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Posttraumatic Stress Disorder and comorbidity: Untangling the Gordian knot

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Abstract

The high rates of psychiatric comorbidity for individuals with posttraumatic stress disorder (PTSD) have long been noted. The conceptual, clinical and etiological relationships between PTSD and other disorders are so interwoven and multi-determined that understanding and treating posttraumatic psychopathology can feel like trying to untangle the legendary Gordian knot. This paper examines the varying streams of research seeking to better understand this extensive comorbidity. These streams of research include examination of the bi-directional relationships in the development of PTSD and key mood, anxiety and substance use disorders; the study of the shared manifest and common higher order features across these disorders and investigations of underlying biopsychosocial vulnerabilities. Finally the paper examines the preliminary findings emerging using the new DSM-5 criteria for PTSD and queries whether these revised criteria will address the issue of comorbidity and assist in untangling the knot of posttraumatic comorbidity.

The high rates of psychiatric comorbidity for individuals with posttraumatic stress disorder (PTSD) have long been noted. Data from the US National Comorbidity Surveys (NCS) has shown that 88.3% of men and 79.0% of women with PTSD also met criteria for at least one additional diagnosis, with two-thirds meeting criteria for at least two other diagnoses (Kessler, Sonnega, Hughes, & Nelson, 1995), and that 48-55% of individuals with a lifetime history of PTSD also had a lifetime history of major depression (Elhai, Grubaugh, Kashdan, & Frueh, 2008). In a sample of 1,127 psychiatric outpatients, Brown, Campbell, Lehman, Grisham, and Mancill (2001) found that 92% of those with a principal current diagnosis of PTSD also met criteria for another Axis I condition, with 69% meeting criteria for major depressive disorder (MDD), 38% for generalised anxiety disorder (GAD) and 23% for panic disorder. Furthermore, PTSD was associated with significantly greater risk than other mood and anxiety disorders for any current or lifetime Axis I or mood disorder comorbidity. Fully 100% of participants with current PTSD had met criteria for another Axis I condition at some point in their lives, and of those with a lifetime diagnosis of PTSD, 82% had also experienced MDD and 60% had experienced panic disorder with agoraphobia (PD/A). Individuals with PTSD are three- to five-times more likely to develop a substance use disorder (SUD), resulting in SUD comorbidity in nearly half of all PTSD patients ((Breslau, Davis, & Schultz, 2003; Creamer, Burgess, & McFarlane, 2001; Mills, Teesson, Ross, & Peters, 2006; Perkonigg, Kessler, Storz, & Wittchen, 2000). Conversely, prevalence estimates for PTSD in SUD samples vary from 11% to 41% (Harrington & Newman, 2007; Ouimette, Goodwin, & Brown, 2006; Van Dam, Ehring, Vedel, & Emmelkamp, 2010).

While most research into the PTSD comorbidity focuses on mood, anxiety and substance use disorders, heightened rates of PTSD comorbidity have been observed across a range of psychiatric conditions. A review by Friborg, Martinussen, Kaiser, Overgard, and Rosenvinge (2013) found a rate of Axis II comorbidity with PTSD of 35%, with paranoid, avoidant, borderline and obsessive-compulsive personality disorders being particularly common in patients with PTSD. Sareen, Cox, Goodwin, and Asmundson (2005), using NCS data, found that individuals with PTSD were more likely to endorse one or more psychotic symptoms after adjustment for demographics and other

comorbidities. Conversely, studies of individuals with a primary diagnosis of a psychotic disorder have found rates of comorbid PTSD ranging from 13% to 46% when using structured interviews (see Grubaugh, Zinzow, Paul, Egede, and Frueh (2011) for a review).

Pervasive comorbidity is perceived as problematic as it makes it difficult for researchers to identify 'pure' cases and, assuming such 'pure' cases could be found, complicates the application of research findings to clinical contexts (Brown et al., 2001; Krueger & Markon, 2006). In addition, high rates of comorbidity raise a number of interesting questions about the nature of PTSD and its relationship to other conditions. Does trauma exposure, or the presence of PTSD symptoms, lead to other disorders in addition to PTSD? Or does the presence of other disorders predispose individuals to PTSD, either by increasing the risk of exposure to trauma, or by increasing vulnerability to the development of PTSD symptoms given trauma exposure? Or is there a reciprocal relationship between trauma exposure and/or PTSD, and other disorders?

Another potential source of PTSD comorbidity may be how PTSD is currently defined. PTSD comprises a broad and heterogeneous collection of symptoms (Blanchard, Hickling, Taylor, Loos, & Gerardi, 1994), including symptoms that also define other disorders such as MDD and GAD, which may result in spuriously inflated comorbidity rates and potential misdiagnoses ((Frueh, Elhai, & Acierno, 2010; McNally, 2003; Rosen & Lilienfeld, 2008; Spitzer, First, & Wakefield, 2007; Watson, 2005). Alternatively, PTSD may not be broadly enough defined to encompass the broad range of symptoms that may follow exposure to traumatic events (van der Kolk, Roth, Pelcovitz, Sunday, & Spinazzola, 2005), leading to an over-reliance on other diagnostic categories to capture the full clinical picture of posttraumatic psychopathology. However, attempts to define a categorical posttraumatic syndrome that is both unique and specific yet comprehensive enough to cover the diverse range of reactions to trauma exposure may not be possible if PTSD and other conditions are underpinned by common etiologies and/or vulnerabilities that vary across disorders in a continuous fashion. This paper will briefly explore hypothesised causal relationships between PTSD and other disorders, before exploring in detail the possibility that symptom overlap between PTSD and other disorders or common underlying vulnerabilities may account for high rates of comorbidity.

Does PTSD predispose individuals to develop other disorders?

The features of an existing disorder may increase vulnerability to subsequent conditions. For example, the physiological reactivity triggered by intrusive recollections of traumatic events in PTSD may evolve into PD/A if fear of these somatic symptoms is present (Brown et al., 2001). In fact, temporal sequence analyses by Brown et al. (2001) found that the onset of PTSD more frequently preceded that of PD/A than vice versa. In a similar vein, many studies have presented data suggesting that PTSD is the primary response to trauma exposure, with MDD developing as a consequence of PTSD (Breslau, Davis, Peterson, & Schultz, 1997; Ginzburg, Ein-Dor, & Solomon, 2010; Jordan, Schlenger, Hough, Kulka, & et al., 1991; Kessler et al., 1995; McFarlane & Papay, 1992; Mellman, Randolph, Brawman Mintzer, Flores, & et al., 1992; Skodol, Schwartz, Dohrenwend, Levav, & et al., 1996); however, many of these studies were cross-sectional and relied on retrospective reports of symptom onset (Erickson, Wolfe, King, King, & Sharkansky, 2001). A latent variable cross-lag panel model study (Erickson et al., 2001) found that evidence for a reciprocal relationship between PTSD and depression, although initial PTSD symptoms were more predictive of later depression than vice versa. The magnitude of the standardized path from PTSD avoidance and numbing symptoms to depression in the Erickson et al. (2001) study was larger, suggesting that reduced positive interactions and affective dampening arising with avoidance and numbing symptoms could be driving the increase in symptoms of depression.

Among the theories proposed to explain the high comorbidity between PTSD and SUD, the most evidence exists for the self-medication hypothesis (van Dam, Ehring, Vedel, & Emmelkamp, 2013; van Dam, Vedel, Ehring, & Emmelkamp, 2012). The self-medication hypothesis (Khantzian, 1997; Stewart & Conrod, 2002) proposes that substances are used to alleviate or suppress pre-existing PTSD symptoms. Research findings in support of this include that: (i) SUD is preceded by PTSD more often than vice versa (Stewart & Conrod, 2003); (ii) increased PTSD symptoms is a key predictor of relapse following SUD treatment (H. W. Clark, Masson, Delucchi, Hall, & Sees, 2001); (iii) improvements in PTSD symptoms are associated with improvements in substance dependence (Back, Brady, Sonne, &

Verduin, 2006; D. A. Hien et al., 2010); and (iv) trauma-related cues may trigger a craving for substances (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Coffey et al., 2002).

PTSD has also been implicated in the development and maintenance of psychotic illnesses. The neurodevelopmental effects of childhood trauma may lead to high stress responsivity among individuals with schizophrenia (Read, Perry, Moskowitz, & Connolly, 2001); (Read, van Os, Morrison, & Ross, 2005) and subsequent trauma exposure and PTSD symptoms may exacerbate symptoms of psychosis or precipitate relapse (Grubaugh et al., 2011; Rosenberg, Lu, Mueser, Jankowski, & Cournos, 2007). PTSD symptoms also may mediate the relationship between trauma exposure, psychotic symptoms, and service use directly through symptoms of avoidance, distress, and over-arousal, and indirectly through substance abuse, re-victimisation and distrust of service providers (Mueser, Rosenberg, Goodman, & Trumbetta, 2002).

Does the presence of other disorders predispose individuals to PTSD?

In contrast to the findings listed above, other researchers have found that PTSD follows depression, perhaps as a result of the latter increasing the risk of exposure to traumatic events, or increasing trauma victims' susceptibility to PTSD (Ginzburg et al., 2010). O'Toole, Marshall, Schureck, and Dobson (1998) found that when PTSD and depression are comorbid, depression onset usually preceded PTSD onset. King, King, McArdle, Shalev, and Doron-LaMarca (2009) found that increases in depression symptom severity predict subsequent increasees in PTSD symptoms of intrusion, numbing and hyperarousal shortly after the traumatic event. They speculated that depressive ruminations in the wake of trauma are experienced by victims as powerful reminders of the event characteristic of PTSD intrusions symptoms, and that the poor sleep and concentration symptoms of depression symptoms trigger PTSD hyperarousal, including exaggerated startle response and vigilance. Alternatively, high levels of depression may reflect a sense of helplessness, and loss of mastery, which would attenuate motivation to resolve PTSD symptoms through help-seeking and other adaptive responses(King et al., 2009).

As an alternative to the self-medication hypothesis, the high risk hypothesis proposes that SUD places individuals at greater risk for experiencing trauma and thereby at greater risk of developing PTSD (D. Hien, Cohen, & Campbell, 2005). In line with this, there is some evidence to suggest that in some cases SUD precedes PTSD and that treatment of SUD leads to a reduction in PTSD symptoms (see van Dam et al. (2013) for a review). Indeed, a reciprocal relationship between the disorders may best account for the high rates of co-morbidity between PTSD and SUD (Stewart & Conrod, 2003; van Dam et al., 2013; van Dam et al., 2012). This hypothesis is also supported by findings that SUD patients frequently first reported trauma, then substance use, which again was followed by additional traumatic experiences, and further substance use (van Dam et al., 2013).

There may also be a reciprocal relationship between psychotic conditions and PTSD. Some cases of PTSD among individuals with psychotic illnesses may be attributable to the high rates of traumatic experiences, such as sexual and physical assaults, that occur in psychiatric settings, as well as the inherently traumatic nature of experiencing a psychotic episode ((Frueh et al., 2005; Grubaugh et al., 2011; Mueser, Rosenberg, & Wolfe, 2010).

Does trauma exposure cause other disorders in addition to PTSD, or does PTSD capture the full range of posttraumatic psychopathology?

While other disorders such as MDE and SUD may develop as a consequence of (untreated) PTSD, it is possible that trauma exposure itself drives the onset of these and other disorders, in turn driving high rates of comorbidity. Exposure to traumatic events is implicated in the development of a number of mental disorders other than PTSD, including acute stress disorder, adjustment disorder, MDD, GAD, panic disorder, borderline personality disorder, specific phobias, substance use disorders and dissociative identity disorder (Brewin, Lanius, Novac, Schnyder, & Galea, 2009; Dell & O'Neil, 2009; Fullerton & Ursano, 2005; Gabriel et al., 2007; Handley, Salkovskis, Scragg, & Ehlers, 2009; Herman, Perry, & Van der Kolk, 1989; Leskin & Sheikh, 2002; McQuaid, Pedrelli, McCahill, & Stein, 2001). With respect to psychotic disorders, rates of trauma exposure in general are higher among individuals with serious mental illness than in the general population (Mueser et al., 2001;

Neria, Bromet, Sievers, Lavelle, & Fochtmann, 2002), ranging from 50% to 100% and including high rates of both physical and sexual assault (see Grubaugh et al. (2011) for a review). In contrast to the findings reviewed above, some studies show that PTSD and MDD have simultaneous onset following trauma exposure (Bleich, Koslowsky, Dolev, & Lerer, 1997; Shalev et al., 1998), and as such may be independent sequelae of traumatic events (Shalev et al., 1998), possibly reflecting differences in the type of trauma exposure (see Momartin et al, 2004 for a review).

Alternatively, high rates of comorbidity may be an artefact of failing to define PTSD in a way that captures the full range of psychopathology that occurs after traumatic exposure (van der Kolk et al., 2005). Exposure to traumatic events may be followed by a variety of symptoms, not all of which are encompassed by existing PTSD diagnostic criteria, including anxiety, dysphoria, anhedonia, guilt, shame, derealisation, depersonalisation, aggressive behaviour and negative appraisals about oneself and the world (Friedman, Resick, Bryant, & Brewin, 2011; Resick & Miller, 2009). In particular, individuals exposed to severe and protracted traumatic exposure of an interpersonal nature – typically childhood sexual abuse victims, adult refugees, and adult torture survivors – often meet criteria for PTSD, but also experience emotional and behavioural dysregulation (rage, despair, impulsivity, aggression, sexual acting out and self-harm) as well as somatization, interpersonal difficulties and symptoms of dissociation and identity disturbance (Friedman et al., 2011; Herman, 1992a; van der Kolk et al., 2005). ‘‘Complex PTSD’’ was proposed by Herman (1992b) to encompass these reactions to ongoing, inescapable trauma of an interpersonal nature. The DSM-IV Work Group renamed this syndrome Disorders of Extreme Stress Not Otherwise Specified (DESNOS) but rejected it for inclusion in DSM-IV on the basis of a field trial that found only 8% of individuals meeting criteria for DESNOS did not also meet criteria for PTSD (Friedman et al., 2011; van der Kolk et al., 2005). Thus, such “complex” presentations may not reflect the presence of a distinct disorder, but rather a subtype of PTSD (Friedman et al., 2011).

The potential need for subtyping of PTSD as a result of the diversity of posttraumatic psychopathology is illustrated by both dissociative and psychotic symptoms. Dissociative symptoms such as flashbacks and psychogenic amnesia are included as part of PTSD diagnostic criteria.

However, evidence suggests that dissociative symptoms following trauma such as derealization (i.e., feeling as if the world is not real) and depersonalization (i.e., feeling as if oneself is not real) are accompanied by specific biological and psychopathological correlates and treatment responses. This evidence includes latent class analyses (Steuwe, Lanius, & Frewen, 2012; Wolf et al., 2012) that have identified subgroups (12% - 30%) of individuals with PTSD reporting higher rates of flashbacks, depersonalisation and derealisation, along with higher rates of sexual trauma, Axis I comorbidity, overall PTSD severity and childhood abuse and neglect. A review of epidemiological data by Stein et al. (2013) also found evidence for a dissociative subtype of PTSD associated with repeated traumatization, early adverse experiences, early onset of PTSD symptoms, comorbid anxiety disorders, greater suicidality and functional impairment. Evidence also suggests dissociative symptoms in PTSD are neurobiologically distinct from re-experiencing/ hyperarousal symptoms in that the latter are associated with reduced activation in the medial prefrontal- and the rostral anterior cingulate cortex and increased amygdala reactivity. Dissociative symptoms, on the other hand are associated with increased activation in the rostral anterior cingulate cortex and the medial prefrontal cortex (Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012; Lanius et al., 2010). Finally, individuals with PTSD and dissociative symptoms tend to respond better to treatments that included cognitive restructuring and affective and interpersonal skills training in addition to the usual exposure-based therapies (Cloitre, Petkova, Wang, & Lu Lassell, 2012; Resick, Suvak, Johnides, Mitchell, & Iverson, 2012). With respect to psychotic symptoms, a review by Braakman, Kortmann, and van den Brink (2009) concluded that PTSD with secondary psychotic features is a syndrome, distinguishable from schizophrenia, consisting of PTSD followed by hallucinations and delusions, which are pervasive and related to traumatic events.

The diversity of posttraumatic psychopathology may also reflect cultural differences, which may in turn influence comorbidity (Hinton & Lewis-Fernández, 2011), The DESNOS conceptualisation of posttraumatic symptomatology may be particularly helpful here because it emphasizes dissociation and somatization, two symptoms that are often seen in traumatized non-Western cohorts (Kirmayer, 1996). Culture-specific posttraumatic reactions such as *ataque de nervios* among Latino populations,

ihahamuka among Rwandan genocide survivors and *khyal* among Cambodian refugees emphasis symptoms of panic, which may lead to greater comorbidity between panic disorder and PTSD in these groups ((Hagengimana, Hinton, Bird, Pollack, & Pitman, 2003; Hinton, Hofmann, Pitman, Pollack, & Barlow, 2008; Hinton & Lewis-Fernández, 2011). Similarly, comorbidity between PTSD and MDD may be enhanced in refugee groups who have endured not only war or genocide but bereavement, separation from loved ones and loss of language or cultural rituals (Eisenbruch, 1991; Hinton & Lewis-Fernández, 2011; Hinton & Nickerson, 2010).

Does symptom overlap account for high rates of comorbidity with PTSD?

An alternative perspective on PTSD comorbidity holds that the diagnostic criteria for PTSD include symptoms that are also part of the diagnostic criteria for other disorders. The majority of the research into PTSD comorbidity has been undertaken with the DSM-IV classification system; thus it would be useful to review DSM-IV diagnostic criteria for PTSD here. In addition to exposure to a traumatic event, DSM-IV diagnostic criteria (American Psychiatric Association, 1994) for PTSD require at least 1 of 5 re-experiencing symptoms (B1-B5; distressing recollections, nightmares, flashbacks, and psychological and physiological distress in relation to trauma-related cues); at least 3 of 7 avoidance and numbing symptoms (C1-C7; avoidance of thoughts about the trauma, avoidance of people or places associated with the trauma, psychogenic amnesia, diminished interest, feeling detached and estranged from others, restricted affect and sense of foreshortened future) and at least 2 of 5 arousal symptoms (D1-D5; poor sleep, irritability, poor concentration, hypervigilance and exaggerated startle response). However, confirmatory factor analyses (CFAs) of the latent structure of PTSD symptoms suggest that they would be better classified into four groups, based on either one of two four-factor models specified by King, Leskin, King, and Weathers (1998) and Simms, Watson, and Doebbeling (2002) respectively (see Elhai and Palmieri (2011) or Yufik and Simms (2010) for a review). The King et al. (1998) four-factor model comprises a Re-experiencing factor (DSM-IV PTSD symptoms B1-B5), an Avoidance factor (C1-C2), a Numbing factor (C3-C7) and a Hyperarousal factor (D1-D5). The Simms et al. (2002) four-factor model comprises an Intrusions factor (items B1–B5), an Avoidance factor (C1–C2), a Dysphoria factor (C3–C7; D1–D3) and a Hyperarousal factor (D4–D5).

Notably, the Simms et al. (2002) Dysphoria factor comprises items such as diminished interest (C4), restricted affect (C6), sense of foreshortened future (C7), difficulty sleeping (D1), irritability (D2) and poor concentration (D3), which are also symptoms of MDD and/or GAD (American Psychiatric Association, 1994). Simms et al. (2002) argued that their Dysphoria factor may reflect the non-specific general distress or negative affectivity component identified by L. A. Clark and Watson (1991) and Brown, Chorpita, and Barlow (1998) as common to many mood and anxiety disorders. When investigating the convergent and discriminant validity for their four-factor model, Simms et al. (2002) found that their Dysphoria factor was significantly more highly correlated with measures of GAD and MDD symptoms than were symptoms of Intrusions, Avoidance or Hyperarousal. Palmieri, Weathers, Difede, and King (2007) also found that Simms et al. (2002) Dysphoria symptoms were more highly correlated with measures of anger, depression and general distress than were other PTSD symptoms.

The presence of these overlapping or 'Dysphoria' symptoms in the diagnostic criteria for PTSD might therefore account for the high rates of comorbidity between PTSD and other mood and anxiety disorders (Brewin et al., 2009; Forbes, Parslow, et al., 2010; Rosen & Lilienfeld, 2008; Simms et al., 2002; Spitzer et al., 2007). Accordingly, a number of proposals have been made to delete some or all of these symptoms – or more – from the diagnostic criteria, in order to limit cases of spurious comorbidity. In addition to Dysphoria symptoms C3-C7 and D1-D3, Brewin et al. (2009) argued that symptom B1 (recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions) conflates intrusive and involuntary trauma-related imagery with the rumination typically seen in depression, thus rendering the symptom too nonspecific to PTSD. Likewise, Brewin et al. (2009) argued that symptoms B4 and B5 (emotional and physiological arousal) following exposure to traumatic reminders) are too similar to symptoms found in specific and social phobic disorders. As such, Brewin et al. (2009) proposed reducing the diagnostic criteria for PTSD to (i) at least one of symptoms B2 and B3 (nightmares and flashbacks), (ii) at least one of symptoms C1 and C2 (avoidance of thoughts or feelings and avoidance of people or places associated with the traumatic event; and (iii) at least one of symptoms D4 and D5 (hypervigilance and

exaggerated startle response). Using data obtained through structured interviews of treatment-seeking civilian trauma survivors, van Emmerik and Kamphuis (2011) comparing rates of comorbid depression and other anxiety disorders using both the reformulated criteria of Brewin et al. (2009) and the original DSM-IV criteria for PTSD. Prevalence rates of PTSD in the van Emmerik and Kamphuis (2011) sample were the same regardless of the criteria used; however 13% of participants lost or gained a PTSD diagnosis using the Brewin criteria. Interestingly, however, while rates of comorbid depression and other anxiety disorders were marginally lower under the Brewin criteria, these differences did not reach significance.

Along similar lines, Spitzer et al. (2007) argued for the removal of symptoms C3 (psychogenic amnesia), C4 (diminished interest), D1 (sleep difficulties), D2 (irritability), and D3 (poor concentration), and combining the remaining Criterion C and D symptoms into a single avoidance/hyperarousal cluster, from which at least four symptoms would be required to make the diagnosis. Using data from the NCS, Elhai et al. (2008) found that using the Spitzer et al. (2007) criteria had little impact PTSD comorbidity rates, a finding that was borne out in a military sample (Grubaugh, Long, Elhai, Frueh, & Magruder, 2010) and an adolescent sample (Ford, Elhai, Ruggiero, and Frueh (2009); with the exception of lower rates of comorbid MDE in the Ford et al. (2009) study when only three avoidance/hyperarousal symptoms were required). Thus, despite distinctively high correlations between Dysphoria symptoms and measures of symptoms of depression, anxiety or general distress, removing these and other arguably nonspecific symptoms from the DSM-IV diagnostic criteria for PTSD had little impact on comorbidity rates. Indeed, a counterargument to removing Dysphoria symptoms is that they emphasise negative mood states and cognitions that are integral to PTSD (Friedman et al., 2011). The Simms et al. (2002) Dysphoria factor also encompasses the Numbing symptoms which, despite their apparent overlap with symptoms of MDD, have been found to be specific to PTSD (Breslau, Reboussin, Anthony, & Storr, 2005; Kashdan, Elhai, & Frueh, 2006; Ruscio, Weathers, King, & King, 2002), distinct from depression (Flack, Litz, Hsieh, Kaloupek, & Keane, 2000; Litz et al., 1997), and to contribute to the prediction of PTSD after depression has been controlled for (Feeny, Zoellner, Fitzgibbons, & Foa, 2000). Foa, Riggs, and Gershuny (1995)

argued that PTSD should not be diagnosed in the absence of numbing symptoms, after finding that numbing symptoms better distinguished those with PTSD from those without PTSD than other symptoms and were associated with greater symptom severity.

Do common underlying etiologies or vulnerabilities account for the high rates of comorbidity between PTSD and other disorders?

The investigations into the impact of overlapping symptoms on the high rates of comorbidity outlined above have implicitly assumed that PTSD and other disorders are inherently categorical, and that it is possible to "carve nature at its joints" in order to create a psychiatric nosology in which symptom overlap and hence comorbidity between different conditions is minimised. This approach is epitomised by a classic paper by Robins and Guze (1970) in which the five phases of establishing the diagnostic validity of psychiatric illnesses – clinical description, laboratory studies, delimitation from other disorders, follow-up studies and family studies – were outlined. The third requirement –that disorders exhibit distinct boundaries from each other – is arguably failed by the high rates of comorbidity in PTSD, or indeed by high rates of comorbidity across many disorders. However, as discussed above, other explanations for high rates of comorbidity include that some disorders play causal roles in others, or the existence of common genetic or environmental vulnerabilities that predispose an individual to a range of disorders (Hyman, 2011). As such, existing psychiatric nosologies may be mistakenly distinguishing conditions that are minor variations of broader underlying syndromes (Brown et al., 2001). The latter possibility is highlighted by the failure to find "zones of rarity" between diagnoses based on symptomatic overlap and epidemiologic findings (Kendell & Jablensky, 2003), as well as the molecular genetic findings of the Cross-Disorder Group of the Cross-Disorder Group of the Psychiatric Genomics Consortium and Genetic Risk Outcome of Psychosis (GROUP) Consortium (2013) which point to common vulnerabilities for neurodevelopmental disorders (autism spectrum disorder and attention deficit hyperactivity disorder), schizophrenia, bipolar disorder, and major depressive disorder (Regier, Friedman, Kraemer, Narrow, & Kupfer, 2013). With regard to PTSD, behaviour genetic studies suggest that common genetic factors may account for the co-occurrence of PTSD with other disorders including substance

dependence (Koenen et al., 2005; Xian et al., 2000), MDE and dysthymia (Fu et al., 2007; Koenen et al., 2003), and GAD, and panic disorder (Chantarujikapong et al., 2001). As such, PTSD, MDD, GAD, and SUD may be a spectrum of related disorders that have common genetic and environmental exposure vulnerabilities, and the clinical course and response to treatment of PTSD may be "moderated" by these comorbidities (Regier, Friedman, et al., 2013). Common underlying vulnerabilities are also suggested by findings of increased risk for major depression in persons with PTSD, but not in trauma-exposed persons without PTSD (Breslau, Davis, Peterson, & Schultz, 2000), and that PTSD, depression and comorbid PTSD and depression, particularly in the chronic phase, have the same set of predictors (O'Donnell, Creamer, & Pattison, 2004). In addition, taxometric analyses (Forbes, Haslam, Williams, & Creamer, 2005; Ruscio, Ruscio, & Keane, 2002) have conceptualised PTSD as the upper end of a stress–response continuum rather than a categorical clinical syndrome. Such findings suggest that PTSD and other disorders may not exist as discrete entities as Robins and Guze (1970) assume, that symptoms and etiology vary across existing diagnostic categories in a continuous fashion (Kendell & Jablensky, 2003) and that psychopathology in the aftermath of trauma may be best conceptualized as a unitary condition (O'Donnell et al., 2004). This does not mean, however, that PTSD and other diagnostic categories lack utility, provided that they provide useful information about prognosis or treatment outcome, and/or testable propositions about biological and social correlates (Kendell & Jablensky, 2003). Indeed, even if highly comorbid disorders emerge from the same diatheses, they may manifest as apparently different disorders as a function of exposure to differing environmental influences, other genetic/biologic factors, and so on (Brown et al., 2001).

Factor analytic studies are well placed to elucidate relationships between symptoms of different disorders, as they identify a set of latent variables, or factors, which are dimensional in nature and may reflect distinct underlying causes of groups of symptoms (Cattell, 1978; Floyd & Widaman, 1995; Strauss & Smith, 2009). A number of studies have investigated the latent structure of PTSD symptoms in relation to the latent structure of symptoms of highly comorbid mood and anxiety disorders. Blanchard and Penk (1998) conducted a CFA of PTSD and depression symptoms in a

sample of MVA survivors, comparing a two-factor model with PTSD and depression symptoms loading onto separate factors with a single-factor model. The two-factor model fitted best, suggesting that depression and PTSD symptoms reflect different underlying processes; however, the two factors were highly correlated. Grant, Beck, Marques, Palyo, and Clapp (2008) conducted a CFA of PTSD, GAD and depression symptoms in a treatment-seeking sample of MVA survivors. While construct level analyses found that PTSD, MDD, and GAD are distinguishable but highly correlated disorders, symptom level analyses suggested that the Dysphoria factor was a higher order factor that correlated with the PTSD, MDD, and GAD factors, and thus not unique to PTSD. Using data drawn from a large sample of bereaved individuals, Boelen, van de Schoot, van den Hout, de Keijser, and van den Bout (2010) compared the fit of a one factor model with that of models in which symptoms formed three distinct correlated higher-order dimensions, PTSD, prolonged grief disorder and depression, and found that a model in which these disorders were distinguished fitted best. Gros, Simms, and Acierno (2010) conducted an exploratory factor analysis of PTSD symptoms and symptoms of depression in treatment-seeking veterans. Results using their self-report data supported a two-factor model broadly corresponding to depression and PTSD; however, symptoms C4-C7 (diminished interest, feeling detached and estranged from others, restricted affect and sense of foreshortened future) and D3 (poor concentration) loaded onto the same factor as the majority of depression symptoms, rather than the PTSD factor. In the Gros et al. (2010) sample, these PTSD symptoms were predictive of comorbid MDD and greater depression symptoms in patients with PTSD. Elhai, Contractor, Palmieri, Forbes, and Richardson (2011) investigated correlations between the factors of the Simms et al. (2002) model of PTSD symptoms and a four-factor model of depression symptoms as measured by the CES-D. They found that the CES-D Depressive Affect and Somatic Problems factors were more highly correlated with the PTSD Dysphoria factor than with the other PTSD factors.

Consistent with evidence that depression and PTSD symptoms are associated with distinct physiological predictors or concomitants (Jovanovic et al., 2010; Kendall-Tackett, 2000; Maes et al., 1999; Morris, Compas, & Garber, 2012; Shalev et al., 1998), these findings suggest that PTSD, GAD and MDD are broadly distinguishable conditions. But, along with the findings of Simms et al. (2002)

and Palmieri et al. (2007), they also suggest that the Dysphoria or Numbing symptoms of DSM-IV PTSD are more closely related than other PTSD symptoms to other disorders, despite not accounting for high rates of comorbidity between them. However, other findings suggest that the relationship between Dysphoria or Numbing symptoms and symptoms of other disorders is not specific and that other PTSD symptoms are also related to depression and general distress. After adjusting for depression severity, Elklit, Armour, and Shevlin (2010) found that dysphoria's factor loadings were the most attenuated, but loadings of symptoms on other factors were attenuated as well. Marshall, Schell, and Miles (2010) found that PTSD Dysphoria symptoms were no more correlated with measures of general distress than were other PTSD items. Similarly, Simms, Gros, Watson, and O'Hara (2008) showed that traumatic intrusions (i.e., PTSD reexperiencing symptoms) have a very large general distress component. Using Rasch modelling, Elhai, Carvalho, et al. (2011) found that PTSD and major depressive episode symptoms were represented by a single, underlying construct, even when they removed the disorders' overlapping symptoms.

It is important to note that the high rates of comorbidity for PTSD occur in the context of high rates of comorbidity across a range of disorders, particularly mood and anxiety disorders. In the Brown et al. (2001) study, 55% of participants with principal diagnosis of a mood or anxiety disorder had an additional mood or anxiety disorder at the time of evaluation, with lifetime comorbidity rates rising to 76%. Research into the comorbidity and continuity between PTSD and other disorders should thus be contextualised within the broader program of research into the latent structure of psychopathology more generally. One early attempt to account for comorbidity among mood and anxiety disorders was Watson and colleagues' (Watson & Tellegen, 1985; Watson, Wiese, Vaidya, & Tellegen, 1999) two-factor model distinguishing two dimensions of emotional experience: Positive Affect and Negative Affect. Negative Affect covers feelings of distress and dissatisfaction, including fear, anger, sadness, guilt, and disgust. Positive Affect, on the other hand, reflects positive mood states such as happiness, joy, excitement and confidence. The presence of Negative Affect was proposed as a common feature of mood and anxiety disorders that explained the high rates of comorbidity among them. Low Positive Affect, in contrast, was thought to be a specific feature of depression, thus distinguishing it from

anxiety disorders. This model was extended by L. A. Clark and Watson (1991) by the addition of a third factor, Autonomic Arousal, characterised by a rapid heart rate, shortness of breath, and trembling, as a specific feature of anxiety disorders. A further refinement was provided by Mineka, Watson, and Clark (1998) in light of findings that Autonomic Arousal was not a general characteristic of anxiety disorders but specific to panic disorder only, and that the absence of Positive Affect was not uniquely related to depression but also to social phobia (Brown et al., 1998). In the Mineka et al. (1998) integrative hierarchical model, each individual disorder was hypothesized to contain both a shared and a unique component. Consistent with Watson and colleagues' models, the shared component driving high rates of comorbidity was identified as Negative Affect. However, in addition, each disorder was proposed to include unique and differentiating features. For example, Autonomic Arousal was no longer viewed as characteristic of all anxiety disorders but as specific to PD/A; yet no set of symptoms were thought to be perfectly specific to one disorder, e.g. the presence of low Positive Affect as a distinguishing feature of both depression and social phobia (Brown & Barlow, 2009; Watson, 2005).

In addition, in the Mineka et al. (1998) integrative hierarchical model, the contribution of shared and unique components was proposed to vary across disorders, such that depression and GAD were accounted for by Negative Affect more so than were other disorders such as specific phobia. This meant, however, that the Mineka et al. (1998) model failed to fully account for comorbidity among mood and anxiety disorders, as disorders with less of the shared Negative Affect component, such as social phobia and specific phobia, are still highly comorbid. Thus other aspects of the model are required to account for comorbidity, e.g. low PA for depression and social phobia, AA between panic and PTSD (Brown & Barlow, 2009; Watson, 2005). Two more recent, broadly consistent models were proposed by Krueger (1999) and Watson (2005). Using NCS data, Krueger (1999) specified two correlated higher order factors underpinning common mental illnesses: Internalising, a general liability toward negative-affect-laden mood and anxiety disorders; and Externalizing, a general liability toward disinhibitory disorders such as substance use and antisocial behaviour disorders (Achenbach & Edelbrock, 1978; Krueger, 1999; Krueger & Markon, 2006). Subsumed under the

Internalising factor were two lower order factors, which divided mood and anxiety disorders into Fear (social phobia, specific phobia, agoraphobia and panic disorder) and Anxious-Misery (major depression, dysthymia and generalized anxiety disorder). The Watson (2005) quantitative hierarchical model retained the Krueger (1999) distinction between Fear and Anxious-Misery disorders, but renamed the Anxious-Misery disorders Distress disorders to reflect the high proportion of Negative Affect shared by these disorders.

The location of PTSD within the Krueger (1999) and Watson (2005) framework is still a matter of debate, given then high rates of comorbidity between PTSD and both Fear and Anxious-Misery disorders and the heterogeneity of PTSD symptoms. Following a confirmatory factor analysis of epidemiological data by Cox, Clara, and Enns (2002), Watson (2005) located PTSD within the Anxious-Misery/Distress factor. This would appear to reflect the presence of Dysphoria symptoms within the PTSD diagnostic criteria, corresponding to the non-specific Negative Affect symptoms prominent amongst Anxious-Misery disorders, as well as cognitive mechanisms common to PTSD and depression such as rumination (Ehlers, Mayou, & Bryant, 1998). However, factor loadings for PTSD on the Anxious-Misery factor were relatively weak in both the Cox et al. (2002) and subsequent Slade and Watson (2006) studies, particularly when ICD-10 criteria, which include fewer Dysphoria symptoms than DSM-IV criteria, were used (Slade & Watson, 2006). Indeed, there are strong theoretical and empirical arguments for locating PTSD on the Fear factor, given conceptualisations of it as a fear-based disorder (Creamer, Burgess, & Pattison, 1992; Foa, Steketee, & Rothbaum, 1989) associated with persisting autonomic arousal (Brown & McNiff, 2009) and phobic responses to trauma, and responsive to prolonged exposure therapy (Keane & Kaloupek, 1982). In addition, Brown and McNiff (2009), following up on the high rates of subsequent PD/A noted in individuals in PTSD in the Brown et al. (2001) study, found that, along with PD/A, PTSD had significant direct effects on Autonomic Arousal, even when controlling for PD/A comorbidity. While Brown and McNiff (2009) also found that Negative Affect had its largest direct effects on GAD and PTSD, affirming PTSD's placement within Anxious-Misery disorders in the Watson (2005)

model, specifying PTSD and PD/A to load onto separate factors fails to capture this shared Autonomic Arousal component and consequent comorbidity.

Cox et al. (2002) and Slade and Watson (2006) treated PTSD as a single entity that could load onto either the Fear and Anxious-Misery factors. Given findings by Grant et al. (2008) that the Intrusions, Avoidance and Hyperarousal factors of the Simms et al. (2002) model of PTSD symptoms were more specific to PTSD, attempts have been made to disaggregate PTSD into its underlying factors and test their relationships with the Fear and Anxious-Misery factors separately. Accordingly, Forbes, Parslow, et al. (2010), using data from a sample of 714 injury survivors, tested the fit of a model in which mood and anxiety disorders other than PTSD were specified to load onto Fear and Anxious-Misery factors as per Krueger (1999) and Watson (2005). The Fear and Anxious-Misery factors were allowed to correlate with each of the Simms et al. (2002) four PTSD symptom factors. The Intrusion, Avoidance and Hyperarousal factors were significantly more correlated with the Fear factor than with the Anxious-Misery factor, while the Dysphoria factor was significantly more correlated with the Anxious-Misery factor. However, an attempt to replicate this finding (Forbes et al., 2012) in a veteran's general outpatient sample found that the PTSD Intrusions, Avoidance or Hyperarousal factors did not correlate more with Fear than Anxious-Misery nor did the PTSD Dysphoria factor correlate more with the Anxious-Misery factor than the Fear factor; however the Dysphoria factor was more highly correlated with the Anxious-Misery factor than were the other three PTSD factors.

The heterogeneity of PTSD symptoms may span not only the Fear and Anxious-Misery divide, but the Internalising and Externalising divide as well. Miller and colleagues (Miller, Greif, & Smith, 2003; Miller, Kaloupek, Dillon, & Keane, 2004; Miller & Resick, 2007) undertook cluster analytic studies of individuals with PTSD and other disorders, and found evidence of internalising and externalising subtypes in both male veteran and female civilian samples. Those participants classified as externalisers were characterized by elevated levels of anger and aggression, substance-related disorders, antisocial and borderline personality features, and high disconstraint and negative emotionality. In contrast, internalisers exhibited high rates of major depression and panic disorder, schizoid and avoidant personality features, high negative emotionality and low positive emotionality.

The finding of internalising and externalising subtypes of PTSD was also confirmed using latent class analysis (Forbes, Elhai, Miller, & Creamer, 2010). Conversely, given the high rates of comorbidity between drug and alcohol disorders and PTSD and other Internalising disorders and the possible common genetic factors underlying same (Kendler, Prescott, Myers, & Neale, 2003; Lin et al., 1996; Merikangas, Risch, & Weissman, 1994), drug and alcohol use and dependence may also have both an Internalising and an Externalising component. CFAs by Miller, Fogler, Wolf, Kaloupek, and Keane (2008) in a sample of 1,325 Vietnam veterans, found that the Krueger (1999) model with PTSD specified to load onto the Anxious-Misery factor, fitted best. However, alcohol abuse/dependence and drug abuse/dependence, while loading primarily on the Externalising factor, also showed significant cross-loadings on the Anxious-Misery factor. This finding may help contextualise models of the relationship between substance abuse and PTSD such as the self-medication, high risk and reciprocal hypotheses outlined above. Conceptualising PTSD as having both Internalising and Externalising manifestations may also help contextualize the broad range of comorbidity that prompted formulation of the DESNOS diagnosis. 'Complex' PTSD, in contrast to 'simple' PTSD, may reflect the presence of additional internalizing symptoms such as somatisation, or externalizing behaviors such as aggression, substance abuse and self-harm (Friedman et al., 2011).

PTSD and comorbidity in DSM-5: initial empirical findings

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-5 (American Psychiatric Association, 2013)] was published in May 2013. This presented an opportunity to modify DSM-IV PTSD diagnostic criteria from DSM-IV in response to recently accumulated evidence regarding the scope and latent structure of PTSD symptoms. For example, given the diversity of emotional responses to trauma exposure and associated comorbidity (Resick & Miller, 2009), in DSM-5 PTSD has been moved out of the Anxiety Disorders sections and classified within a separate category of event or trauma-related disorders (Friedman et al., 2011). Otherwise, in contrast to DSM-IV, Criterion A of DSM-5 PTSD seeks to reduce 'bracket creep' by excluding events witnessed exclusively via electronic media, or learning about a loved one's death from natural causes or old age. However, it is now specified that indirect exposure may also involve persistent or prolonged exposure

to aversive details of a gruesome trauma through electronic media as part of one's occupation (Friedman et al., 2011). In addition, Criterion A2 of the DSM-IV criteria - initial subjective reactions of intense fear, helplessness, or horror to the stressor event – has been removed, given that studies have generally not found that Criterion A2 predicts development of PTSD (Bovin & Marx, 2011).

Additional amendments have been made to the symptom criteria. DSM-IV required at least one of five Criterion B or "re-experiencing" symptoms, three of seven Criterion C or "avoidance and numbing symptoms" and two of five Criterion D "arousal" symptoms. The DSM-5 symptom criteria, in contrast, require symptoms drawn from four groups: at least one of five 'intrusion' symptoms (Criterion B), at least one of two 'avoidance' symptoms (Criterion C), at least two of seven symptoms of 'negative alterations in cognitions and mood' (Criterion D), and at least two of six 'arousal and reactivity' symptoms (Criterion E). This change was motivated by consistent findings, as noted above, of a four-factor structure of PTSD symptoms, with avoidance symptoms loading onto a separate factor from numbing symptoms (Friedman et al., 2011). The five symptoms included under Criterion B have remained largely unchanged, apart from some fine-tuning to enhance clarity and precision of symptoms B2 and B3 (nightmares and flashbacks) and to emphasize the intrusive as opposed to ruminative quality of trauma-related memories of symptom B1 as discussed above (Friedman et al, 2011). The new Criterion C comprises the two DSM-IV symptoms C1 and C2, relating to avoidance of memories, thoughts and feelings regarding external reminders of the traumatic event. DSM-IV numbing symptoms C3-C6 have been included in the new Criterion D. Slight modifications have been made to two of these symptoms, i.e. to emphasize the dissociative nature of the amnesia symptom and the inability to experience positive emotions. Key changes, however, are the additions of three new symptoms: (i) persistent and exaggerated negative beliefs about oneself, others or the world; (ii) persistent distorted blame of self or others; and (iii) persistent negative emotional state. DSM-IV symptom C7 (sense of foreshortened future), does not appear in the DSM-5 criteria for PTSD as such, but is reflected in the first of these new symptoms (Friedman et al., 2011). Finally, all of the DSM-IV 'arousal' symptoms have been retained in DSM-5 Criterion E; however, the description of DSM-IV symptom D2 (irritability) has been significantly expanded to include verbal or physical aggressive

behaviour. A new symptom, reckless or self-destructive behaviour, has also been included in Criterion E. A dissociative subtype of PTSD characterised by symptoms of derealisation and depersonalisation has also been added to the DSM-5 criteria, based on the findings reviewed above. DESNOS was not included in DSM-5, either as an alternative to, or subtype of, PTSD, but the addition of new symptoms, such as persistent negative emotional state, persistent distorted blame of self or others and reckless or self-destructive behaviour, arguably increases the alignment of DSM-5 PTSD criteria with the DESNOS construct (Friedman, 2013).

As noted above, the DSM-IV criteria for PTSD were extensively criticised for their overlap with symptoms of depression (McHugh & Treisman, 2007; Rosen & Lilienfeld, 2008), with speculation that this overlap artificially increased comorbidity rates between the two disorders. However, some of the new DSM-5 Criterion D symptoms (i.e. a pervasive negative emotional state, persistent exaggerated negative perceptions of oneself, others or the world) would appear to increase the degree of overlap. Elhai et al. (2012) used confirmatory factor analysis to explore whether this added depression content increased correlations between DSM-5 PTSD factors and depression scores relative to DSM-IV factors and found no significant increase in correlations with depression scores, even when comparing DSM-IV emotional numbing symptoms with DSM-5 negative alterations in cognitions and mood symptoms. However, Koffel, Polusny, Arbisi, and Erbes (2012), using pre- and post-deployment data from a sample of 213 soldiers who were deployed to Iraq, found that the new symptoms of persistent negative expectations about the world (D2) and aggressive behaviours (E1) showed equivalent correlations with symptoms of PTSD, depression, and substance use, suggesting that their inclusion in the diagnostic criteria for PTSD may in fact impede differential diagnosis.

Studies of DSM-5 comorbidity are beginning to emerge. While using DSM-IV data drawn from a sample of injury survivors assessed 3 and 12 months post-injury, Forbes et al. (2011) investigated the impact of requiring at least symptom of avoidance (i.e. C1 or C2) on PTSD comorbidity with MDE. They found that requiring at least one of these symptoms (as is the case for the DSM-5 criteria) in conjunction with two or numbing symptoms resulted in significantly lower rates of comorbidity with MDE at 12 months (44% vs. 34%), compared to when the usual DSM-IV diagnostic criteria were

used. This result suggests that requiring both avoidance symptoms in addition to numbing symptoms may reduce spurious diagnoses of PTSD in those with depression. However, using both DSM-IV and DSM-5 data, O'Donnell et al. (under review) found that in a sample of 613 injury survivors, comorbidity of PTSD with MDE was similar when PTSD was diagnosed according to DSM-IV (with A2 removed) compared to PTSD diagnosed according to DSM-5 (61% *vs* 65%, $z = .37$, $p = .71$). However, the fact that participants in the O'Donnell et al. (under review) study were assessed six years post-injury may have enhanced levels of comorbidity, as evidence suggests that depression and PTSD may become indistinguishable as they become chronic (O'Donnell et al., 2004). In the DSM-5 field trials, 41% of a Veterans' Affairs medical centre sample met criteria for DSM-5 PTSD, of which only 29% did not attract an additional diagnosis of MDD, GAD or alcohol use disorder (Regier, Narrow, et al., 2013). Thus, it appears that high rates of comorbidity are maintained despite explicitly requiring avoidance symptoms in addition to numbing/negative alterations in cognitions and mood symptoms, perhaps as a result of adding the new depression-laden symptoms to Criterion D.

Clinical – legal implications

What are the clinical-legal implications of the high rates of disorders occurring comorbid with PTSD following trauma exposure, or indeed, the high rates of psychopathology of any stripe following trauma exposure? In civil or compensation contexts, clinicians and legal practitioners are interested in establishing which symptoms are event- or trauma-related and which are not. As PTSD is unique among chronic, adult-onset mental disorders in that it is defined by exposure to a markedly traumatic event prior to the development of its symptoms, it is easy to assume that PTSD is the most likely disorder to emerge following trauma exposure. As a corollary, it is also easy to assume that any psychopathology that emerges following trauma exposure is PTSD, and conversely, that any other disorder that emerges following trauma exposure is in fact unrelated to said exposure, thus disqualifying the sufferer from compensation. However, as this review indicates, PTSD is just one of a range of mental health problems that may develop, singly or in tandem, following exposure to trauma or other critical incidents. The reasons for both this comorbidity and diversity of outcomes are manifold, as discussed, and may include common underlying vulnerabilities, complex and cyclic

relationships between disorders or inadequate classification symptoms. Rather than relying on a PTSD diagnosis to signify the role of trauma exposure in the development of psychopathology, practitioners are thus obliged to elicit a detailed history of the unfolding of the symptom picture both pre and post event that allows for the possibility that disorders other than PTSD may emerge as a result of trauma exposure. Furthermore, if other disorders are shown to be comorbid with PTSD, it is important to keep in mind that they may reflect either post-traumatic reactions in their own right, or have arisen from PTSD symptoms, and thus may not necessarily indicate a pre-existing disorder or vulnerability to posttraumatic psychopathology.

Conclusion

A feature of PTSD is its extensive comorbidity. The extent of this comorbidity is problematic at conceptual, clinical and etiological levels for those trying to understand and treat posttraumatic psychopathology. As outlined in this paper, the reasons for this pervasive comorbidity are potentially multi-determined. However studies of a) the bi-directional relationships between PTSD and key mood, anxiety and substance use disorders, and b) the potential impact of overlapping diagnostic criteria are unlikely to untangle this Gordian knot. Instead, research that does not rely on a categorical classification system and instead explores the shared manifest and common higher order features across these disorders and their potentially unifying underlying vulnerabilities is more likely to bear fruit.

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