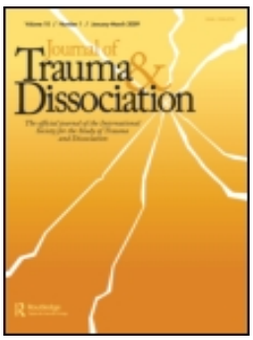

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Where Are We Going? An Update on Assessment, Treatment, and Neurobiological Research in Dissociative Disorders as We Move Toward the DSM-5

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ARTICLES

Where Are We Going? An Update on Assessment, Treatment, and Neurobiological Research in Dissociative Disorders as We Move Toward the *DSM-5*

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The coauthors of this paper are members of (D.S.) or advisors to (B.L.B., R.L., E.V.) the *Diagnostic and Statistical Manual of Mental Disorders–Fifth Edition* (*DSM-5*) Anxiety, Obsessive-Compulsive Spectrum, Post-Traumatic, and Dissociative Disorders Work Group. This paper represents the authors' reports of considerations reviewed by the work group. *Recommendations provided in this paper should be considered preliminary at this time; they do not necessarily reflect the final recommendations or decisions that will be made for the DSM-5, as the DSM-5 development process is still ongoing*. It is possible that this paper's recommendations will be revised as additional data and input from experts and the field are obtained. In addition, the categorization of disorders discussed in this review needs to be harmonized with recommendations from other *DSM-5* work groups and from the *DSM-5* Task Force for the overall structure of the *DSM-5*.

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This article provides an overview of the process of developing the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders *(*DSM-5*) of the American Psychiatric Association with a focus on issues related to the trauma-related disorders, particularly the dissociative disorders (DD). We also discuss the highlights of research within the past 5 years in the assessment, treatment, and neurobiological basis of trauma disorders. Recent research shows that DD are associated with severe symptoms as well as a higher rate of utilization of mental health treatment compared with other psychiatric disorders. As a result, DD, like other complex posttraumatic disorders, exact a high economic as well as personal burden for patients and society. The latest research indicates that DD patients show a suboptimal response to standard exposure-based treatments for posttraumatic stress disorder as well as high levels of attrition from treatment. An emerging body of research on DD treatment, primarily of naturalistic and open trials, indicates that patients who receive specialized treatment that addresses their trauma-based, dissociative symptoms show improved functioning and reduced symptoms. Recent studies of the underlying neurobiological basis for dissociation support a model of excessive limbic inhibition in DD that is consistent with the phenomenology and clinical presentation of these patients. We are optimistic that the forthcoming* DSM-5 *will stimulate research on dissociation and the DD and suggest areas for future studies.*

KEYWORDS dissociative, trauma, DSM*, diagnosis, assessment, treatment*

THE *DSM* PROCESS

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) of the American Psychiatric Association can be thought of as an update of psychiatry's software, improving clinical pattern recognition and therefore treatment. First, one visible change is the use of the Arabic numeral 5 rather than the Roman numeral V in its abbreviated title. This is meant to imply a computer software analogy that connotes greater ongoing mutability—a *DSM* 5.1, 5.2, and so on. The hope is that this edition will be updated frequently and will be seen more as a work in progress. Second, an effort is being made to include continuum as well as categorical assessments. Many disorders will have a brief scale composed of a limited number of

symptom items rated on a Likert scale. This will allow for measures of severity that can also index change over time, including response to treatment. Third, there will be cross-cutting symptoms rating distress and disability, cross-cultural issues in diagnosis, gender, and developmental issues.

The *DSM* task force is composed of 13 work groups on the major psychiatric disorders. Of special interest to those interested in trauma and dissociation is the Anxiety, Obsessive-Compulsive Spectrum, Post-Traumatic, and Dissociative Disorders Work Group chaired by Kathy Phillips, MD. It has three sub–work groups: Anxiety; Obsessive-Compulsive Spectrum; and Post-Traumatic and Dissociative Disorders. The latter group is composed of Matthew Friedman, MD (Chair), Roberto Lewis-Fernandez, MD, Robert Ursano, MD, and David Spiegel, MD. This group is aided by a number of advisors, including the coauthors of this article.

The work of this subgroup has included several review articles (Bryant, Friedman, Spiegel, Ursano, & Strain, 2010; Friedman, Resick, Bryant, & Brewin, 2010; Friedman et al., 2011; Spiegel, 2010), the preparation of symptom severity measures, review of Web comments about proposed changes in diagnostic criteria, field trials of proposed new diagnostic criteria, and the writing of proposed text for the *DSM-5.* Changes in the *DSM-5* are based on specific empirical validators. These include symptom similarity, comorbidity, familiality, course of illness, treatment response, shared cognitive and emotional processing abnormalities, shared neural substrates, shared biomarkers, shared temperamental antecedents, shared genetic risk factors, and shared causal environmental risk factors. Another issue being addressed is the meta-structure, that is, how diagnoses will be grouped. An effort is being made to link this meta-structure to that of the International Classification of Diseases-11 (ICD-11). The current plans include sections on trauma- and stressor-related disorders, dissociative disorders (DD), and somatic symptom disorders. The *DSM-5* is scheduled for publication in 2013.

PROPOSED CHANGES IN THE SUBGROUPING OF STRESSOR- AND TRAUMA-RELATED DISORDERS

Consideration has been given in the deliberations over the *DSM-5* to creating a section that would group together stressor- and trauma-related disorders, including adjustment disorders, acute stress disorder and posttraumatic stress disorder (PTSD), and the DD. This would provide official acknowledgement that environmental stress and trauma are major etiological factors in these types of psychopathology. By design, the *DSM-III* and *DSM-IV* were steadfastly descriptive and atheoretical, in part in reaction to earlier psychodynamic formulations about the etiology of psychopathology. However, even in the current less restrictive climate there is a spectrum of linkage between stressors and mental disorders. It ranges from those in which the

connection is included in the definition of the disorder (e.g., adjustment disorder and the "A criteria" of acute stress disorder and PTSD), through observations that symptoms are often trauma related (dissociative amnesia [DA] and dissociative identity disorder [DID]), through disorders that may but do not always have pre-occurring stress or trauma (depersonalization/derealization, depression, obsessive-compulsive disorder). Members of the Anxiety, Obsessive-Compulsive Spectrum, Post-Traumatic, and Dissociative Disorders Work Group have been examining this issue (Friedman et al., 2011). Arguments have been made for and against including the DD with the adjustment and trauma-related disorders. The fact that a stressor is not part of the diagnostic criteria for DD has been used as an argument against such inclusion, whereas the important role of proximate and antecedent trauma, such as childhood physical and sexual abuse, in the etiology of many DD is cited in its favor. Efforts are also being made to make categories in the *DSM-5* as similar as possible to those in ICD-11, so both may have up to 24 categories (using letters minus *I* and *O* rather than numbers from 1 to 10). When it was thought that there could be no more than 10 overall categories of psychopathology, inclusion of the DD in the trauma grouping was favored. However, with the decision to have up to 24 categories of mental disorders, the work group is leaning toward placing DD after the stressor- and trauma-related disorders in a separate category of its own, analogous to schizophrenia, mood, anxiety, and somatic symptom disorders. A final decision has not been made. The current proposals for the disorders can be found online at www.dsm5.org.

DEVELOPMENTS IN ASSESSMENT

There have been several important developments related to the assessment of dissociation within the past 5 years. First, in the past few years three new measures of dissociation have been developed. The Multiscale Dissociation Inventory (Briere, 2002) was normed and standardized on 444 trauma-exposed individuals from the general population and validated in clinical, community, and university samples. Scores can be converted to *T* scores, allowing for empirically based interpretation of dissociative symptoms. It is available from its author, John Briere (http://www.johnbriere.com/multiscale.htm). The Multidimensional Inventory of Dissociation (Dell, 2006) yields a comprehensive dissociative profile and is the only measure of self-report dissociation that has validity scales. It is available on the International Society for the Study of Trauma and Dissociation's (ISSTD) website (http://www.isst-d.org/). The Dissociative Experiences Scale–Revised (Dalenberg & Carlson, 2010) is a new version of the Dissociative Experiences Scale (Bernstein & Putnam, 1986) that uses a Likert response scale (from *never* to *at least once per week*) rather than percentages. The Dissociative Experiences

Scale–Revised appears to be useful in that scores from community samples are normally distributed.

Second, new studies have focused on distinguishing genuine from feigned DID. Many personality tests have validity scales that include dissociative and trauma-related items; unfortunately, this results in many traumatized and DD patients being incorrectly assessed as exaggerating or feigning (B. L. Brand, Armstrong, & Loewenstein, 2006; Klotz Flitter, Elhai, & Gold, 2003). Especially in forensic and disability assessment cases, the diagnosis of a dissociative disorder or some other type of trauma disorder versus malingering and/or factitious presentations of dissociation needs to be made particularly carefully (International Society for the Study of Trauma and Dissociation, 2011). A recent study (B. L. Brand, McNary, Loewenstein, Kolos, & Barr, 2006) found that one third of individuals with reliably diagnosed DID were misclassified as "feigning" psychiatric illness on a forensic "gold standard" interview for assessing the feigning of psychiatric symptoms called the Structured Interview of Reported Symptoms (SIRS; Rogers, Kropp, Bagby, & Dickens, 1992). Elevations in the DID patients' scores were due to the participants endorsing two dissociative symptoms and symptoms commonly found among chronically traumatized populations that are included on the SIRS. B. L. Brand, McNary, et al.'s (2006) findings prompted the author of the SIRS to develop a new trauma index that appears to be more useful in detecting feigning among severely traumatized individuals (Rogers, Payne, Correa, Gillard, & Ross, 2009). Furthermore, Rogers warned that the SIRS may not be valid in identifying feigned DID (Rogers et al., 2009; Rogers, Sewell, & Gillard, 2010). Additional research is needed to aid in the accurate diagnosis of genuine versus factitious and/or malingered dissociative and trauma-related disorders.

Third, the American Psychological Association's recently created Division 56, the Trauma Division, has developed guidelines for the assessment of traumatized individuals. The Assessment Guidelines advise clinicians to fully assess the range of potential sequelae of trauma, including dissociation and DD. The Guidelines are expected to be published in *Psychological Trauma: Theory, Research, Practice and Policy*.

DEVELOPMENTS IN TREATMENT

Several treatment guidelines related to DD have recently been or will soon be published. The International Society for the Study of Trauma and Dissociation (2011) published the third revision of *Guidelines for Treating Dissociative Identity Disorder in Adults*. In addition, Division 56, the Trauma Division of the American Psychological Association, is collaborating with the ISSTD to develop the first treatment guidelines for complex PTSD; they will include information on dissociation and DD. Also, the International

Society for Traumatic Stress Studies is in the process of developing treatment guidelines for complex PTSD.

Many books (Boon, Steele, & van der Hart, 2011; Chu, 2011; Courtois & Ford, 2009; Dell & O'Neil, 2009; Forgash & Copeley, 2007; Howell, 2005; Lanius, Vermetten, & Pain, 2010; Paivio & Pascual-Leone, 2010; Ross & Halpern, 2009; Silberg, in press; Sinason, 2011; van der Hart, Nijenhuis, & Steele, 2006; Vermetten, Doherty, & Spiegel, 2007; Wieland, 2011) that address treatment issues among dissociative individuals have been published recently or are in press. Several studies related to treatment have been published in the past 5 years. A study of 36 international DD experts (B. L. Brand et al., in press) determined that a core set of foundational treatment techniques was consistently recommended for individuals with DID and severe dissociative disorder not otherwise specified (DDNOS) patients who have clinical features of DID. The experts advised a carefully staged tripartite treatment structure. The first stage emphasized emotion regulation, impulse control, interpersonal effectiveness, grounding, and containment of intrusive material. In the second stage of treatment, the experts recommended the use of exposure/abreaction techniques (albeit modified to avoid overwhelming dissociative patients) balanced with core foundational interventions. The last stage of treatment was less clearly delineated and more individualized. What is surprising is that the experts reported the unification of self-states in only a minority of DID patients.

A prognostic model designed to predict the treatment outcome for Stage 1 stabilization-oriented therapy for complex PTSD and DID was developed (Baars et al., 2011). Experts from around the world were asked to list patient characteristics that would predict negative treatment. Analyses yielded a set of 46 items that are thought to predict negative outcome for DID patients and 38 items thought to predict negative outcome for complex PTSD. Taken together, the two studies (Baars et al., 2011; B. L. Brand et al., in press), both of which used expert consensus, set the stage for the development of the first manualized, empirically based investigation of DID treatment outcome: The prognostic checklist could be used to predict patient outcomes in a manualized Stage 1 treatment based on the interventions recommended by experts (B. L. Brand et al., in press). Such a study is critical to the development of empirically supported treatment for DID and is of great importance.

Recent studies have provided important results about the impact of dissociation on treatment outcome and utilization. Among treatment-seeking wives of active military personnel, those with DD utilized the highest number of therapy sessions compared to those with all other psychiatric disorders studied (Mansfield et al., 2010). This finding suggests that DD are associated with a substantial economic burden. Data from Massachusetts Medicaid patients from 1993 to 1996 showed that inpatient treatment for

DID cost more than $3 million during the study period, more than the treatment of patients with panic disorders, major depressive disorder, and bipolar disorder, although DID patients made up only 2.6% of the sample of more than 55,000 patients (Macy, 2002). The DID patients accounted for 33.5% of the total Medicaid inpatient costs despite being only a small percentage of the sample. In addition, DD patients have high rates of suicidality and self-injurious behavior compared to individuals with other disorders, leading to long courses of treatment in outpatient psychiatric clinics (Foote, Smolin, Neft, & Lipschitz, 2008). Cost efficacy data support the notion that utilization of the phasic treatment model cited previously for DID is associated with significant cost savings, although cost reductions are most notable in the patients with fewer comorbidities and a less chronic treatment course prior to DD diagnosis (Loewenstein, 1994). More research is needed on the social, occupational, and economic costs associated with DD and whether phasic trauma-focused treatment is associated with significant cost savings across a broad spectrum of DD patients.

The economic cost of DD suggests that a high priority should be developing effective and efficient treatments for dissociation. However, individuals with DD are unrecognized and underserved, according to a study that found that almost one third of those with a DD had not received previous psychiatric treatment (Sar, Akyuz, & Dogan, 2007). Furthermore, recent research suggests that dissociative individuals may drop out of current cognitive–behavioral treatments, indicating that programs that do not specifically address dissociation may not be well tolerated. For example, 55% of individuals with DD prematurely dropped out of treatment for drug abuse compared to 29% of those without DD (Tamar-Gurol, Sar, Karadag, Evren, & Karagoz, 2008). Children with higher parent-reported dissociation were also more likely to drop out of group treatment for sexual abuse than were those with lower levels of dissociation (Hebert & Tourigny, 2010).

Dissociation also appears to be associated with a more difficult, chronic course in treatment. Among inpatients with anxiety disorders, those with high dissociation were more likely to be unresponsive to treatment compared to those with low dissociation (Kleindienst et al., 2011; Spitzer, Barnow, Freyberger, & Grabe, 2007). Similarly, among outpatients receiving exposure therapy for PTSD, 69% of those in the high dissociation group still met criteria for PTSD at follow-up compared to only 10% of those low in dissociation (Hagenaars, van Minnen, & Hoogduin, 2010). However, both groups showed equal rates of change, although those high in dissociation were still clinically worse at the end of treatment. Another study found that dissociation predicted lower rates of abstinence among heroin users in treatment (Somer, 2003). These findings led Somer (2003) to conclude that "without a thorough resolution of trauma-related dissociation, optimal treatment outcome is compromised" (p. 339). In a study of exposure treatment for borderline patients, Ebner-Priemer et al. (2009) found

that state dissociative experience altered acquisition and extinction processes among dissociative borderline patients. Ebner-Priemer and colleagues warned that dissociative patients should be "closely monitored in exposure-based psychotherapy" (p. 214) because they may not respond well to exposure treatment.

Almost all of the current DD treatment research has included uncontrolled case series studies and prospective longitudinal studies that have followed patients during inpatient treatment or from inpatient to outpatient treatment. A recent review (B. L. Brand, Classen, McNary, & Zaveri, 2009) of the DD treatment literature concluded that when treatment is specifically adapted to address the complex traumas and high level of dissociation among these patients, even severely dissociative individuals improve. Eight uncontrolled studies provided data that were used to generate within-patient effect sizes. B. L. Brand, Classen, McNary, et al. (2009) found that the overall effect size of DD treatment was 0.71. The effect sizes for reduction in symptoms were generally large (depression = 1.12, dissociation = 0.70, anxiety = 0.94, somatoform symptoms = 0.83, and substance use = 0.78).

A prospective observational study using the longest follow-up to date is yielding comprehensive information about DD treatment outcome. This study, the Treatment Outcome for Patients with Dissociative Disorders (B. L. Brand, Classen, McNary, et al., 2009) is the largest DD treatment outcome study, with a sample of 280 DID or DDNOS patients and 292 therapists from 19 countries. The cross-sectional results have indicated that patients in the later stages of treatment had fewer symptoms of dissociation, PTSD, and general distress; fewer recent hospitalizations; and better adaptive functioning (e.g., Global Assessment of Functioning (GAF) scores) than patients in the early stages of treatment. The longitudinal results have demonstrated that patients showed less dissociation, PTSD, general distress, depression, and self-harm as well as improved functioning, including an increase in GAF scores, over 30 months of treatment (B. L. Brand et al., 2010).

In terms of pharamacotherapeutic interventions for dissociative symptoms, research using selective serotonin reuptake inhibitors in individuals with depersonalization disorder (DPD) has shown that serotonin agonists such as meta-chlorophenylpiperazine can induce symptoms of depersonalization (Simeon, Hollander, et al., 1995; Simeon, Stein, & Hollander, 1995). Although a number of case studies have suggested that selective serotonin reuptake inhibitors might be effective in treating DPD (as reviewed by Sierra, 2008), a randomized control trial failed to support their therapeutic efficacy (Simeon, Guralnik, Schmeidler, & Knutelska, 2004). Atypical antipsychotic drugs that block both D_2 and 5-HT_{2A} receptors may be of use in treating complex trauma cases with "psychotic features" (Bartzokis, Lu, Turner, Mintz, & Saunders, 2005; Pivac & Kozaric-Kovacic, 2006), although auditory hallucinations and voice hearing in subjects with trauma disorders could be conceptualized as dissociative rather than psychotic in some cases (Brewin &

Patel, 2010). Opioid antagonists have also shown some promise in the treatment of dissociative symptoms. The mu and kappa systems in particular have been implicated in symptoms of depersonalization and analgesia. For example, stress-induced analgesia, a form of dissociation, has been shown to be mediated by the mu opioid system. In addition, enadoline, a kappa opioid agonist, has been shown to induce symptoms of depersonalization in healthy controls (Pfeiffer, Brantl, Herz, & Emrich, 1986; Walsh, Geter-Douglas, Strain, & Bigelow, 2001). Naltrexone, an opioid antagonist, has exhibited some effect in reducing symptoms of DPD (Simeon & Knutelska, 2005) and dissociative symptoms in BPD (Bohus et al., 1999). Several trials are currently under way to examine the use of naltrexone in PTSD patients with comorbid substance abuse (e.g., see Petrakis et al., 2006).

In summary, recent research indicates that dissociative patients are more challenging and costly to treat and that they do not appear to tolerate or respond well to standard exposure therapy despite its strong empirical basis with acute PTSD. Nonetheless, they are able to benefit from specialized treatment. Currently there are no controlled or randomized psychotherapeutic outcome studies and very few randomized controlled trials examining pharmacotherapeutic treatments of DD treatment. Because research using random assignment to control groups provides the strongest empirical support, randomized controlled trials with DD patients are urgently needed. Recent research has made possible the development of the first manualized treatment studies of the stabilization phase for DID treatment.

DEVELOPMENTS IN NEUROBIOLOGY

Animal Defensive Responses as a Model of Dissociation

An informative body of animal and human neurobiological research related to dissociation is emerging, giving rise to a deeper understanding of the neurobiological basis of dissociation. Several investigators have delineated similarities between certain animal defensive responses and trauma-induced dissociative psychopathology in humans (Nijenhuis, Vanderlinden, & Spinhoven, 1998), and it has been suggested that the endogenous opioid system as well as glutamatergic regulation underlies some of these processes (Nijenhuis et al., 1998). The stages involved in animal defensive behavior are hypothesized to include (a) pre-encounter defense involving heightened orientation and diminished interest in food; (b) post-encounter defensive behavior during which the animal can manifest flight, freeze, and fight responses; (c) circa-strike defense during which the animal is about to be attacked, which involves analgesia, emotional numbing, and startle; and (d) post-strike behavior involving the experience of pain and recuperation (Bolles & Fanselow, 1980). Inescapable shock, a condition during which animals are subjected to

inescapable experimental traumatization such as with electrical shocks, starvation, and cold-water swimming, has been used to model all natural stages of animal defense behavior (Fanselow, Lester, & Helmstetter, 1988). Inescapable shock is normally followed by a state of helplessness, hypoarousal, freezing, tonic immobility, and analgesia. Even when animals are presented with a possibility of escape after the experimental traumatization, they usually remain helpless and passively endure continued shock (Seligman, 1972).

Striking similarities between animal defensive responses including freezing responses, tonic immobility, analgesia, and dissociative states in humans have been observed. For example, several studies have shown that a substantial number of women report freezing and paralysis during rape as well as following childhood abuse (Brickman & Briere, 1989; Burgess & Holmstrom, 1976), and the relationship between tonic immobility and dissociative symptoms in PTSD has been discussed (Bovin, Jager-Hyman, Gold, Marx, & Sloan, 2008; Fiszman et al., 2008; Heidt, Marx, & Forsyth, 2005; Humphreys, Sauder, Martin, & Marx, 2010; Rocha-Rego et al., 2009). In addition, psychometrically measured tonic immobility has been shown to correlate positively with dissociative symptoms (Abrams, Carleton, Taylor, & Asmundson, 2009).

Historical research in analgesia has informed current research. Both male and female patients suffering from dissociative symptomatology have been shown to present with analgesia when faced with painful stimuli (Beecher, 1946; Boon & Draijer, 1993; Ludascher et al., 2010). Beginning with World War II, soldiers have been found to exhibit significant analgesia to the point where they do not require morphine (Beecher, 1946; Pitman, van der Kolk, Orr, & Greenberg, 1990; van der Kolk, Greenberg, Orr, & Pitman, 1989). It has been hypothesized that emotional responses accompanying these reactions rely on prefrontal-amygdala cortex pathways (LeDoux, 2002). This pathway has been hypothesized to play an important role in the neural circuitry underlying states of depersonalization and derealization in humans (Lanius et al., 2010; Ludascher et al., 2010) and states of analgesia in response to thermal pain stimuli in patients with PTSD and with BPD (Geuze et al., 2007; Kraus et al., 2009; Ludascher et al., 2010; Mickleborough et al., 2011; Schmahl et al., 2006) as described below.

Neurological Etiologies of Dissociative Symptomatology in Humans' Emotional Under- and Overmodulation

We use the terminology outlined by van der Kolk, van der Hart, and Marmar (1996) to distinguish different types of dissociation. Reexperiencing and flashback responses are referred to as *primary dissociation;* symptoms of depersonalization, derealization, and analgesia are referred to as *secondary dissociation;* and *tertiary dissociation* refers to the development

of ego states that contain a traumatic experience, or complex identities with distinctive cognition, affective, and behavioral patterns. Researchers have studied the neuronal circuitry underlying reexperiencing/hyperarousal (primary dissociation) and depersonalization/derealization dissociative (secondary dissociation) responses in PTSD predominantly related to childhood abuse using the script-driven, symptom-provocation paradigm (reviewed in Lanius, Bluhm, Lanius, & Pain, 2006). In these studies, patients construct a narrative of their traumatic experience including as many sensory details as possible. These narratives are subsequently read to the patients, who are instructed to recall the traumatic memory as vividly as possible during a functional magnetic resonance imaging scan. Researchers have found that approximately 70% of patients relive their traumatic experience showing a predominant reexperiencing/hyperarousal response with an increase in heart rate whereas the remaining 30% have a predominant secondary dissociative response involving states of depersonalization and derealization with no significant concomitant increase in heart rate (Lanius, Vermetten, Loewenstein, et al., 2010).

Primary dissociation and emotional undermodulation: Failure of corticolimbic inhibition. Emotional undermodulation refers to symptoms of reexperiencing, flashbacks, and hyperarousal commonly associated with Cluster B symptoms of PTSD. These symptoms have also been referred to as *primary dissociative symptoms* because they involve intrusion into conscious awareness of fragmented traumatic memories, primarily in sensory rather than verbal form (van der Kolk et al., 1996). The traumatized group who experienced reexperiencing and hyperarousal symptoms as assessed by the Responses to Script-Driven Imagery Scale (Hopper, Frewen, Sack, Lanius, & van der Kolk, 2007) while hearing their trauma narratives concomitantly exhibited abnormally *low* activation in the medial prefrontal cortex and the anterior cingulate cortex, brain regions that are involved in modulating arousal and regulating emotion more generally (Etkin & Wager, 2007; Lanius et al., 2006). Consistent with the finding of impaired cortical modulation of affect and arousal, increased activation of the limbic system, especially the amygdala (a brain structure that plays a key role in fear conditioning), has often been observed in PTSD patients after exposure to traumatic reminders and to masked fearful faces (Etkin & Wager, 2007). Studies in PTSD patients have also recently shown direct inhibitory influence of the prefrontal cortex on the emotional limbic system. For example, positron emission tomography studies have shown a negative correlation between blood flow in the left ventromedial prefrontal cortex and the amygdala during emotional tasks and negative correlations between the medial prefrontal cortex and the amygdala during exposure to fearful faces (Shin et al., 2005). Thus, the *low* activation of medial prefrontal regions described in the reexperiencing/hyperaroused PTSD subgroup is consistent with failed inhibition of limbic reactivity and is associated with reexperiencing/hyperaroused emotional undermodulation.

We conceptualize this group of patients as experiencing *emotional undermodulation* in response to traumatic reminders such as a subjective reliving of the traumatic event, including flashbacks and reliving nightmares. These symptoms can be viewed as a form of emotion dysregulation that involves emotional undermodulation mediated by failure of prefrontal inhibition of limbic regions.

Secondary dissociation and emotional overmodulation: Excessive corticolimbic inhibition. Emotional overmodulation refers to symptoms of depersonalization, derealization, and analgesia. These symptoms have also been referred to as *secondary dissociative symptoms* because they involve the mental "leaving" of the body and observing of what happens from a distance during the recollection of trauma (e.g., depersonalization/derealization) or during the experience of reduced pain perception (e.g., analgesia; van der Kolk et al., 1996). A recent review proposed clinical and neurobiological evidence for a dissociative subtype of PTSD (Lanius, Vermetten, Loewenstein, et al., 2010). In that review, Lanius, Vermetten, Loewenstein, et al. (2010) provided evidence across various researchers in different labs showing that, in contrast to the reexperiencing/hyperaroused group, the group experiencing secondary dissociative symptoms, including states of depersonalization and derealization, exhibited abnormally *high* activation in the anterior cingulate cortex and the medial prefrontal cortex. The depersonalization/derealization dissociative PTSD patients can therefore be conceptualized as experiencing emotional overmodulation in response to recalling a traumatic memory, accompanied by increased activation of medial prefrontal structures and hyperinhibition of limbic regions, including the amygdala (see Figure 1).

A study by Felmingham et al. (2008) provided further evidence for the corticolimbic inhibition model. In this study, brain activation during the processing of consciously and nonconsciously perceived fear stimuli was compared. Patients with high dissociation scores showed enhanced activation in the ventral prefrontal cortex during conscious fear processing compared to patients with low secondary and tertiary dissociation scores as measured by the Clinician-Administered Dissociative States Scale (Bremner et al., 1998). The authors suggested that these data support the theory that dissociation, including states of depersonalization and derealization, is a regulatory strategy invoked to cope with extreme arousal in PTSD through hyperinhibition of limbic regions and that this strategy is most active during the conscious processing of threat.

Emotional overmodulation: Lessons from analgesia. The neurobiology literature focusing on pain is also providing emerging support for the hyperinhibition of the limbic system, including the amygdala, during dissociative states. For example, Roeder, Michal, Overbeck, van der Ven, and Linden (2007) reported decreased amygdala activity in response to painful stimulation during hypnosis-induced states of depersonalization in healthy subjects.

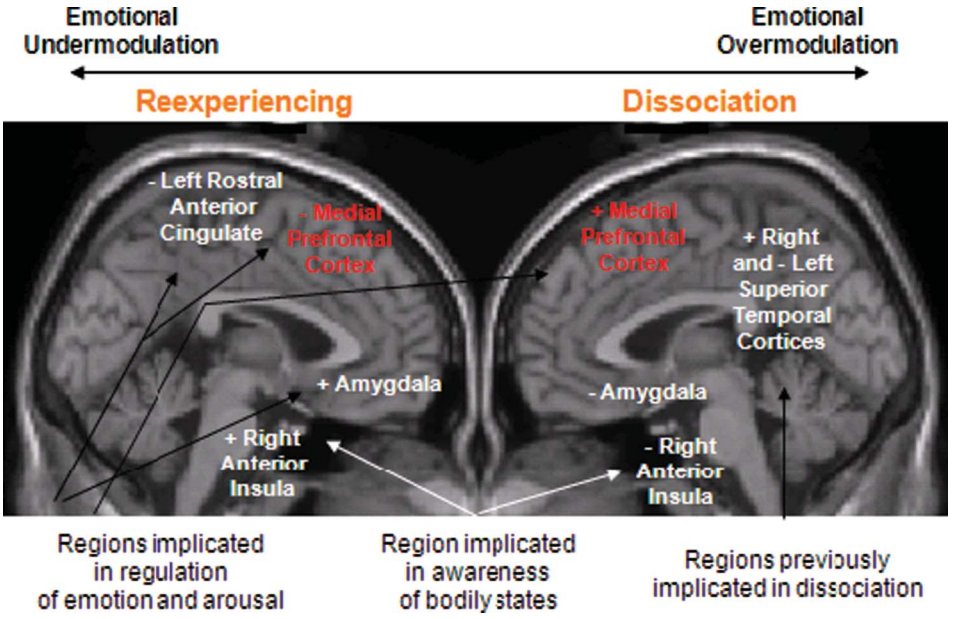

FIGURE 1 Emotion dysregulation in posttraumatic stress disorder. In this model, reexperiencing/hyperarousal reactivity to traumatic reminders is viewed as a form of emotion dysregulation that involves emotional undermodulation mediated by failure of prefrontal inhibition of limbic regions. In contrast, the dissociative reactions to traumatic reminders are a form of emotion dysregulation that involves emotional overmodulation mediated by midline prefrontal inhibition of the same limbic regions. Copied with permission from the *American Journal of Psychiatry* (color figure available online).

In patients with PTSD and BPD, amygdala deactivation was also observed in response to thermal pain stimuli (Geuze et al., 2007; Kraus et al., 2009; Schmahl et al., 2006), and right amygdala response was negatively correlated with trait dissociation as measured by the Dissociative Experiences Scale in PTSD (Mickleborough et al., 2011). The script-driven imagery paradigm has also been utilized to specifically induce secondary dissociative states in patients with BPD while also assessing pain sensitivity in response to thermal pain stimuli (Ludascher et al., 2010). In this study, individual situations eliciting secondary dissociative symptoms were depicted for each patient. Higher levels of secondary dissociation as assessed by the Dissociation-Tension-Scale (Stiglmayr, Schmahl, Bremner, Bohus, & Ebner-Priemer, 2009) were found during the presentation of these scripts in comparison to during the presentation of neutral scripts. In addition, pain sensitivity was significantly lower during the presentation of the trauma-induced dissociative scripts compared to the neutral scripts. On a neural level, higher activity in the dorsolateral prefrontal cortex was found during these dissociative states. In a subgroup analysis of 10 patients with both BPD and PTSD, increased activity was found in the right insula and left cingulate cortex during dissociation,

suggesting cortical inhibition and thus providing further evidence for the corticolimbic inhibition model.

Emotional overmodulation: Lessons from DD. Studies of DA, dissociative fugue, DPD, and DID provide additional evidence for the corticolimbic inhibition model. Neurobiological studies of individuals with DA and/or dissociative fugue have shown inhibition of the hippocampus and occipital cortex areas, similar to neural network patterns found in experimental studies of memory suppression and hypnotic amnesia (Hennig-Fast et al., 2008; Kikuchi et al., 2010). A recent study has also shown that DA has been associated with decreased metabolism within the right inferolateral prefrontal cortex using fluorodeoxyglucose positron emission tomography (Brand et al., 2009).

An investigation of a group of DPD patients examined event-related functional magnetic resonance imaging in response to neutral, mild, and intensely happy and sad facial expressions with simultaneous measurements of skin conductance levels (Lemche et al., 2007). Compared to healthy controls, DPD patients showed a decrease in subcortical limbic activity to increasingly intense happy and sad facial expressions. Psychophysiologically speaking, for both happy and sad facial expressions, DPD patients but not healthy controls exhibited negative correlations between skin conductance measures and activation in the bilateral dorsal prefrontal cortices. This study supports the hypothesis that DPD subjects exhibit increased prefrontal activity and/or decreased limbic activity resulting in the hypoemotionality frequently reported in these patients, adding weight to the overmodulation model to explain states of depersonalization. In terms of DID, Reinders et al. (2006) examined a group of patients with DID in two identity states: a neutral state that inhibits access to the traumatic memories and thus enables daily life functioning and a traumatic state that has access to the traumatic memories. Results revealed different patterns of regional cerebral blood flow in response to neutral and traumatic scripts in the two dissociative identity states. Specifically, trauma-focused identity states showed increased amygdala and insula activation with associated hyperarousal compared to trauma-avoidant identities, which showed decreased medial prefrontal activation with little or no autonomic activation.

Structural imaging has also examined limbic structures, including the hippocampus and amygdala, in DD. Although Vermetten and colleagues reported a reduced volume of the hippocampus and amygdala in patients with DID (Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006), these results were not replicated in subsequent studies, in which structural abnormalities were associated with PTSD but not with DD without PTSD (Irle, Lange, Sachsse, & Weniger, 2009; Weniger, Lange, Sachsse, & Irle, 2008). Future studies will need to further examine the issue of hippocampal volume in DD and PTSD, especially in light of more recent well-controlled

studies that did not report hippocampal volume changes in PTSD (Francati, Vermetten, & Bremner, 2007; Woodward et al., 2006).

The findings described here support the corticolimbic inhibition model of excessive limbic inhibition resulting in secondary dissociation symptoms in PTSD as well as in other trauma spectrum disorders such as BPD, DPD, and DID. They are also consistent with the phenomenology and clinical presentation of these patients, who often present with symptoms of depersonalization and derealization as well as analgesia.

SUMMARY AND FUTURE DIRECTIONS

Researchers' understanding of DD has been facilitated not only by advances in neuroimaging technology and developments in empirically based investigation tools, strategies, and methodologies but also by a willingness on behalf of mainstream researchers and theoreticians to acknowledge the importance of traumatic dissociation in psychopathology and to investigate its underpinnings (Dalenberg et al., 2007). Compared to other psychiatric disorders, DD are associated with severe symptoms, including frequent suicide attempts and self-injurious behaviors, as well as a high rate of utilization of mental health treatment. As a result, DD exact a high economic as well as personal cost on patients and society. Research in the past 5 years indicates that DD patients show a poor response to standard trauma treatment as well as high levels of attrition from treatment. An emerging body of naturalistic and open trials suggests that patients who receive specialized treatment that addresses their trauma-based, dissociative symptoms show improved functioning and reduced symptoms. Expert-recommended treatment interventions and prognostic indicators have recently been developed, making the creation of a manualized treatment of the stabilization phase for DID feasible for the first time. Manualized and controlled treatment studies of DD are urgently needed. In terms of assessment, research is needed to aid in the accurate diagnosis of DD, particularly genuine versus factitious and/or malingered dissociative and trauma-related disorders.

Recent studies of the underlying neurobiological basis for dissociation support a model of inadequate limbic inhibition underlying reexperiencing such as flashbacks. In contrast, excessive limbic inhibition is proposed to underlie symptoms of depersonalization, derealization, analgesia, and DA. Future neurobiological research should prospectively examine dissociative processes to determine how these responses change with exposure to stressors, treatment, and the progression of illness and to determine the exact relationship between traumatic experience and dissociative symptomatology. Furthermore, neurobiological research needs to use larger sample sizes so that conclusions drawn from the studies can be made with more certainty. Additional research priorities include the identification of

dissociative phenotypes that may help guide treatment and the investigation of biological processes underlying dissociation before and after treatment. In particular, it will be important to study neurobiological changes associated with treatment.

It is promising for our field that studies about dissociation are gaining a foothold in a wide range of psychiatric journals in part because of exciting neurobiological research that shows dissociative responses in brain imaging studies. Much remains to be learned about the neurobiology, assessment, diagnosis, and treatment of DD and trauma disorders. We are optimistic that the forthcoming *DSM-5* will stimulate more research on dissociation and the DD.

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