (DES) has been reported among individuals with CD, and dissociative identity disorder represented the most common diagnosis in the DD group (Tezcan et al., 2003). A two-year follow-up study of 38 consecutive outpatients in Sivas City, Turkey, demonstrated that 47.4 % of individuals diagnosed as having CD previously had DD (Sar et al. 2004). Kuloglu et al. (2003) reported a lower comorbidity rate (9 % of individuals), but the authors did not specifically assess DD as in the two other studies (Kuloglu et al., 2003).

The dysregulation of the stress response seems to be an important factor associated with both disorders and a key feature of their pathophysiology. According to Sandi and Haller (2015), the stress response corresponds to the activation of coordinated neurophysiological responses in the brain and periphery, including the sympathetic nervous system and the hypothalamic–pituitary– adrenal (HPA) axis, to restore homeostasis disturbed by environmental demands or stressors (Sandi and Haller, 2015). The activation of the sympathetic nervous system, which is part of the autonomic nervous system (ANS), along with parasympathetic efferences results in the release of catecholamines (epinephrine and norepinephrine) in the bloodstream (Brindley et al., 2017). Other peripheral markers are associated with ANS activation such as alpha-amylase secretion in saliva samples (Ali and Nater, 2020). The HPA cascade results in cortisol secretion in body fluids, including blood, urine and saliva. These bodily changes play a substantial role in arousal by facilitating the interaction with the environment (Carcone and Ruocco, 2017) and prepare the organism to face stressing conditions (Bangasser et al., 2019). HPA and ANS function may be assessed at baseline, and after submitting patients to experimental stress using the Trier Social Stress Test (TSST), a psychological task designed to trigger the stress response under controlled conditions (Birkett, 2011).

A previous literature review suggested a potential relationship between the level of dissociation and arousal in individuals with PTSD (Lanius et al., 2010). More recently, functional and morphological brain imaging highlighted a possible connection between dissociative and conversion disorders and abnormal stress response in CD (Conejero et al., 2018), but also in DD. Neuroimaging studies have reported the decrease of the pituitary gland volume in patients with CD, which supports the possibility of a modified response to stress (Atmaca et al., 2016). Furthermore, the decrease of cortical thickness and cortical area in DD has been suggested to be the consequence of altered stress reactivity following childhood trauma (Reinders et al., 2018, 2019). Indeed, early life stress (e.g., reported childhood trauma) seems to be an important risk factor to develop DD and CD (Chu and Dill, 1990; Kisiel and Lyons, 2001; Ludwig et al., 2018; Nijenhuis et al., 1998). The actual onset of the disorders is associated with other risk factors, for example physical injury in CD (Stone et al., 2009b).

Although stress axis dysregulation has been investigated in mood and post-traumatic stress disorders (Morris et al., 2012), few studies have investigated its role in DD and CD. Therefore, we performed a systematic literature review to summarize the existing findings on the stress response role in patients with DD and CD. A better understanding of the pathophysiology of these functional disorders may help identify new therapeutic targets for their treatment.

2. Methods

2.1. Search criteria

Articles in Medline and Web of Science were systematically searched using the Medical Subject Headings (MeSH) "((conversion disorder) OR (functional neurological disorder) OR (psychogenic non-epileptic seizure) OR (dissociative disorder)) AND ((stress) OR (autonomic nervous system) OR (sympathetic nervous system) OR (parasympathetic nervous system) OR (epinephrine) OR (norepinephrine) OR (cortisol) OR (amylase) or (catecholamines) OR (pituitary adrenal system) OR (hypothalamo-hypophyseal system))" following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009; Shamseer et al., 2015). CB and IC independently reviewed the retrieved records and abstracts, assessed the exhaustiveness of data extraction, and examined the quality rating of the studies.

2.2. Selection criteria

Studies were included if they met the following criteria: (i) original articles or case reports on dissociative symptoms, DD, or CD; (ii) related to stress axis dysregulation; and (iii) written in English. Exclusion criteria were: (i) studies on somatoform disorders; (ii) literature reviews, duplicates, letters, editorials, historical articles, or comments; (iii) stress markers not part of the HPA axis or the autonomous nervous system; and (iv) written in other languages than English (Fig. 1). Among the 3169 studies identified, 37 met our inclusion criteria. Additional records were retrieved from the reference lists of the selected articles and were included in the systematic review in accordance with inclusion and exclusion criteria, for a total of 39 articles.

2.3. Presentation of the results

Most of the selected studies assessed the link between stress and dissociative symptoms, such as depersonalization, derealization or dissociative amnesia. Dissociative symptoms were examined in isolation or within a particular mental disorder. Some studies included patients with diagnostic criteria of DD or CD. In this review, we followed current DSM-5 classification, and Dissociative symptoms and DD were separated from CD for better clarity, and to avoid misleading diagnostic classification or confusion bias. Therefore, the retrieved data were classified in four different groups: i) Isolated dissociative symptoms, ii) Dissociative symptoms in other psychiatric disorders, iii) DD, and iv) CD. Fig. 2 summarizes the results. The methodological quality of each study was assessed using a 6-item index developed in a previous meta-analysis (O'Connor et al., 2016). A score from 0 to 2 was given to each item, to calculate the total quality score (from 0 to 12). The six methodological criteria are listed in Table 1, and quality scores are reported for each study in Tables 2 and 3.

3. Results

3.1. Isolated dissociative symptoms (Table 2)

3.1.1. HPA axis

The association of dissociative symptoms and HPA axis changes has been assessed in basal conditions, and also following experimental task (TSST). A study on 21 victims of the World Trade Center attacks found a negative association between the severity of dissociative symptoms and the basal plasma cortisol level following morning awakening. The association between the dissociative experiences and cortisol secretion in response to the TSST remained negative (Simeon et al., 2008).

In contrast, in healthy individuals, dissociative symptoms in response to experimental stress seem to be accompanied by the activation of the HPA axis. A study involving 67 undergraduate students measured dissociation and salivary cortisol concentration before and after the TSST. Following the stress task, a positive correlation was observed between the dissociative experience and salivary cortisol increase (Giesbrecht et al., 2007). Research in an army training laboratory also found a positive correlation between dissociative symptoms and plasma cortisol levels during stress exposure (Morgan et al., 2001, 2004).

The results presented highlight that the activation of HPA axis under stressful conditions in humans reporting dissociative symptoms depends upon their clinical status: decreased in victims of trauma, or increased in healthy research participants.

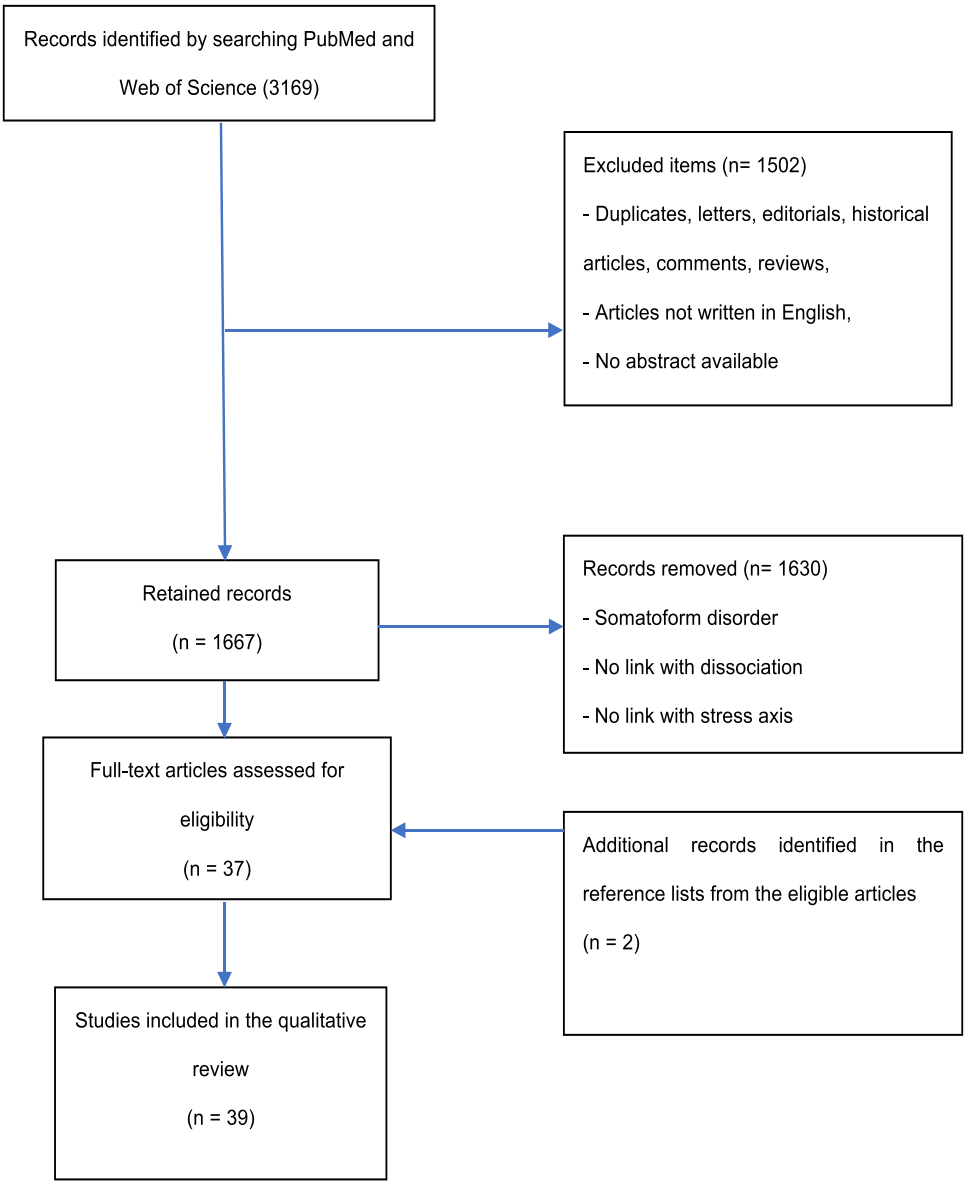

Fig. 1. Study selection.

3.1.2. ANS

Two studies evaluated the relationship between dissociative symptoms and ANS functioning in adolescents, with conflicting results. One study involving adolescent psychiatric patients found an increased heart rate (HR) in the high dissociation group compared with those showing low dissociation during an attentional task (Brunner et al., 2008), whereas more severe dissociative symptoms were associated with lower HR in delinquent (Koopman et al., 2004).

In adult victims of trauma with severe dissociative symptoms, reactions to script-driven imagery revealed reduced sympathetic activation (lower mean HR and maximal HR) (Sack et al., 2012). During trauma recall, systolic blood pressure was significantly lower in the group with dissociative symptoms compared with controls (Pole et al., 2005). The relationship between low systolic blood pressure during TSST and dissociative symptoms was also reported in adults exposed to the World Trade Center attacks (Simeon et al., 2008). However, results from studies including sexual/personal trauma victims contradict these findings. In a sample of women who had suffered physical or sexual assaults, high dissociation scores during trauma recall were associated with an increased sympathetic activity compared to moderate and low scores (Sledjeski and Delahanty, 2012). In 86 female victims of sexual assault, dissociative symptoms were positively associated with an increase of skin conductance in response to a traumatic script (Hetzel--Riggin and Wilber, 2010). Among patients having experienced a motor vehicle accident, no significant association was found between ANS and dissociation scores (Nixon et al., 2005).

Altogether, the studies analyzed suggest that dissociative experience may be associated with decreased autonomic arousal in trauma-exposed victims, except in studies involving individuals with a history of sexual trauma or personal physical assault.

3.2. Dissociative symptoms in other psychiatric disorders (Table 2)

3.2.1. HPA axis

Dissociative symptoms are frequently associated with other psychiatric disorders, such as PTSD, borderline personality disorder (BPD), or depressive disorder.

HPA axis activation seems to be reduced in most trauma victims who develop PTSD. The study by Basu et al. (2013) found more dissociative symptoms in victims of intimate partner violence who had PTSD

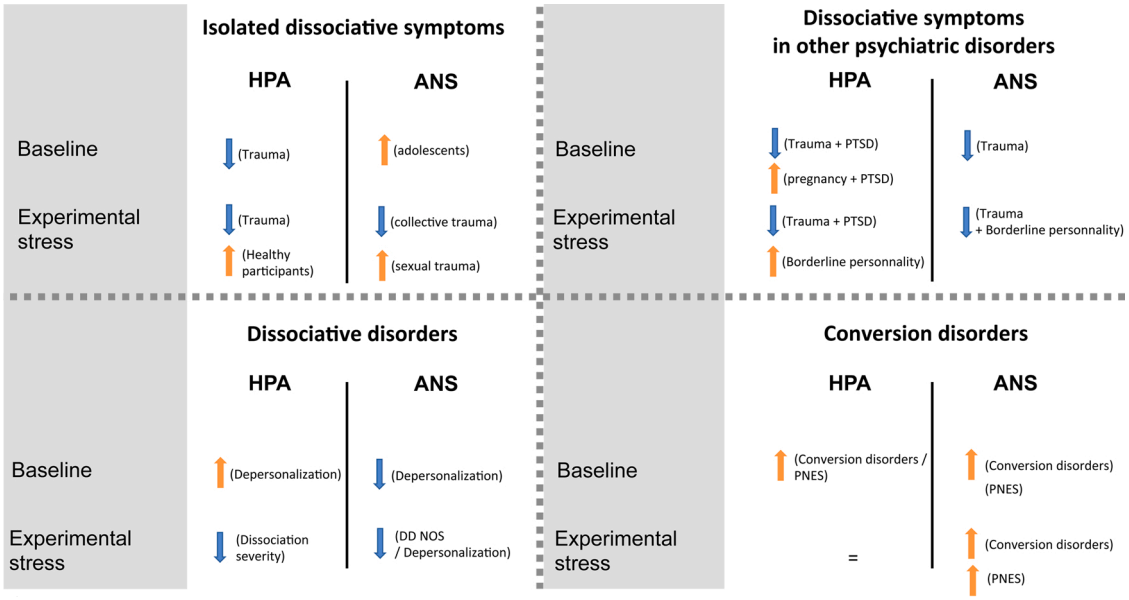

Fig. 2. Synthesis of the main findings. Hyperactivation; Hypoactivation; PTSD: Post-traumatic stress disorder PNES: Psychogenic non-epileptic seizure. HPA: hypothalamo-pituitary axis; ANS: autonomous nervous system; DD NOS Dissociative disorder no other specified.

Table 1
Quality score criteria adapted from O'Connor et al. (2016). DD: dissociative disorders, CD: conversion disorder, Min : minimum.

	Design	Total sample	Dissociation evaluation	Stress markers	Psychiatric conditions	Confounding factors
0	Cross-sectional study non matched	< 41	No information	1 measure	No information	No information
1	Cross-sectional study min. age and sex matched	≥ 41, but unequal	Quantitative questionnaires for DD Clinical evaluation for CD	Multiple measures, 1 day	Scales	Basic (age, sex)
2	Longitudinal study	≥ 41, approximately equal	Specific evaluation for DD, additional investigations for CD	Multiple days	Validated questionnaires	Others

compared to healthy individuals. Moreover, the dissociation intensity was a negative predictor of baseline cortisol secretion in the morning (Basu et al., 2013). In another study, HPA axis reactivity was also analyzed after experimental stress (TSST) in 23 women with PTSD and 18 healthy controls. A non-responder PTSD subgroup showed blunted HPA axis response and lower serum cortisol concentration. Interestingly, the level of dissociation was higher in this subgroup than among responders (Zaba et al., 2015).

In contrast, other studies found conflicting results. Cortisol plasma levels were lower in women with a history of sexual abuse and PTSD compared to those without PTSD, independently of the level of dissociative symptoms (Bremner et al., 2007). In another study, higher cortisol levels during early pregnancy were detected in women with PTSD and dissociative symptoms compared with women with PTSD only and healthy controls (Seng et al., 2018).

Simeon et al. assessed the basal urinary cortisol concentration and its change after experimental stress exposure (TSST) in BPD with high or low levels of dissociative symptoms. They reported increased level of plasmatic cortisol during the TSST in dissociated patients (Simeon et al., 2007a). Bob et al. (2008) did not find any significant association between dissociation intensity and basal plasma cortisol concentration in a group of 40 inpatients with depression (Bob et al., 2008). Hence, the activation of HPA axis in patients reporting dissociative symptoms and diagnosed with another characterized psychiatric disorder appears to be conflicting. Whereas dissociated patients with BPD seem to have increased response to experimental stress, two studies including individuals with PTSD found low HPA activation at baseline and under experimental conditions.

3.2.2. ANS

In an experimental study, HR decreased in BPD patients with trauma-related dissociation symptoms during trauma recall (Bichescu-Burian et al., 2018). Videlock et al. (2008) found a negative correlation between the concentration of NE in plasma or urine, and the level of dissociation in 155 survivors of traumatic events shortly following trauma exposure (Videlock et al., 2008). As in some studies regarding HPA function, dissociation seemed to be related to autonomic under-activation at baseline and after experimental trauma recall in patients who experienced severe trauma.

3.3. Dissociative disorders (Table 2)

3.3.1. HPA axis

Simeon's group conducted two studies assessing HPA axis activation in DD. They found higher basal urinary cortisol concentration, and greater resistance to and faster escape from dexamethasone suppression in 46 patients with DD compared with individuals showing PTSD and healthy controls (Simeon et al., 2007b). In another study, patients with depersonalization symptoms showed increased basal cortisol concentration in serum, as well as a lack of dexamethasone suppression compared to healthy controls (Simeon, 2001). In DD and PTSD, a negative correlation was found between dissociative symptom severity and cortisol reactivity to stress (Simeon et al., 2007b). Therefore, these reports highlight that patients with a diagnosis of characterized DD may be less prone to HPA suppression than psychiatric and healthy controls, whereas the severity of dissociation seems related to lower HPA reactivity.

Table 2
Stress system dysregulation in dissociation. AUC: area under curve, BE: beta endorphin, BP: blood pressure, BPD: borderline personality disorder, DA: dopamine, dBP: diastolic blood pressure, DD: dissociative disorders, DES: dissociative experience scale, DDNOS: dissociative disorder not otherwise specified, DHEA(s): dehydroepiandrosterone (sulfate), DID: dissociative identity disorder, DP: depersonalization DPD: depersonalization disorder, DR: derealization, DST: dexamethasone suppression test, DXM : dexamethasone, E: epinephrine, EDA: electrodermal activity, ECG: electrocardiography, FPV: finger pulse volume, HC: healthy control, HR: heart rate, HRV: heart rate variability, HUT: head up tilt test, HPA: hypothalamic-pituitary-adrenal axis, IBI: inter-beat interval, MDD: major depressive disorder, MPD : multiple personality disorder, MVA: motor vehicle accident, NE: norepinephrine, NPY: neuropeptide, NS: non-significant, NYC: New York city, PD: peritraumatic dissociation, PEP: pre-ejection period, RMSSD: Root Mean Square of Successive Differences, RR: respiratory rate, PTSD: post-traumatic stress disorder, PTSD-D: dissociative subtype of PTSD, QS: Quality score. SA: sexual abuse, sBP: systolic BP, SC: skin conductance, SCL: skin conductance level, SCR: skin conductance response, SNS: sympathetic nervous system, TSST: Trier social stress test.

DISSOCIATION					
Author, date	Population	Tests	Results	Statistics	QS
ISOLATED DISSOCIATIVE SYMPTOMS					
HPA Axis					
Simeon et al. (2008)	21 exposed to 11/9 attacks, 10 non-exposed NYC residents	24 h urinary cortisol, DST with plasma cortisol measure the day after, TSST with plasma cortisol measure before and after	dissociation (DES) : ↓ 8am plasma cortisol	r = -0.56 p < 0.01	5
Giesbrecht et al. (2007)	2 studies: 58 and 67 undergraduate students	Salivary cortisol before, immediately after, 20 min, and 40 min after TSST	Study 1: no correlation between DES and baseline cortisol level or cortisol stress response Study 2: DP/DR: ↑ cortisol stress response. Absorption ↑: basal cortisol level and stress response ↓	r < 0.10 p > 0.47 p < 0.05	5
Morgan et al. (2004)	25 healthy subjects enrolled in military survival school	Salivary plasma cortisol and DHEAs at baseline, during stress, and at recovery	↑dissociative score: ↑ salivary cortisol during stress exposure	r = 0.4 p < 0.05	5
Morgan et al. (2001)	44 healthy males enrolled in US army survival school	Salivary and plasma stress hormones (E, NE, NPY, cortisol) before, immediately after stress, and at recovery	↑dissociative score: ↓ free cortisol rate immediately after stress At recovery,↑cortisol level with dissociative score ↑	r = - 0.49 p < 0.04 r = 0.46 p < 0.04	6
ANS					
Brunner et al. (2008)	49 adolescents (12–18 years old): 19 high dissociators (HD), 20 low dissociators (LD)	HR and skin resistance during computer-based attentional task	↑ HR in HD group compared with LD group	F = 4.46 df = 1.35 p < 0.042	6
Koopman et al. (2004)	41 delinquent adolescents: 25 girls and 16 boys, 11–16-year-old	Mean HR during stress-free or stressful interview	↑ dissociative experience: ↓ HR during stressful interview	p < 0.05	6
Sack et al. (2012)	61 patients exposed to a variety of traumas: high or low re-experiencing/dissociation	ECG, FPV, HRV	↑ peritraumatic dissociation: reduces psychophysiological arousal ↑ acute dissociative symptoms: ↓ HR increase, HR max ↓ stress-induced parasympathetic activation decrease	p = 0.002 p = 0.02 p = 0.029	7
Pole et al. (2005)	19 adults who reported high (9) or low (10) PD	HR, BP during baseline, thinking, talking, and recovery phase	HD group: ↓ baseline dBP HD group: ↓ sBP at baseline (bp) and thinking phase (tp)	BPd = -2.17 df = 13.6 p < 0.05 BPs (bp) = -2.28 df = 17 p < 0.05 BPs (tp) = -2.20 df = 17 p < 0.05	4
Sledjeski and Delahanty (2012)	39 undergraduate women trauma victims, with high (HD), moderate (MD) or low (LD) PD	HR, PEP, respiratory sinus arrhythmia (RSA), RR at baseline, during trauma recall, at rest, during neutral recall, at recovery	During trauma recall: heightened SNS activity: ↑ HR, RSA in HD compared with MD ↓ PEP in HD compared with LD	F2.36 = 3.75 p = 0.033 F2.36 = 3.88 p = 0.030 F2.36 = 3.6 p = 0.038	4
Hetzel-Riggin and Wilber (2010)	86 female victims of sexual assault	Cardiovascular and electrodermal activity: basal and during neutral then trauma script	↑ peritraumatic dissociation: ↑ ΔSCL ↑ PD and ↓ ΔSCR Attempt to inhibit bodily responses and heightened startle responses	t = 3.37 p < 0.001 t = -3.22 p < 0.01	7
Nixon et al. (2005)	17 high PD, 18 low PD (MVA or physical assault)	SC, HR at baseline, during trauma description and at recovery	. HR : tendency to have higher HR throughout the experience . SC : no difference	Baseline : t = 2.33 p < 0.05 Narrative, recovery phase : > 0.1 SC : p > 0.1	6
DISSOCIATIVE SYMPTOMS IN OTHER PSYCHIATRIC DISORDERS					
HPA axis					
Basu et al. (2013)	88 women: 12 HC, 14 PTSD, 43 PTSD + MDD, 19 subthreshold MDD/PTSD	Basal and diurnal salivary cortisol	↑dissociative symptoms: ↓ levels of awakening cortisol	F(1.83) = 4.683 p < 0.05	9
Zaba et al. (2015)	23 adult Caucasian women with PTSD, 18 HC	Basal plasma cortisol and after TSST, basal ACTH	Dissociative symptoms are ↑ in the non-responder group (blunted stress HPA axis response)	F(1.21) = 10.48 p = 0.004	9 8

(*continued on next page*)

Table 2 (*continued*)

Author, date	Population	Tests	Results	Statistics	QS
DISSOCIATION					
Bremner et al. (2007)	43 menopausal women: 19 with SA + PTSD, 11 SA without PTSD, and 13 without SA and PTSD	Plasma hormones/15 min over 24 h (estradiol, cortisol, DHEA, DHEAs)	No correlation between serum basal cortisol and dissociative symptoms severity	r = -0.29 p = 0.145	
Seng et al. (2018)	395 pregnant women (non-exposed, trauma victims without PTSD, with PTSD, with PTSD-D)	Basal salivary cortisol	PTSD dissociative subtype women: ↑ basal salivary cortisol level, mostly in early gestation		9
Simeon et al. (2007b)	46 DD without PTSD, 35 PTSD, 58 HC	Basal 24 h urinary cortisol, basal plasma cortisol, DST, and plasma cortisol 8am and 2 pm the next day. TSST, 3 plasma cortisol measures after the test	↑basal urinary cortisol compared with HC ↑resistance to, and ↑ escape from DXM test// HC Inverse relation between dissociation severity and cortisol stress reactivity in PTSD and DD groups	F(1.95) = 3.84 p = 0.05 F(1.90) = 5.71 p = 0.019	8
Simeon et al. (2007a)	13 BPD (high or low dissociation), 11 HC	24 urinary cortisol, urinary and plasma NE, cortisol before, during, and after TSST	HD BPD patients: ↑ cortisol stress reactivity compared with other groups. No difference between urinary basal NE or cortisol, or NE reactivity.	F = 4.12 p = 0.03	5
Bob et al. (2008)	40 inpatients with diagnosis of MDD	Basal serum cortisol	No statistically significant association between dissociation and cortisol rate.	r = -0.19 p = 0.157	5
ANS					
Bichescu-Burian et al. (2018)	15 BPD PD, 13 BPD, 15 controls (trauma victims)	SC, HR at baseline, during trauma description, and at recovery	HR ↓ during trauma script in BPD PD compared with other groups		9
Videlock et al. (2008)	155 trauma survivors	NE immediately after trauma, 10 day, 1 month and 5 months	NE ↓ immediately after trauma in patients with dissociation symptoms		9
DISSOCIATIVE DISORDERS					
HPA axis					
Simeon et al. (2007b)	46 DD without PTSD, 35 PTSD, 58 HC	Basal 24 h urinary cortisol, basal plasma cortisol, DST, and plasma cortisol 8am and 2 pm the next day. TSST, 3 plasma cortisol measure after the test	↑basal urinary cortisol compared with HC ↑resistance to, and ↑ escape from DXM test// HC Inverse relation between dissociation severity and cortisol stress reactivity in PTSD and DD groups	F(1.95) = 3.84 p = 0.05 F(1.90) = 5.71 p = 0.019	8
Simeon (2001)	9 DPD, 9HC	Basal 24 h urinary cortisol, basal plasma cortisol, DST and plasma cortisol 8am the next day	↓baseline plasma cortisol level in DPD group, ↓suppression to low dose DXM	F = 8.81 f = 1.15 p < 0.01 F = 4.23 f = 1.15 p < 0.05	8
ANS					
Schäflein et al. (2018)	18 women with DDNOS, 18 HC	Self-reported stress and autonomic system activation (IBI, RMSSD, PEP) during self-observation in a mirror	↑ subjective stress and ↓ autonomic reactivity in DDNOS (IBI, RMSSD) compared with HC PEP: not significant	T(df) = T(34.0) = −2.02 p = 0.05 T(df) = T(34.0) = −0.19 p = 0.85	6
Owens et al. (2015)	14 DPD, 16 HC	HR, sBP and dBP, HRV at baseline and in response to physical or emotional stimuli (observation of images with mixed valences)	↓ BP and ↑ HR during physical stimuli in the DPD group ↓ vagal tone during emotional stimuli in the DPD group DPD ↑ during HUT + unpleasant image visualization in the DPD group	p < 0.05	4
Simeon et al. (2003)	9 DPD, 9HC	24 h NE urinary and NE measure in 3 plasma samples (8am, 3 pm, 11 pm)	↑ depersonalization severity: ↓ urinary NE in the DPD group No difference between DPD and HC	r = 0.88 df = 7 p = 0.002 p < 0.05	6
Putnam et al. (1990)	9 MPD, 9 HC	Skin conductance, HR, and breathing in different personality state experimentally induced (hypnosis, simulation, deep relaxation)	ANS difference by changing personality state in each group Controls tended to be more consistently differentiated by SCL Effect on HR was stronger in the MPD group		2
Reinders et al. (2012)	11 DID, 10 high fantasy prone controls, and 8 low fantasy prone controls	BP, HR, HRV in neutral or traumatic script	↑ HR, ↓ HRV in the DID group than in controls In DID groups: HR and BP ↑, HRV ↓ during trauma script compared with neutral script, not found in the two control groups		5
Reinders et al. (2016)	11 DID, 10 high fantasy prone controls and 8 low fantasy prone controls	BP, HR, HRV	Psychophysiological hyperarousal in DID, not found in both control groups		6
Kawai et al. (2001)	24 healthy Balinese men: 15 trance experience (TE), 9 no TE.	15 min before and 6 min after the ritual: plasma catecholamines, metabolites, neuropeptides, and BP/HR	↑ NE, DA, BE in trance group compared with control BP, HR: no difference	p < 0.05 p > 0.05	1

Table 3
Stress system dysregulation in conversion disorders. ACTH: adrenocorticotropic hormone, BP: blood pressure, CD: conversion disorder, EDA: electrodermal activity, GTCS: generalized tonic-clonic seizure, HA: healthy control with abuse, HC: healthy control without abuse, HR: heart rate, HRV: heart rate variability, IBI: cardiac interbeat interval, PNES: psychogenic non-epileptic seizures, QS: Quality score, RSA: respiratory sinus arrhythmia, SCL: skin conductance level, SCR: skin conductance reactivity, TSST: Trier social stress test.

CONVERSION DISORDERS					
Author, date	Population	Tests	Results	Statistics	QS
HPA axis					
Maurer et al. (2015)	33 CD, 33 age- and sex-matched HC	Basal salivary cortisol at 5 time points	No significant difference between CD and HC	NS	7
		9 salivary cortisol samples from 85 min before to 70 min after TSST	↑ background level of cortisol in the CD than control group	$p < 0.05$ $t = 2.27$ $df = 29$	
Apazoglou et al. (2017)	16 CD, 15 HC		After TSST, cortisol changes are comparable	$p > 0.05$	6
		Salivary α amylase at baseline and after TSST	Motor CD: ↑ basal α amylase level compared with HC Group did not react differentially after TSST test	$F\ 1.30 = 8.95$ $p < 0.01$	
Bakvis et al. (2009)	19 PNES, 20 HC	11 assessments of salivary free cortisol level from 60 min before to 140 min after the stressor	Patients and controls do not differ		6
Winterdahl et al. (2017)	15 women with PNES, 60 HC women (with (HA) or without abuse (HC))	Basal serum ACTH and cortisol level, between 6 pm and 8pm	PNES group compared with HC: ↑ ACTH	$F(2.60) = 7.04$ $p < 0.01$	5
			PNES group compared with HA: ↓ cortisol	$F\ (2.71) = 3.34$ $p < 0.05$	
Autonomic nervous system					
Kozlowska et al. (2015)	57 children/adolescents (aged 8−18) with CD, 57 age- and sex-matched HC	HR, HRV at rest and during three different tasks	↑ autonomic arousal at baseline in CD compared with controls. ↓ ANS regulation during task in the CD group	$P < 0.05$	8
Maurer et al. (2016)	35 CD, 38 HC (age- and sex-matched)	Awake and asleep HR, HRV	↓ PNS in CD compared with HC group	$F1.141 = 5.22$ $p = 0.02$ $F1.141 = 4.73$ $p = 0.03$	6
Pick et al. (2016)	40 PNES, 43 controls	Test of facial affect recognition and collection of SCL, SCR	SCL ↑ in PNES group compared with HC	$p = 0.05$	9
			SCR ↓ in a subgroup	$p < 0.05$	
Herrero et al. (2020)	34 women PNES, 34 healthy female volunteers matched for age and level of education.	Exposition to emotional stimuli and collection of physiological response: SCR amplitude, SCR rate, SCR latency, heart rate deceleration	PNES: ↓ SCR amplitude, ↓ HR deceleration, ↓ arousing rating for all images compared with HC group. PNES group: SCR rate ↑ for negative images with low arousal. Dissociation ↑: SCR amplitude ↓, SCR latency, HR deceleration ↓	$p < 0.05$	7
Roberts et al. (2012)	18 PNES, 36 seizure-free (18 with elevated post-traumatic stress (PTS) symptom levels (PTS high) and 18 with lower PTS symptom levels (PTS low).	Exposition to emotional pictures and collection of cardiac IBI and RSA: baseline and RSA reactivity.	RSA reactivity: no difference between groups Basal RSA: PNES patients ↓ basal RSA compared with PTS low, not differ from PTS high	$p > 0.05$	7
Van der kruijs et al. (2016)	20 patients PNES (18 W, 2 M)	HR and HRV before, during, and after PNES	↑ sympathetic system before the seizure, ↑ PNS functioning during and after PNES GTCS: higher ANS activity compared with PNES		4
Reinsberger et al. (2015)	11 PNES, 9 GTCS, 106 neither PNES nor GTCS	HR and HRV before, during, and after PNES	PNES: ↓ EDA response compared with GTCS, often lacking the typical large peak		7

3.3.2. ANS

Assessment of ANS in DD shows heterogeneous results and suggests different responses to stress depending on the DD subtype. Autonomic reactivity, both sympathetic and parasympathetic, was blunted in 18 patients with DD (unspecified) compared with 18 healthy subjects (Schäflein et al., 2018). Similarly, parasympathetic activity was reduced and sympathetic excitation was blunted in 14 adults with depersonalization disorders (DPD) compared with 16 healthy controls during emotional stimuli (Owens et al., 2015). In a small study involving nine patients with DPD and nine healthy controls, 24 -h urinary NE concentration at rest in the DPD group was negatively associated with depersonalization severity (Simeon et al., 2003).

Dissociative identity disorder (DID) and dissociative trance states have also been assessed with respect to ANS activation. In 1990, Putman reported sympathetic marker changes between different experimentally induced personality states in patients with DID and in healthy controls: HR varied in the DID group, and skin conductance level varied in the control group (Putnam et al., 1990). Reinders et al. showed higher HR during exposure to neutral scripts and lower HR variability during exposure to trauma scripts in 11 individuals with DID compared with 18 healthy controls (Reinders et al., 2012, 2016). Physiological correlates of trance states were compared between 15 individuals who showed possession trance behavior and nine controls simulating trance behavior during a Balinese ritual. In both groups, plasma catecholamines and

neuropeptides levels were higher following trance compared with baseline. However, the increase of NE and dopamine levels was higher in participants with possession trance behavior (Kawai et al., 2001). These findings suggest that autonomic reactivity is decreased in patients with DD and DPD, whereas the activation of ANS remains highly variable when dissociative states are provoked in experimental or cultural contexts. These latter studies are difficult to interpret because of low experimental samples and overall poor quality, with QS ranging from 1 to 6.

3.4. Conversion disorder (Table 3)

3.4.1. HPA axis

Basal cortisol measurement in 33 patients with CD and 33 sex- and age-matched healthy subjects did not highlight any significant difference between groups (Maurer et al., 2015). Another study comparing salivary cortisol before and after the TSST in 16 patients with CD and 15 healthy controls found higher level of cortisol in the CD group at baseline, whereas the response to stress remained comparable between groups (Apazoglou et al., 2017). The cortisol concentration in saliva was related to the number of adverse life events only in the CD group (Apazoglou et al., 2017).

Some studies specifically evaluated the HPA axis in patients with PNES. These paroxysmal manifestations relate to involuntary behavioral patterns that mimic epileptic seizures, but without organic etiology. Salivary cortisol levels at baseline and in laboratory stress conditions (TSST) did not differ between 19 patients with PNES and 20 healthy controls (Bakvis et al., 2009). In contrast, basal serum concentration of ACTH was higher in 15 women with PNES compared with 60 healthy women (Winterdahl et al., 2017).

Hence, studies regarding HPA function at baseline or in experimental stress conditions show heterogeneity of results in CD patients (either no difference or higher HPA activation compared with healthy controls).

3.4.2. ANS

Higher salivary amylase level in adults with CD compared to healthy controls indicates greater activation of the basal sympathetic system in resting conditions (Apazoglou et al., 2017). Increased sympathetic activity (higher HR and lower vagal tone) was also detected in young patients with CD (aged between 8 and 18 years) compared with healthy controls at rest. HR increase was less attenuated in the CD group during cognitively demanding tasks compared with controls (Kozlowska et al., 2015). The study by Maurer et al. (2016) also reported lower basal vagal tone in patients with CD (Maurer et al., 2016).

ANS modifications are intrinsic to PNES episodes, but also appear in the context of laboratory challenges. Indeed, two studies of skin conductance reported an increased autonomic activity at baseline compared with the controls without PNES (Pick et al., 2016; Herrero et al., 2020). When using respiratory sinus arrhythmia, Roberts and al. found basal decreased activity of parasympathetic system (Roberts et al., 2012). The evaluation of autonomic regulation during experimental stress (TSST) suggests a state of hypervigilance in patients diagnosed with PNES (Bakvis et al., 2009).

Other findings reported that the sympathetic nervous system is activated in the minutes before PNES onset, whereas the parasympathetic tone is increased during and following the paroxysmal episode (Van der Kruijs et al., 2016). A recent study suggested that autonomic function modifications may help to distinguish PNES from organic seizures (Reinsberger et al., 2015). Although ANS seems over-activated in CD, further studies including larger patient samples should be performed to determine more precisely the course of ANS modifications underlying PNES.

4. Discussion

4.1. Main findings

Our review highlights a growing body of evidence concerning existing modifications of the stress response in individuals with dissociative symptoms. However, they appear to be contradictory. In participants without psychiatric history, high cortisol secretion is related to high dissociation scores. In contrast, other authors have provided evidence of blunted autonomic and endocrine responses in clinical populations of trauma victims showing dissociative states. Lanius et al. (2010), and more recently Wolf et al. (2012), extended this concept further by characterizing a dissociative subtype of PTSD (affecting up to one third of patients) which can be distinguished clinically from non-dissociative PTSD, and showing unique neurobiological features (Lanius et al., 2010; Wolf et al., 2012). Hence, conflicting results regarding the association between HPA, ANS and dissociative symptoms may be due to not considering underlying PTSD, or the history of trauma exposure.

Chronic over-activation of the stress system is associated with neuroanatomic alterations that may concern regions where glucocorticoid receptors are highly expressed (hippocampus, prefrontal cortex, and amygdala) (Lupien et al., 2018). These three regions play a key role in self-awareness integration (prefrontal cortex), short- and long-term memory (hippocampus, amygdala), and emotional response (amygdala). These alterations are related to the production of dissociative symptoms, but are also implicated in stress regulation. Therefore, their structural and functional modification may result in coupling between acute stress response and dissociation (Kelley-Puskas et al., 2005; Sierra and Berrios, 1998; de Lange et al., 2010). Although we have reported that this association likely depends on the history of trauma, the impact of chronic exposure to stressful events remains to be determined in longitudinal studies or in specific clinical populations.

Lastly, few studies have investigated CD and have yielded conflicting results. There seems to be a tendency to HPA axis hyperactivation and increased autonomic arousal in patients with CD compared with healthy controls, although the results are heterogeneous. Important clinical factors should be taken into account to homogenize the study populations, such as duration of the disorder, its intensity, the association with other dissociative symptoms or traumatic events which are potentially involved as mediators between the neurological symptoms and stress response. Also, it appears that the evaluation of stress response in patients with CD is insufficiently powered in a majority of cases.

A better understanding of the pathophysiology of these disorders may help therapeutic research. Some authors have already assessed the effectiveness of treatments focusing on stress regulation, such as relaxation, meditation, or transcranial Direct Current Stimulation (tDCS), with encouraging results in patients with DD and CD (Antal et al., 2014; Chellew et al., 2015; Gerardi et al., 2010; Pascoe et al., 2017).

4.2. Limitations of our review

Studies on the biological correlates of stress are a new research field in DD and CD. Small clinical samples may lead to lack of statistical power and to under-detection of relevant associations. The generalizability of the results may be limited because studies were heterogeneous in terms of experimental design, and because results were sparsely or not replicated in the different population subtypes. Moreover, the clinical scales used to assess dissociative symptoms and the laboratory methods used to evaluate HPA or ANS activation differed widely between studies. Hence, the clinical heterogeneity did not allow performing a meta-analysis. Although most individuals with DD and CD are outpatients (Foote et al., 2006), several studies retrieved in our review included hospitalized participants. Potential confounding factors, such as medication intake, smoking, substance use disorder and menstrual cycle,

were not taken into account in many studies, although they are known to influence neuroendocrine activity (Wheelock et al., 2016). The search of scientific articles related to DD and CD in research databases was limited by the heterogeneity of key words used for indexing. Indeed, clinical categories diverge between ICD-11 and DSM-5 as well as their naming. Therefore, to ensure the most exhaustive extraction of studies we had to enlarge our research to non-MeSH terms.

Finally, we did not register the review protocol on PROSPERO (International prospective register of systematic reviews) as data extraction started before the launch of this repository, and retrospective registration is not permitted, as mentioned in the service information page (PROSPERO, 2019).

Future clinical studies should address these issues. First, clinical homogeneity should be considered through the standardized clinical assessment of dissociative symptoms, distinguishing trait and state markers. Moreover, the link between HPA or autonomous activation and CD should integrate data from clinical neurological scales for the fine assessment of motor or sensitive symptoms. Finally, ecological monitoring of the stress response to daily life events is a promising research field to better understand stress activation patterns specific to each patient and to the context in which the symptoms develop.

4.3. Strengths of our review

Our review is the first to systematically assess the literature on the stress-dissociation relationship. We used the PRISMA Statement recommendations on systematic reviews. In addition to the high number of included articles, this review focused on a specific endophenotype (i.e arousal) that underlies DD and CD, in line with the Research Domain Criteria methodology (Torous et al., 2017).

5. Conclusions and perspectives

Although the presence of stress factors is not considered as a diagnostic criterion for DD and CD in the DSM-5 (American Psychiatric Association, 2013; Ludwig et al., 2018), stress response changes seem to be associated with the emergence and persistence of these disorders. However, the heterogeneity of the stressors and of their timing, as well as the individual differences (culture, personality, associated clinical conditions) lead to inconclusive findings. The directionality of this relationship appearing rather specific to clinical sub-groups. Interestingly, dissociated individuals with history of acute interpersonal trauma might show a specific stress response with blunted cortisol secretion and blunted autonomic activation, suggesting a “dissociation” between current stress experience and arousal patterns.

Our results may help physicians to develop new treatments and pave the way to a dimensional understanding of DD and CD. Such comprehensive models should encourage monitoring the stress response and examining more closely the history of stress exposure in both populations, in future larger studies.

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Declaration of Competing Interest

The authors report no declarations of interest.

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