Original Article

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Symptom structure of PTSD and co-morbid depressive symptoms – a network analysis of combat veteran patients‡

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Abstract

Background. Despite extensive research, symptom structure of posttraumatic stress disorder (PTSD) is highly debated. The network approach to psychopathology offers a novel method for understanding and conceptualizing PTSD. However, extant studies have mainly used small samples and self-report measures among sub-clinical populations, while also overlooking co-morbid depressive symptoms.
Methods. PTSD symptom network topology was estimated in a sample of 1489 treatment-seeking veteran patients based on a clinician-rated PTSD measure. Next, clinician-rated depressive symptoms were incorporated into the network to assess their influence on PTSD network structure. The PTSD-symptom network was then contrasted with the network of 306 trauma-exposed (TE) treatment-seeking patients not meeting full criteria for PTSD to assess corresponding network differences. Finally, a directed acyclic graph (DAG) was computed to estimate potential directionality among symptoms, including depressive symptoms and daily functioning.
Results. The PTSD symptom network evidenced robust reliability. Flashbacks and getting emotionally upset by trauma reminders emerged as the most central nodes in the PTSD network, regardless of the inclusion of depressive symptoms. Distinct clustering emerged for PTSD and depressive symptoms within the comorbidity network. DAG analysis suggested a key triggering role for re-experiencing symptoms. Network topology in the PTSD sample was significantly distinct from that of the TE sample.
Conclusions. Flashbacks and psychological reactions to trauma reminders, along with their strong connections to other re-experiencing symptoms, have a pivotal role in the clinical presentation of combat-related PTSD among veterans. Depressive and posttraumatic symptoms constitute two separate diagnostic entities, but with meaningful between-disorder connections, suggesting two mutually-influential systems.

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder characterized by a prolonged and maladaptive response to traumatic events (American Psychiatric Association, 2013). It has a significant toll on both society and the individual and is associated with significant psychological dysfunction and health impairments (Stein *et al.*, 1997; Kessler, 2000; Deykin *et al.*, 2001; Westphal *et al.*, 2011). While lifetime prevalence is estimated at 6% (Goldstein *et al.*, 2016), for military veterans, a highly trauma-exposed population, prevalence rates are even higher, reaching 23% (Fulton *et al.*, 2015), with increased severity and comorbidity rates (Tsai *et al.*, 2015).

Despite extensive research, PTSD symptom structure is still highly debated (Hoge *et al.*, 2016; McNally, 2016, 2017; Armour *et al.*, 2017; McNally *et al.*, 2017*a*), as reflected in the ongoing discussion surrounding its diagnosis following the publication of the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5; Galatzer-Levy and Bryant, 2013; Hoge *et al.*, 2014; Hoge *et al.*, 2016), which presented marked differences in the diagnostic criteria of PTSD, (Hoge *et al.*, 2014; Hoge *et al.*, 2016) including, among others, a more restrictive definition of criterion A and marked changes in the number and nature of individual symptoms and symptom-clusters required for diagnosis (Armour *et al.*, 2017). Importantly, this has led to lower PTSD prevalence rates compared with DSM-IV (Kilpatrick *et al.*, 2013).

Noticeable diagnostic differences also exist between DSM-5 and the International Classification of Diseases-11 (ICD-11; World Health Organization, 2018), which includes only six mandatory symptoms assumed to reflect core PTSD symptoms not shared by other disorders (Cloitre et al., 2013; Maercker et al., 2013; Mitchell et al., 2017). This difference has resulted, once more, in striking differences in PTSD rates (Hoge et al., 2014; Stein et al., 2014; Hansen et al., 2015; Friedman et al., 2016; Guina, 2016; Hoge et al., 2016; Wisco et al., 2016b; Mitchell et al., 2017), found to be 10%-to-30% lower according to ICD-11, compared to DSM-5, among trauma-exposed individuals (Hansen et al., 2015; Wisco et al., 2016b). While different treatments for PTSD are available, including psychotherapy and pharmacotherapy (Bradley et al., 2005; Sullivan and Neria, 2009; Steckler and Risbrough, 2012), research consistently shows that more than one-third of PTSD patients never fully remit, even if treated (Difede et al., 2014). As importantly noted in the guidelines of the National Institute for Health and Care Excellence (NICE) PTSD, treatment efficacy can only be achieved if the disorder is first accurately recognized (National Institue for Clinical Excellence, 2005; Spoont et al., 2015).

Recently, a novel network perspective on psychopathology has emerged, offering an alternative approach for understanding and conceptualizing symptomatology, which may be of use also in discerning the central and fundamental features of PTSD (McNally, 2016, 2017; Fried et al., 2017; Mitchell et al., 2017; Fried et al., 2018). According to the network perspective, psychopathology is not the result of underlying latent variables, but rather is the constitution of symptoms associated in dynamic and causal relations, interacting and possibly self-reinforcing each other (Borsboom et al., 2003; Cramer et al., 2010b; Borsboom and Cramer, 2013; Schmittmann et al., 2013; Boschloo et al., 2015; McNally et al., 2015; McNally, 2016, 2017; Fried et al., 2017). To use an example put forward by Birkeland and Heir (2017), in the aftermath of traumatic event, intrusive memories of the event might occur, leading to hyperarousal and sleep difficulties, which in turn lead to concentration deficiencies, which can be then looped back to the intrusive memories, creating feedback loops of symptoms that maintain each other. In the corresponding network structure, symptoms are represented by nodes, and the associations or connections between pairs of symptoms/nodes are represented by edges, establishing a specific disorder (Jones et al., 2017). The importance of each node within a specific network is quantified by measures of node centrality. As nodes are activated, their activation is transmitted to connected nodes, via the connecting edges, and an episode of a disorders unfolds (McNally et al., 2015). Thus, network findings can guide clinicians and researchers in measuring disorders and their symptoms, and eventually, in refining the nosology and classification of different psychopathologies. In PTSD, network analysis has been explicitly suggested as a vital tool for selection of diagnostic criteria, and for assessing its occurrence and severity (Phillips et al., 2018).

Extensive research implementing network models in PTSD among trauma-exposed adult populations, including several in veterans, has been conducted over the last several years, aiming to elucidate the symptom structure of PTSD (McNally et al., 2015; Knefel et al., 2016; Armour et al., 2017; Birkeland and Heir, 2017; Bryant et al., 2017; Haag et al., 2017; Mitchell et al., 2017; Spiller et al., 2017; Afzali et al., 2017a, 2017b; McNally et al., 2017a; Benfer et al., 2018; Epskamp et al., 2018; Fried et al., 2018; Greene et al., 2018; Moshier et al., 2018; Papini et al., 2018; Phillips et al., 2018; Ross et al., 2018; Sullivan et al.,

2018; Vanzhula et al., 2018; von Stockert et al., 2018; Price et al., 2019). While some similarities in findings across studies exist, important disparities emerge (Birkeland and Heir, 2017, Phillips et al., 2018). For example, while amnesia is found to be the least central symptom in most PTSD network studies (McNally et al., 2015, Armour et al., 2017, Birkeland and Heir, 2017, Bryant et al., 2017, Mitchell et al., 2017, Spiller et al., 2017, Afzali et al., 2017a, McNally et al., 2017a, Benfer et al., 2018, Fried et al., 2018, Moshier et al., 2018, Papini et al., 2018, Phillips et al., 2018, Ross et al., 2018, Vanzhula et al., 2018, von Stockert et al., 2018), symptoms emerging as most central vary considerably across studies, including, among others, getting emotionally upset due to trauma reminders, hypervigilance, intrusive thoughts, concentration difficulties, nightmares, future foreshortening, negative trauma related emotions, detachment, loss of interest, emotional numbing, physical reactions to trauma reminders, and flashbacks (Phillips et al., 2018). Recently, it has been suggested that these mixed findings might be the result of corresponding differences in traumatic events, such as, for example, man-made trauma v. natural disasters, as this has been shown to affect PTSD presentation, and hence, network structure (Ross et al., 2018; Sullivan et al., 2018). Interestingly, when limiting past research to include only veteran samples, a more consistent result pattern emerges, demonstrating high centrality of getting emotionally upset by trauma reminders (Armour et al., 2017; Mitchell et al., 2017; Fried et al., 2018; Moshier et al., 2018; von Stockert et al., 2018). Other reasons implicated as responsible for observed inconsistencies across studies are differences in sample size, sample type (treatment-seeking, survey data), participants' clinical status (PTSD, probable PTSD, subthreshold PTSD, trauma-exposed healthy participants), and the PTSD measure used for network construction (self-report, clinician-administered).

While extant network research in PTSD has advanced our knowledge in the field, important gaps still remain, which we aim to address in the present study. First, no study to date has used a sample comprised exclusively of treatment-seeking veterans with PTSD, while also basing analyses on clinician-rated measures only. Importantly, in clinical assessments, self-report measures do not allow for additional inquiries of ambiguous or vague answers (Trull et al., 2001), pose a risk for response biases, and are subjected to wording-effects (Moskowitz, 1986; Schwarz, 1999). In PTSD, self-reports can only result in a diagnosis of 'probable' PTSD (Wisco et al., 2016a), imperfectly capturing the examined pathology (McNally, 2016). Finally, while a recent study comparing PTSD network structures based on clinician-rated and patient-rated data reported similar network structures, results also showed that their global structure was not statistically identical and that networks also differed on node-clustering (Moshier et al., 2018). Indeed, most PTSD network studies have mentioned both using self-reports and non-clinical samples as limitations necessitating additional research (McNally et al., 2015; Knefel et al., 2016; Armour et al., 2017; Birkeland and Heir, 2017; Mitchell et al., 2017; Spiller et al., 2017; Afzali et al., 2017a, 2017b; Greene et al., 2018; Ross et al., 2018; Sullivan et al., 2018; Vanzhula et al., 2018; von Stockert et al., 2018).

Second, while sample size is crucial for establishing a reliable network structure, with robust estimation of edges and centrality metrics powered to detect even small coefficients (Epskamp et al., 2018; Epskamp and Fried, 2018; Fried et al., 2018), most studies used small sample sizes (McNally et al., 2015; Knefel et al., 2016; Armour et al., 2017; Birkeland and Heir, 2017; Haag et al., 2017;

Spiller *et al.*, 2017; Afzali *et al.*, 2017*a*; McNally *et al.*, 2017*a*; Epskamp *et al.*, 2018; Greene *et al.*, 2018; Ross *et al.*, 2018; Vanzhula *et al.*, 2018). For adequate power, sample size should be considerably larger than the number of parameters estimated in analyses, which given the number of variables in PTSD-related networks, tends to be relatively high (Spiller *et al.*, 2017; Afzali *et al.*, 2017*a*, 2017*b*; McNally *et al.*, 2017*a*, Fried *et al.*, 2018)[1†]. To date, six studies used large samples of about 1000 participants (Bryant *et al.*, 2017; Fried *et al.*, 2018; Phillips *et al.*, 2018; Sullivan *et al.*, 2018; von Stockert *et al.*, 2018; Price *et al.*, 2019). Still, four assessed trauma-exposed participants with low-to-none rates of probable PTSD (Bryant *et al.*, 2017; Sullivan *et al.*, 2018; von Stockert *et al.*, 2018; Price *et al.*, 2019), the fifth pooled data from four datasets differing on country of origin, symptoms assessed, and assessment language and tools (Fried *et al.*, 2018), and, as stated previously, all six studies assessed PTSD symptoms based on self-report measures only.

Finally, PTSD and depression symptoms frequently co-occur (Neria and Bromet, 2000; Lapierre *et al.*, 2007; Au *et al.*, 2013), with approximately 50% comorbidity rates between PTSD and major depressive disorder (MDD; Kessler *et al.*, 1995; Elhai *et al.*, 2008; Rytwinski *et al.*, 2014; Flory and Yehuda, 2015). Compared to PTSD alone, patients with PTSD-MDD exhibit greater distress, higher suicide risk, and poorer treatment outcome (Blanchard *et al.*, 1998; Oquendo *et al.*, 2003; Green *et al.*, 2006; Ramsawh *et al.*, 2014; Flory and Yehuda, 2015), with co-morbid patients shown to be more likely to drop out from treatment, to be non-responders to prolonged exposure treatment, and to necessitate longer psychotherapy (Gillespie *et al.*, 2002; Bryant *et al.*, 2003; McDonagh *et al.*, 2005; Stein *et al.*, 2012). Thus, understanding the underlying structure of the PTSD-MDD comorbidity can enhance extant efforts to better assess and treat PTSD-MDD patients (Flory and Yehuda, 2015; Afzali *et al.*, 2017*b*). Past research aiming to explore the PTSD-MDD comorbidity has mainly focused on shared features or similarities between disorders. For example, some have suggested that both disorders are high on a psychopathology-related diagnostic dimension of general distress, leading to increased comorbidity rates (i.e. the quadripartite model of psychopathology; Watson, 2009), while others have focused on more specific content-overlap between disorders (Elhai *et al.*, 2008; Elhai *et al.*, 2011). Research efforts undertaken to support these ideas have employed, among others, exploratory (Blanchard *et al.*, 1998; Grant *et al.*, 2008; Gros *et al.*, 2010; Contractor *et al.*, 2015; Price and van Stolk-Cooke, 2015) and confirmatory factor analytic approaches (Simms *et al.*, 2002; Armour and Shevlin, 2010; Miller *et al.*, 2010). However, an important limitation shared by all of these analyses is that they all assume symptoms to be independent constructs, related only via their corresponding factor, thereby missing important facets of the interplay between specific symptoms of different disorders (Afzali *et al.*, 2017*b*; Price *et al.*, 2019). Conversely, as described above, the network approach views symptoms as being in dynamic and causal associations, interacting and possibly self-reinforcing each other, hence tapping this important aspect. In line with this view, the network approach conceptualizes comorbidity as the overall constellation of symptom-level associations, including those that exist between symptoms of different disorders (Cramer *et al.*, 2010*a*; Borsboom *et al.*, 2011; Afzali *et al.*, 2017*b*; Price *et al.*, 2019).

These between-disorder symptom associations are termed *bridge nodes*, and their importance is measured using centrality measures in a similar fashion to that used for within-disorder nodes. Thus, network analysis can be readily used to examine the role of more specific causes for high PTSD-MDD comorbidity rates such as between-disorder overlapping symptoms as sleep and concentration difficulties, which are part of both depression and PTSD (Spitzer *et al.*, 2007; Cramer *et al.*, 2010*a*; Afzali *et al.*, 2017*b*). Importantly, the topic of overlapping symptoms gained renewed attention following the addition of Cluster D (i.e. Negative alterations in cognitions and mood associated with the traumatic event) to PTSD diagnosis per DSM-5 (American Psychiatric Association, 2013), which increased the number of potential overlapping symptoms between PTSD and depression (Mitchell *et al.*, 2017; Price *et al.*, 2019; but see O'Donnell *et al.* (2014) showing similar PTSD-MDD comorbidity rates based on DSM-IV and DSM-5). Still, while providing a novel approach to conceptualize and understand the PTSD-MDD comorbidity, to date, only four studies included depressive symptoms in their network analysis of PTSD. Yet, one measured lifetime occurrence, not current major depressive disorder (MDD) symptoms (Afzali *et al.*, 2017*b*), and three used self-reported measures of PTSD and depression (Armour *et al.*, 2017; Mitchell *et al.*, 2017; Price *et al.*, 2019).

In line with the above-mentioned gaps in knowledge, here we examined PTSD symptom structure in a sample of clinically-diagnosed, treatment-seeking Israel Defense Forces combat-exposed veterans. Our goal was to extend current knowledge in the following ways: (1) analyze PTSD symptom networks using data from structured clinician-administered interviews; (2) use a large sample ($N = 1489$); (3) re-estimate network structure when including clinician-rated depressive symptoms; (4) compare the PTSD network to that of trauma-exposed (TE) treatment-seeking combat veterans not meeting PTSD diagnostic criteria; and (5) explore potential directionality among symptoms including depressive symptoms and a daily functioning measure, as the DSM classification system specifically requires significant impairment in one or more areas of functioning for a PTSD diagnosis. Several hypotheses were made. First, due to lack of consensus in the literature on central symptoms, we hypothesized that re-experiencing symptoms would emerge as highly central based on findings of most network studies focusing on trauma-exposed veterans (Armour *et al.*, 2017; Mitchell *et al.*, 2017; Fried *et al.*, 2018; Moshier *et al.*, 2018; von Stockert *et al.*, 2018). In line with numerous network studies across different traumatic populations, we also predicted low centrality for amnesia. Second, based on previous studies incorporating depressive symptoms in the network structure of military veterans (Armour *et al.*, 2017; Mitchell *et al.*, 2017), we hypothesized that while the introduction of depressive symptoms would result in several significant bridge nodes, this would have little effect on the PTSD symptom structure. Third, we hypothesized greater overall connectivity in the clinical PTSD group, compared with the trauma-exposed (TE) treatment-seeking patients not meeting full criteria for PTSD, which in accordance with the conceptualization of psychopathology per the network approach and with the only study to date that examined this possibility in veterans with PTSD compared with subthreshold PTSD (Phillips *et al.*, 2018). Still, we would like to emphasize at this juncture that the current study is the first to employ a network analysis approach using a large sample comprised exclusively of treatment-seeking veterans with PTSD, while also basing analyses on clinician-rated measures only. Thus,

†The notes appear after the main text.

present analyses should be regarded as partly exploratory in nature. Put differently, as previous research has implicated numerous factors (e.g. sample size, sample type, participants' clinical status, trauma type, and the PTSD measure used for network construction) in results heterogeneity across studies, current hypotheses are in part extrapolations based on extant findings in the field.

Methods

Participants

Participants were 1795 male veterans seeking treatment from the Israel Defense Forces Unit for Treatment of Combat-Related PTSD (UTC-PTSD), an outpatient clinic specializing in assessing and treating combat-related PTSD. Upon contacting the clinic, veterans were first phone-screened to ascertain past exposure to a combat-related event. Veterans fulfilling this requirement were then invited for a formal clinical assessment by one of the clinic's assessors, namely, psychiatrists, clinical psychologists, or social workers with 12 or more years of experience in PTSD diagnosis in veterans. Importantly, as assessors also completed the mandatory Israel Defense Forces service, they were familiar with the language, manners, behavioral norms, belief system, and rituals of Israeli military culture (Levi *et al.*, 2016; Levi *et al.*, 2017). Next, semi-structured diagnostic interviews based on DSM-IV-TR were administered as part of the routine admission process to the clinic. Interviews followed the UTC-PTSD assessment manual, developed within the UTC-PTSD, which comprises an anamnestic section to collect socio-demographic and personal background, as well as general medical information, and a diagnostic section using both clinician-rated measures (i.e. the clinician-administered PTSD Scale (CAPS-IV; Blake *et al.*, 1995) and the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979)) and self-report questionnaires (for full measures description see Measures below). Next, each patient's assessment record was presented in the clinic's staff meeting, and final decisions relating to diagnoses (and ensuing treatment course) were made (Levi *et al.*, 2016). Veterans with active or past psychosis or current severe substance use disorder were not accepted for treatment at the clinic and were referred out to specialized clinics. Veterans with high levels of active suicidality, as indicated by concrete suicidal plans, were taken to a psychiatric emergency room for immediate intervention. Finally, veterans receiving psychotherapy or pharmacotherapy elsewhere were also excluded from the clinic's care. The present study analyzed the assessment-data collected from 1795 male veterans that were admitted to the clinic's care between 2006-to-2014. Of note, about 15% of patients were still part of the military, but only as reserve forces, during their assessment.

In total, of the 1795 treatment-seeking male veterans, 1489 met diagnostic criteria for PTSD while 306 did not (See Table 1 for demographic characteristics of the two groups), with all being exposed to combat-related traumatic events (i.e. DSM-IV criterion A). Specifically, these events included: (1) participating in direct combat, including incoming mortar and rocket attacks, while participating in one of Israel's major wars (e.g. 'Second Lebanon War'); (2) receiving incoming small fire-arms and/or experiencing detonations of improvised explosive devices (IEDs) while participating in one of Israel's combat operations (e.g. 'Operation Cast Led'); (3) routine security measures including clearing and searching operations while undergoing extensive Molotov cocktail and/or stone throwing attacks; and (4) personally knowing someone seriously injured or killed in one of the aforementioned wars

or combat operations[2]. A clinical diagnosis of PTSD was established using CAPS-IV (Blake *et al.*, 1995), based on the relatively lenient F1/I2 item rule (i.e. Frequency $\geqslant 1$, Intensity > 2; Blake *et al.*, 1995). Accordingly, PTSD diagnosis necessitated endorsing at least one re-experiencing symptom, three avoidance symptoms, and two hyperarousal symptoms. For the purpose of the present study, those not meeting this requirement were regarded as trauma-exposed (TE) treatment-seeking patients not meeting full criteria for PTSD. Of note, of the 306 TE patients, exactly half ($n = 153$) met criteria for subthreshold PTSD, defined as fulfilling symptom-requirement of two out of the three symptom-clusters (Keane and Barlow, 2002; Phillips *et al.*, 2018). The study was approved by the Israel Defense Forces Medical Corps Ethics Committee.

Measures

Clinician-rated PTSD symptoms
Severity of PTSD symptoms was measured using CAPS-IV (Blake *et al.*, 1995), a 17-item structured interview used for diagnosing PTSD based on DSM-IV criteria, considered the gold standard in PTSD assessment. Each item/symptom is rated separately on frequency and intensity on a 0-to-4 scale, for an item total score of 0-to-8. Summed item scores yield an estimate of three symptom clusters (i.e. Cluster B, Re-experiencing; Cluster C, Avoidance, and Numbing; and Cluster D, Hyperarousal) and an overall PTSD severity score. The CAPS has excellent reliability, convergent and discriminant validity, diagnostic utility and sensitivity to clinical change in military veterans and other populations (Weathers *et al.*, 2001; Pupo *et al.*, 2011). Cronbach's α in the current sample was 0.91.

Clinician-rated depressive symptoms
Clinician-evaluated levels of depressive symptoms were measured using the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), a 10-item questionnaire assessing core depressive symptoms during the past week, each rated on a 0-to-6 scale (no evidence to pervasive evidence). It has high inter-rater reliability, convergent validity, and similar rates of sensitivity to change compared to other measures of depression (Montgomery and Asberg, 1979; Khan *et al.*, 2002; Khan *et al.*, 2004). Cronbach's α in the current sample was 0.90.

Functioning
Functioning in different life domains were assessed using the Psychotherapy Outcome Assessment and Monitoring System-Trauma Version (POAMS-TV) Assessment Questionnaire (Green *et al.*, 2003). This self-report includes 10 items, each rated on a 0-to-5 scale (extreme distress/dissatisfaction to optimal functioning/satisfaction). A global functioning score is derived by averaging scores across items (Levi *et al.*, 2016; Levi *et al.*, 2017). The POAMS-TV has been shown to be reliable in other samples of Israel Defense Forces veterans (Svetlicky *et al.*, 2010). Cronbach's α in the current sample was 0.81.

Data analysis

Network analysis
Network models estimating the associations between symptoms are usually constructed using the Graphical Gaussian Model (GGM; Epskamp and Fried, 2016), through the R-package *qgraph* (Epskamp *et al.*, 2012). Within the graphical network, each node

Table 1. Demographic characteristics by group

	PTSD group		TE group		Statistics	
	M	S.D.	M	S.D.	Statistic	*p* Value
Age at assessment (years)	36.13	13.95	34.99	12.78	$t = 1.318$	0.19
Age at event (years)	23.97	5.58	24.79	5.93	$t = 2.265$	0.02
Education (years)	12.49	1.90	12.76	2.30	$t = 2.173$	0.03
Family status (%)					$\chi^2 = 0.61$	0.89
Single	47.75	–	47.38	–		
Married	42.71	–	44.44	–		
Divorced	9.27	–	7.85	–		
Widowed	0.27	–	0.33	–		
Number of children (*N*)	3.70	63.44	1.38	1.62	$t = 0.567$	0.57
Employed (%)	59.10	–	69.28	–	$\chi^2 = 10.58$	<0.01
Military occupation (%)					$\chi^2 = 4.03$	0.04
Combat soldiers	85.02	–	89.44	–		
Specialist military personnel	14.98	–	10.56	–		
Officers (%)	7.46	–	11.51	–	$\chi^2 = 5.52$	0.02
Injured (%)	12.89	–	9.80	–	$\chi^2 = 2.24$	0.13
Past Psychotherapy (%)	56.22	–	28.95	–	$\chi^2 = 22.87$	<0.01
Past pharmacotherapy (%)	28.71	–	20.72	–	$\chi^2 = 8.08$	<0.01

PTSD, posttraumatic stress disorder; TE, trauma-exposed.

depicts a symptom, and edges depict regularized partial correlations between two symptom nodes. Line thickness reflects association strength; blue and red edges represent positive and negative associations, respectively.

Here, as we had two different samples of participants (i.e. PTSD patients and TE participants) for which we constructed the same network structure based on the CAPS 17-symptom-items, we used the fused graphical lasso (FGL; Danaher *et al.*, 2014). The FGL is a network estimation technique, which is an extension of the graphical lasso, that allows estimating several GGMs jointly, yielding a more accurate estimation of network structures than estimating each network individually using separate GGMs (Danaher *et al.*, 2014; Costantini and Epskamp, 2017; Fried *et al.*, 2018). Thus, we used FGL to plot the network structure for the PTSD and TE samples using the CAPS 17-symptom-items (CAPS-items and TE-CAPS-items networks, respectively). For the PTSD sample, we used GGM to plot the network structure incorporating both the CAPS 17-symptom-items and the MADRS depressive symptom-items (CAPS + MADRS-items network), as this network was conducted only for the PTSD sample.

Node centrality measures
Within-network symptoms importance was characterized using the one-step expected influence (EI) centrality measure indexing node strength (Robinaugh *et al.*, 2016), as it takes into account negative as well as positive edges (Wang *et al.*, 2018). It is considered the most reliable, stable and accurate measure of node centrality compared with other centrality measures, such as betweenness and closeness (Fried *et al.*, 2018; Wang *et al.*, 2018), which were recently deemed less suitable as measures of

node importance in psychological networks (Bringmann *et al.*, 2018; Hallquist *et al.*, 2019).

EI analyses used the R-package *bootnet* (Epskamp *et al.*, 2018) and included the one-step expected influence measure (Robinaugh *et al.*, 2016), which reflects the summed weight of positive and negative edges with the neighboring nodes in the network (Heeren *et al.*, 2018). Expected influence was computed for all networks. For the CAPS + MADRS-items network, EI was also computed for bridge nodes (nodes which have symptom-level connections with nodes of the other disorder), reflecting between-disorder symptom associations (Jones *et al.*, 2019). For all measures, higher values of EI reflect greater node centrality (McNally, 2016; Bringmann *et al.*, 2018; Fried *et al.*, 2018; Hallquist *et al.*, 2019).

Network robustness (accuracy and stability)
Network accuracy was computed using the R-package *bootnet* (Epskamp *et al.*, 2018) employing a non-parametric bootstrap approach. We estimated edge weights accuracy at a 95% confidence intervals (CIs) by sampling the data 1000 times (with replacement), thereby generating a distribution of edge weights. *Network stability* was assessed using a bootstrap person-dropping procedure (Costenbader and Valente, 2003) providing a correlation stability (CS)-coefficient. While CS-coefficient ⩾0.25, and preferably ⩾0.50, reflects adequate network stability, those under 0.25 reflect insufficient network stability (Epskamp *et al.*, 2018).

Network comparison
For network comparison analysis we first randomly sampled 306 PTSD patients from the original PTSD sample to ensure an even number of participants in the PTSD and TE samples. Next, a *Network Comparison Test* (NCT R-package; van Borkulo and

Millner, 2016) was used to compare the CAPS-items and TE-CAPS-items networks. We used an omnibus test evaluating invariance of the *network structure* across groups, and also tested the differences in *global strength* between the networks, comparing the sum of absolute edge weight values.

Directed acyclic graph (DAG) analysis

The DAG is a Bayesian network approach that models a network in which edges are directed and noncircular. Thus, the DAG gives us information about both the strength and the direction of connections between symptoms, which are regarded as clues as to which associations between symptoms might be causally important, that is, which symptoms may play a causal role in creating other symptoms (Jones *et al.*, 2018). Here, a Bayesian network analysis applying the R-package *bnlearn* (Scutari, 2010) was used to produce DAGs aiming to discern directionality among nodes from cross-sectional data (McNally, 2016). For the present study, we used the completed partially DAG (CPDAG) which accounts for some of the shortcomings of equivalent separate DAGs (Scutari and Denis, 2014). DAG analysis considered CAPS and MADRS single-items as well as the daily functioning total score.

See Supplemental Material for a more comprehensive description of data analyses including the original analytic code (R-scripts) and the underlying co-variance matrices of the different presented networks.

Results

Psychopathology measures

Mean scores of the PTSD sample were 81.77 (s.d. = 17.21) for the CAPS, 29.23 (s.d. = 10.825) for the MADRS, and 2.07 (s.d. = 0.74) for the POAMS-TV. In the trauma-exposed (TE) treatment-seeking patients not meeting full criteria for PTSD sample, mean scores were 33.95 (s.d. = 18.26), 25.31 (s.d. = 9.68), and 2.67 (s.d. = 0.76), respectively. Independent-samples *t* tests revealed significant group differences on all measures, all $ps < 0.0001$. Of the PTSD group, 57% also met diagnostic criteria for MDD (i.e. a PTSD-MDD comorbidity), while only 32% of the TE sample met MDD criteria.

CAPS-items network

The CAPS-items network of the PTSD sample is depicted in Fig. 1a (for the TE-CAPS-items network see Fig. 1b and section below). The stability of the estimated network (CS-coefficient) was 0.75 for expected influence (Fig. 2a), reflecting a highly stable network. For edge-weight accuracy, see Fig. 2b.

The strongest edges were *physiological reactivity by trauma reminders* (B5)-to-*feelings of detachment from others* (C5); *physiological reactivity by trauma reminders* (B5)-to- *getting emotionally upset by trauma reminders* (B4); *getting emotionally upset by trauma reminders* (B4)-to-*intrusive thoughts* (B1); and *flashbacks* (B3)-to-*avoidance of thoughts* (C1).

The standardized estimate of the expected influence centrality measure is depicted in Fig. 3. *Flashbacks* (B3) and *getting emotionally upset by trauma reminders* (B4) emerged as the most influential symptoms, with *amnesia* (C3) and *irritability* (D2) emerging as the least influential.

See online Supplementary Figs S1 and S2 for significant tests between edge weights and nodes, respectively.

CAPS + MADRS-items network

CAPS and MADRS items formed two separate clusters within the co-morbidity network (Fig. 1c). Network stability remained high for expected influence (0.75; online Supplementary Fig. S3A) reflecting a highly stable network. For edge-weight accuracy, see online Supplementary Fig. S3B.

Within the PTSD cluster, same edges as in the CAPS-item network emerged as strongest. Within the depressive symptoms cluster, strongest edges were *suicidality* (Q10)-to-*pessimistic thoughts* (Q9); *reported sadness* (Q2)-to-*apparent sadness* (Q1); and *lassitude* (Q7)-to-*concentration difficulties* (Q6).

The standardized estimate of expected influence for the CAPS + MADRS-items network is depicted in online Supplementary Fig. S4. G*etting emotionally upset by trauma reminders* (B4) and *flashbacks* (B3) emerged once more as the two most influential PTSD symptoms in the network. Depressive symptoms of *reported sadness* (Q2), *lassitude* (Q7), and *inner tension* (Q3) also demonstrated high expected influence. As in the CAPS-item network, *amnesia* (C3) and *irritability* (D2) were found to be the lowest on EI. *Reduced appetite* (Q5) and *detachment from others* (C5) also demonstrated low EI.

See online Supplementary Figs S5 and S6 for significant tests between edge weights and nodes, respectively.

Considering only bridge-nodes (online Supplementary Fig. S7), results showed that the most influential bridge-nodes were (depression-related) *reduced sleep* (Q4), *reported sadness* (Q2), *inner tension* (Q3), (PTSD-related) *disturbed sleep* (D1), *avoidance of thoughts* (C1), and *getting emotionally upset by trauma reminders* (B4). *Reduced appetite* (Q5) and *physiological reactions from trauma reminders* (B5) were the least influential bridge-nodes.

TE-CAPS-items network (v. CAPS-items network)

The stability of the TE network showed a lower CS-coefficient of 0.52 compared with the PTSD-related networks (0.75 for both the CAPS-items and the CAPS + MADRS-items). However, this score is still above the recommended score of 0.5, reflecting a stable enough network (online Supplementary Fig. S8A). For edge-weight accuracy, online Supplementary Fig. S8B.

The strongest positive edges in the TE network were *intrusive thoughts* (B1)-to-*flashbacks* (B3); *anhedonia* (C4)-to-*detachment from others* (C5); *irritability* (D2)-to-*concentration deficits* (D3); and *hypervigilance* (D4)-to-*startle response* (D5).

The standardized estimate of the expected influence centrality measure is depicted in online Supplementary Fig. S9. *Intrusive thoughts* (B1), *flashbacks* (B3), *irritability* (D2), and *nightmares* (B2) were the strongest nodes, with the weakest being *amnesia* (C3), *foreshortened future* (C7), and *disturbed sleep* (D1).

See online Supplementary Figs S10 and S11 for significant tests between edge weights and nodes, respectively.

The two networks differed significantly on structure ($p = 0.0018$) and global strength ($p = 0.0262$). As seen in Fig. 1, the network structure of the PTSD sample (Fig. 1a) is more interconnected relative to the TE sample (Fig. 1b).

Directed acyclic graph (DAG) analysis

In the DAG analysis (Fig. 4), *flashbacks* (B3) emerged once more as the most pivotal network node. While not being triggered by any higher located nodes, it triggered nine other PTSD symptoms, with the strongest edges being with *intrusive thoughts* (B1) and *physiological reactivity by trauma reminders* (B5), with all three
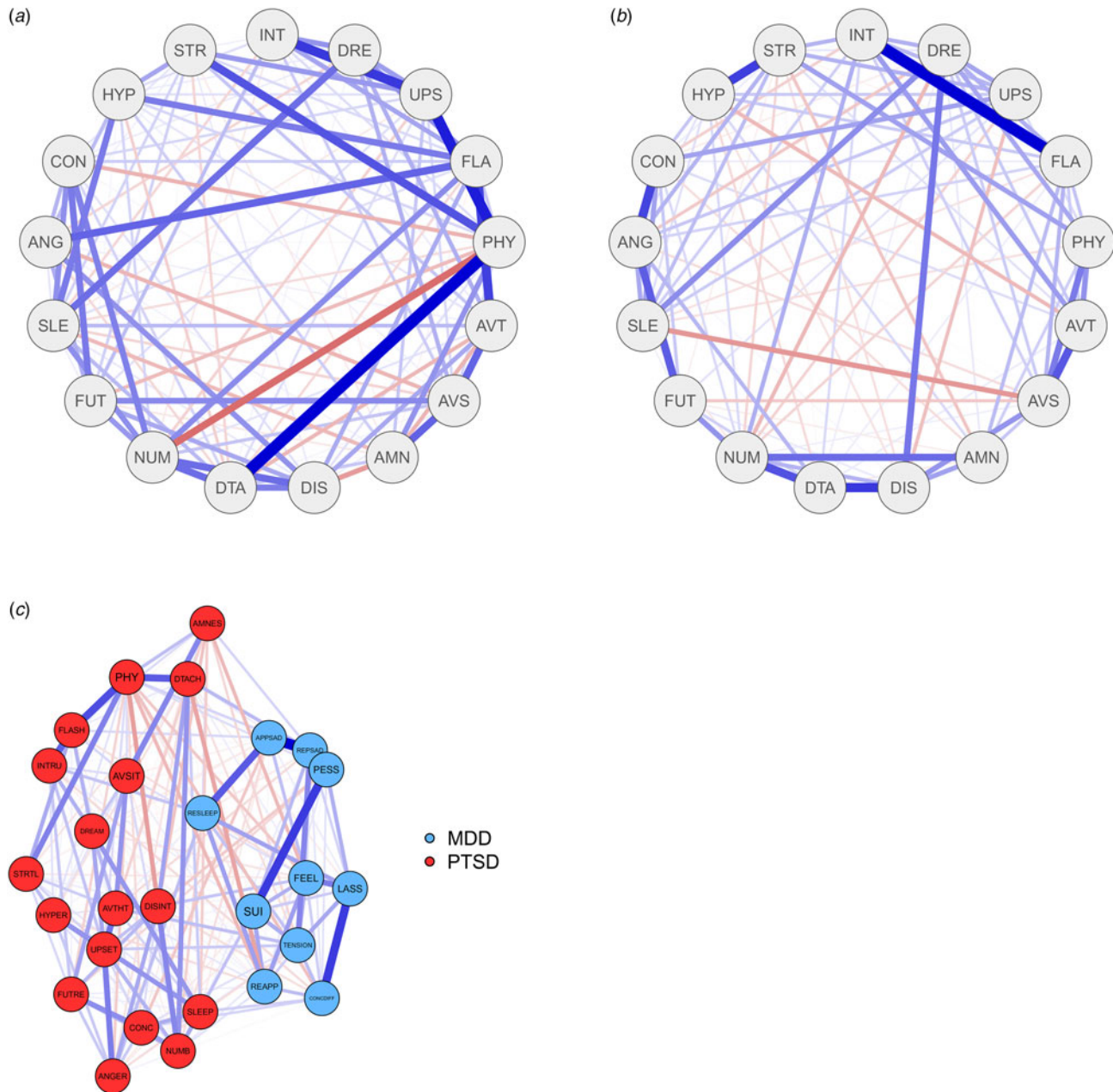
Fig. 1. Symptom-items Networks. (*a*) The clinician-administered PTSD Scale (CAPS-IV) 17-symptom-items network among PTSD patients (CAPS-items network). Positive edges appear in blue and negative appear in red. The stronger and saturated edges represent stronger regularized partial correlations. The item label abbreviations for the CAPS are: AMN, amnesia; ANG, irritability; AVS, avoidance of situations; AVT, avoidance of thoughts; CON, concentration deficits; DIS, disinterest in activities; DRE, nightmares; FLA, flashbacks; FUT, foreshortened future; HYP, hypervigilance; INT, intrusions; NUM, emotional numbing; PHY, physiological reactivity; SLE, sleep disturbance; STR, startle response; and UPS, upset by reminders. (*b*) The clinician-administered PTSD Scale (CAPS-IV) 17-symptom-items network among treatment-seeking patients who did not meet full criteria for PTSD (TE-CAPS-items network). Positive edges appear in blue and negative appear in red. The stronger and saturated edges represent stronger regularized partial correlations. The item label abbreviations for the CAPS are the same. (*c*) The network of the clinician-administered PTSD Scale (CAPS-IV) 17-symptom-items combined with the 10-symptom-items of the clinician-rated Montgomery–Asberg Depression Rating Scale (MADRS) among PTSD patients. The items from the CAPS-IV are colored red and the items from the MADRS are colored blue (CAPS + MADRS-items network). Positive edges appear in blue and negative appear in red. The stronger and saturated edges represent stronger regularized partial correlations. The item label abbreviations for the CAPS (red circles) are: AMNES, amnesia; ANGER, irritability; AVSIT, avoidance of situations; AVTHT, avoidance of thoughts; CONC, concentration deficits; DISINT, disinterest in activities; DREAM, nightmares; DTACH, detachment from others; FLASH, flashbacks; FUTRE, foreshortened future; HYPER, hypervigilance; INTRU, intrusions; NUMB, emotional numbing; PHY, physiological reactivity; SLEEP, sleep disturbance; STRTL, startle response; and UPSET, upset by reminders. The item abbreviation labels for the MADRS (blue circles) are: APPSAD, apparent sadness; REPSAD, reported sadness; TENSION, Inner Tension; RESLEEP, reduced sleep; REAPP, reduced appetite; CONCDIFF, concentration difficulties, LASS, lassitude; FEEL, inability to feel; PESS, pessimistic thoughts; SUI, suicidal thoughts.

triggering *getting emotionally upset by trauma reminders* (B4), *hypervigilance* (D4), and *avoiding trauma-related thoughts* (C1). The most downstream PTSD symptoms (i.e. triggered nodes that trigger no other nodes) were *nightmares* (B2), *irritability* (D2) and *foreshortened future* (C7) with *concentration difficulties* (D3) being mostly triggered by other nodes.
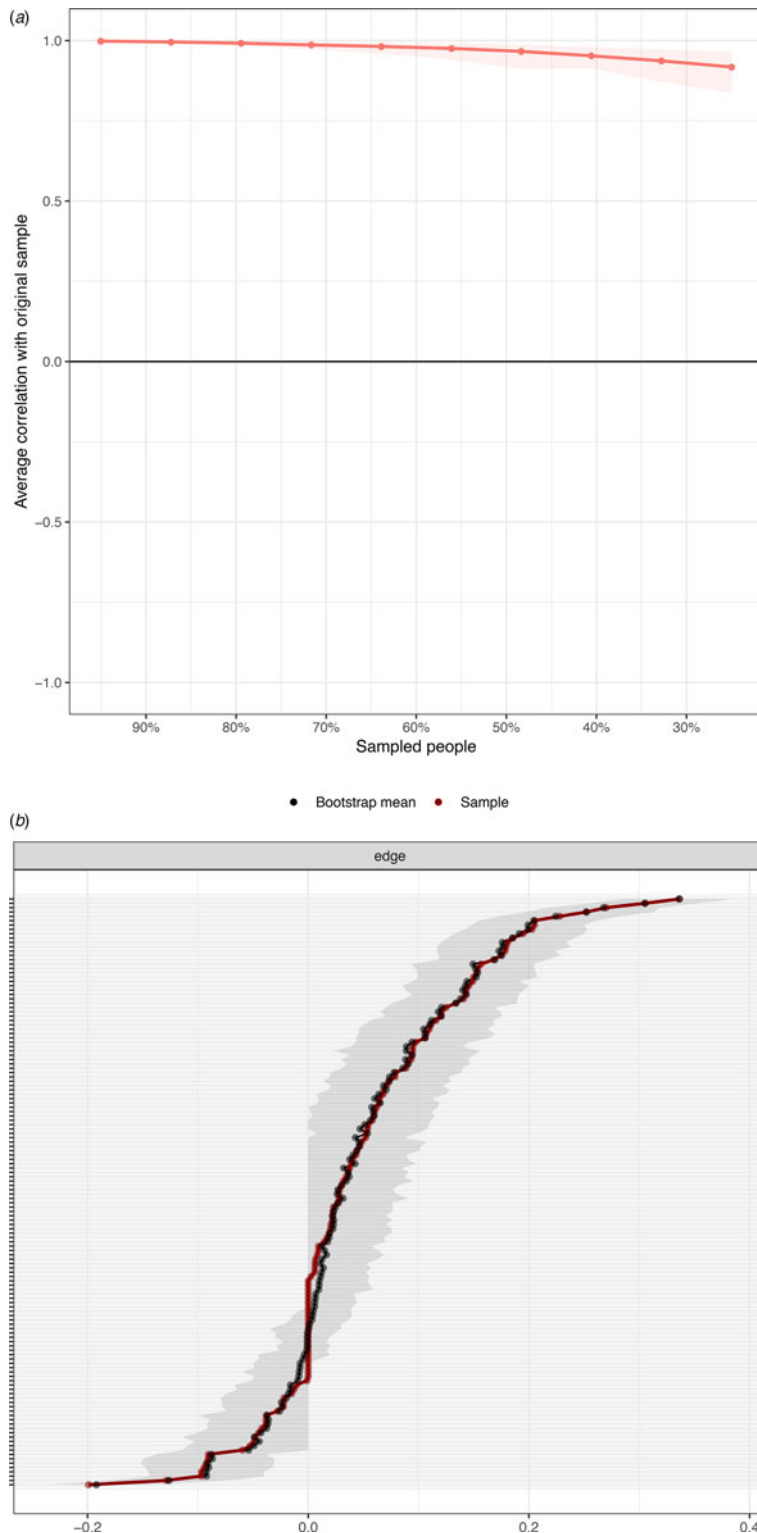
Fig. 2. Network Robustness Measures (Accuracy and Stability). (*a*) Bootstrapped node expected influence of the clinician-administered PTSD Scale (CAPS-IV) 17-symptom-items network among PTSD patients. (*b*) Bootstrapped confidence intervals of all edge weights of the clinician-administered PTSD Scale (CAPS-IV) 17-symptom-items network among PTSD patients. The red line represents sample values, the black line represents bootstrap means, and the gray area is the bootstrapped CIs. Each horizontal line represents one edge of the network, ordered from the edge with the highest edge-weight to the edge with the lowest edge-weight.

Of note, PTSD and depressive symptoms, while showing some between-disorders edges in the DAG, were once more clustered separately from each other. Importantly, most of the existing between-disorders edges were PTSD-to-depressive symptoms edges, with almost none of the opposite direction. Daily functioning was directly influenced by several PTSD-related symptoms, including *disturbed sleep* (D1), *anhedonia* (C4), and *numbness* (C6), but only by one depressive symptom of *reduced sleep* (Q4). In turn, daily functioning showed a triggering effect on *foreshortened future* (C7), *concentration difficulties* (D3), and *irritability* (D2), all PTSD-related symptoms.

Discussion

This study examined PTSD network structure in treatment-seeking veterans with PTSD (*n* = 1489). To our knowledge, this is the largest single-sample PTSD network study, and the first
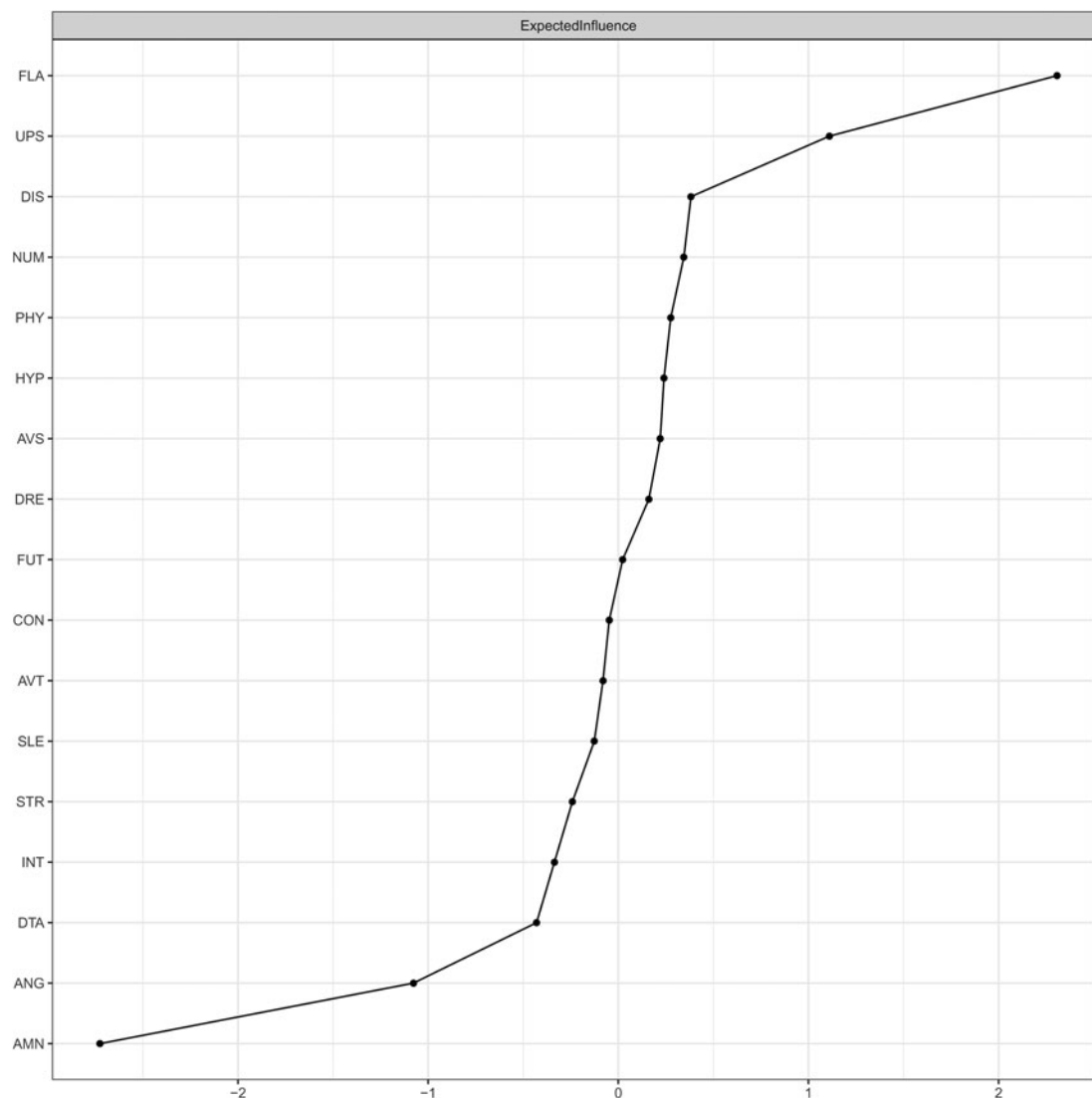
Fig. 3. Network Centrality – Expected Influence. The expected influence measure for the clinician-administered PTSD Scale (CAPS-IV) 17-symptom-items network among PTSD patients.

to include participants meeting full diagnostic criteria for PTSD, while basing network structure exclusively on clinician-administered measures. Network structure was further assessed after introducing depressive symptoms, and again using a DAG analysis, including also depressive symptoms and a functioning measure, to better discern association directionality (McNally, 2016; McNally *et al.*, 2017a).

Flashback and getting emotionally upset by trauma reminders emerged as the most central symptoms across all PTSD-related networks, highlighting their importance in the clinical presentation of PTSD among treatment-seeking veterans, echoing prior results in various populations (Spiller *et al.*, 2017; Afzali *et al.*, 2017a; Epskamp *et al.*, 2018; Fried *et al.*, 2018; Greene *et al.*, 2018), including veterans (Armour *et al.*, 2017; Mitchell *et al.*, 2017; Fried *et al.*, 2018; von Stockert *et al.*, 2018), for which their clinical importance was specifically emphasized (Armour *et al.*, 2017). *Amnesia* emerged as the least central symptom across all networks, reaffirming previous findings (Birkeland and Heir, 2017; Bryant *et al.*, 2017; Mitchell *et al.*, 2017; Spiller *et al.*, 2017; Afzali *et al.*, 2017a; McNally *et al.*, 2017a; Fried *et al.*, 2018; Moshier *et al.*, 2018; Phillips *et al.*, 2018; Ross *et al.*, 2018; von

Stockert *et al.*, 2018), which have led some to question amnesia as a core PTSD symptom (Armour *et al.*, 2017). Low centrality of amnesia is also in line with factor-analysis studies (Yufik and Simms, 2010; Armour *et al.*, 2015; Forbes *et al.*, 2015) and memory research demonstrating similarities in the clearness and vividness of traumatic and non-traumatic memories, with the former found to be more potent amongst PTSD patients compared with trauma-exposed-non-PTSD individuals (Porter and Birt, 2001; Megias *et al.*, 2007; Ross *et al.*, 2018).

The *physiological reactivity by trauma reminders*-to-*getting emotionally upset by trauma reminders*-to-*intrusive thoughts* edges (all re-experiencing symptoms), as well as three additional edges involving re-experiencing nodes (*physiological reactivity by trauma reminders*-to-detachment, *flashbacks*-to-avoidance of thoughts, and *physiological reactivity by trauma reminders*-to-startle response) were found to be of the strongest in the network. The DAG analysis further underscored the importance of re-experiencing symptoms, as *physiological reactivity by trauma reminders* and *intrusive thoughts* emerged as additional influential nodes, with *flashbacks* found to drive both these symptoms, with all three driving *getting emotionally upset by trauma reminders*.
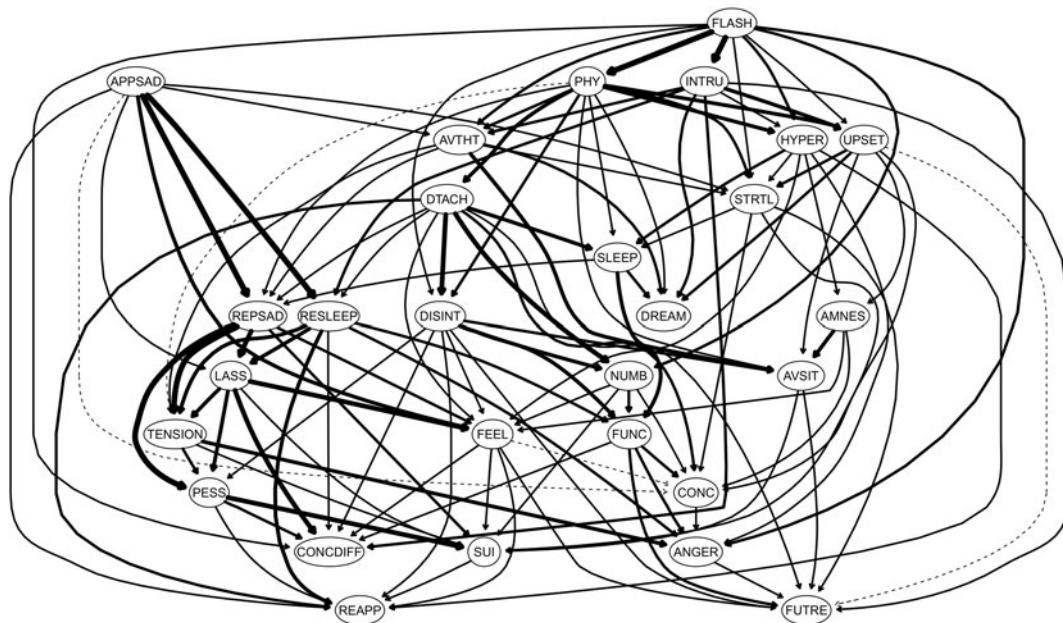
Fig. 4. Directed Acyclic Graph (DAG). Directed acyclic graph (DAG) of the clinician-administered PTSD Scale (CAPS-IV) 17-symptom-items (PTSD), the clinician-rated Montgomery–Asberg Depression Rating Scale (MADRS) 10-symptom-items (depression), and the psychotherapy outcome assessment and monitoring system-trauma version (POAMS-TV) total score reflecting overall functioning levels (functioning) among PTSD patients. Nodes represent symptoms and edges represent directed connections between symptoms. The item label abbreviations for the CAPS are: AMNES, amnesia; ANGER, irritability; AVSIT, avoidance of situations; AVTHT, avoidance of thoughts; CONC, concentration deficits; DISINT, disinterest in activities; DREAM, nightmares; DTACH, detachment from others; FLASH, flashbacks; FUTRE, foreshortened future; HYPER, hypervigilance; INTRU, intrusions; NUMB, emotional numbing; PHY, physiological reactivity; SLEEP, sleep disturbance; STRTL, startle response; and UPSET, upset by reminders. The item abbreviation labels for the MADRS are: APPSAD, apparent sadness; REPSAD, reported sadness; TENSION, Inner Tension; RESLEEP, reduced sleep; REAPP, reduced appetite; CONCDIFF, concentration difficulties; LASS, lassitude; FEEL, inability to feel; PESS, pessimistic thoughts; SUI, suicidal thoughts. The item abbreviation label for the POAMS-TV is FUNC.

These results are in line with previous networks studies emphasizing the importance of re-experiencing symptoms in PTSD (Knefel et al., 2016; Armour et al., 2017; Bryant et al., 2017) and with research using structural equation modeling reporting a positive association between trauma-exposure and re-experiencing symptoms severity in veterans (Miller et al., 2008). The importance of re-experiencing symptoms as maladaptive reactivity to trauma-reminders in the symptom structure of PTSD is also in accordance with early and more recent theoretical accounts of PTSD (Brewin and Holmes, 2003). For example, the stress response theory (Horowitz, 1976; Horowitz, 1986), one of the earliest theoretical formulations of PTSD, suggests that a failure in assimilating an overflow of new trauma-related information with prior knowledge results in persistent posttraumatic reactions, as trauma memories continuously break into consciousness (i.e. re-experiencing symptoms such as intrusions and flashbacks). As a defensive response, the individual employs avoidance of trauma reminders. Thus, trauma information continues to repeatedly intrude and be avoided, creating a re-experiencing and avoidance cycle (Horowitz, 1986). Interestingly, in addition to the importance of re-experiencing symptoms in the PTSD network structure, results of the DAG analysis further showed most avoidance symptoms (e.g. avoidance of thoughts, anhedonia, detachment) to be directly triggered mostly by re-experiencing symptoms (or by other avoidance symptoms connected to re-experiencing symptoms), echoing the suggestion of the stress response theory. A more recent theory, the dual representation theory of PTSD (Brewin et al., 1996; Brewin, 2001; Brewin et al., 2010), also assign importance to re-experiencing symptoms in PTSD. According to this theory, posttraumatic pathological responses, and especially uncontrollable re-experiencing symptoms, emerge when traumatic memories are dissociated and stored separately from ordinary memories. Specifically, trauma stimuli that receive insufficient processing to be stored as regular autobiographical memories in the 'verbally accessible memory' (VAM), are stored instead in the parallel operating, but separate, image-based 'situationally accessibly memory' (SAM) system. In the context of trauma reminders, these trauma-related memories give rise to uncontrollable intrusions and to maladaptive psychological and physiological responses (Brewin and Holmes, 2003). Another recent theory acknowledging the importance of re-experiencing symptoms in PTSD is Ehlers and Clark's cognitive model (Ehlers and Clark, 2000). Per this model, a pathological reaction following a traumatic event unfolds when the processing of traumatic information produces a continuous current sense of threat. As in the dual process theory, a trauma-related memory that lacks elaboration, that is not given a complete context, and that is inadequately integrated into the autobiographical memory system results in a memory that is hard to retrieve intentionally, leading to re-experiencing symptoms. The model further suggests that retrieval of trauma-related information from the associative memory system is mainly cue-driven and unintentional, priming the individual to trauma-reminders and leading directly to re-experiencing symptoms in response to relevant cues (Brewin and Holmes, 2003). Importantly, in comparison to avoidance and hyperarousal symptoms, also implicated in other psychopathologies (Joiner et al., 1999; Chawla and Ostafin, 2007), re-experiencing symptoms are regarded as more unique features of PTSD, less overlapping with other disorders (Chemtob et al., 1988; Brewin and Holmes, 2003; Ehlers, 2015). Thus, in conjunction with previous findings and theories, current results could be interpreted as

suggesting re-experiencing symptoms, and especially flashbacks and getting emotionally upset by trauma reminders, as potential treatment targets for veterans with PTSD. Still, as the present study is cross-sectional in nature, this possibility should be taken with cautious and rigorously explored in future studies (Fried and Cramer, 2017; Dablander and Hinne, 2018; Phillips *et al.*, 2018).

The comorbidity network revealed several important results. First, a distinct clustering of PTSD and depressive symptoms emerged, creating two discrete sub-networks. This differential clustering is in line with previous network research showing similar clustering when including depressive symptom as single nodes (Mitchell *et al.*, 2017), and no change in the PTSD network structure after including depression as a single-node covariate (Armour *et al.*, 2017). Second, same edges emerged as strongest in the CAPS-items network and within the PTSD cluster of the CAPS + MADRS-items network, suggesting minimal influence for the introduction of depression items on PTSD symptoms connectedness. Also, only slight changes in node centrality of PTSD symptoms within the co-morbid network were found, with *flashbacks* and *getting emotionally upset by trauma reminders* remaining the most central nodes, and *amnesia* and *irritability* the least central nodes. Finally, the DAG analysis yielded the same distinct clustering of PTSD and depressive symptoms. Together with findings of previous network studies, current results suggest that within-disorder (i.e. PTSD and depression) symptom connectivity is greater than between-disorder connections, even when co-occurrence of disorders is high. This suggestion is in accordance with previous research exploring the PTSD-MDD comorbidity using different analytic approaches, which supported the notion that while PTSD and MDD are highly correlated among traumatized individuals, they are also two distinct, independent and distinguishable constructs/responses to traumatic events (Blanchard *et al.*, 1998; Grant *et al.*, 2008; Gros *et al.*, 2010; Post *et al.*, 2011). Clinically, these findings might suggest that treatment of co-morbid PTSD-MDD should include components specifically addressing each pathology. Indeed, the above-cited research suggested to incorporate specific evidence-based treatment components for MDD into extant PTSD protocols to enhance treatment outcomes (Gros *et al.*, 2010), as PTSD-MDD patients, compared to patients with PTSD alone, exhibit poorer treatment response following PTSD-focused treatment (Bernardy and Friedman, 2015), necessitating novel treatment strategies for PTSD-MDD (Flory and Yehuda, 2015).

Examining bridge nodes to explore between-disorders connections revealed that *sleep difficulties* per PTSD and depression emerged as major bridging nodes, replicating previous network studies (Mitchell *et al.*, 2017; Afzali *et al.*, 2017b). This fact is not surprising considering the high comorbidity rates of sleep disturbances with psychopathology in general, and more specifically with anxiety- and depression-related pathologies, with about 50–80% of psychiatric patients reporting sleep difficulties (Morin and Ware, 1996). Moreover, many DSM-based diagnoses, including PTSD and depression, entail sleep difficulties as one of their potential symptoms (American Psychiatric Association, 2000, 2013). Thus, the bridging role of sleep difficulties is in line with research considering overlapping symptoms as origins of high comorbidity in PTSD (Boschloo *et al.*, 2015; Afzali *et al.*, 2017b), supporting the notion that the PTSD-MDD comorbidity might reflect imprecisions in symptom classification into two discrete categorical diagnoses, suggesting a nosology artifact (Flory and Yehuda, 2015). However, *avoidance of thoughts* as

well as *getting emotionally upset by trauma reminders* also emerged as a key bridge-nodes, replicating previous findings (Mitchell *et al.*, 2017). Importantly, these symptoms are not overlapping symptoms, reflecting more unique pathways between PTSD and depression. Indeed, research has shown that removing overlapping symptoms from network analysis does not necessarily collapse the comorbidity networks (Afzali *et al.*, 2017a, 2017b), and that overlapping symptoms cannot exclusive explain the PTSD-MDD association (Blanchard *et al.*, 1998; Elhai *et al.*, 2008; Elhai *et al.*, 2011; Boschloo *et al.*, 2015). Thus, the high centrality of non-overlapping bridge symptoms supports an alternative conceptualization of the PTSD-MDD comorbidity, namely, that this comorbidity is not a nosology artifact, but rather a distinct trauma-related phenotype, or even a subtype of PTSD, reflecting a fundamental dimension of risk for psychopathology following trauma exposure (Flory and Yehuda, 2015). On a more speculative note, current findings can be also viewed in light of research examining the temporal order of PTSD and MDD, in general and more specifically in combat-related PTSD, trying to ascertain whether pre-existing MDD is a risk factor for developing PTSD following trauma-exposure, whether MDD is a reaction to PTSD, considering PTSD as a risk factor for MDD, or whether there is a more complex, bi-directional relationship between PTSD and MDD, with shared risk factors and vulnerabilities (Stander *et al.*, 2014; Angelakis and Nixon, 2015). While not addressing these options directly, due to the cross-sectional nature of our data, the differential clustering of PTSD and depressive symptoms in the CAPS + MADRS network, the results of the DAG analysis showing a similar differential clustering of PTSD and depressive symptoms, and the emergence of significant non-overlapping bridge symptoms, all allude to the conceptualization of the PTSD-MDD comorbidity as a trauma-related reaction comprised of mutual influential, yet distinct, symptom structures.

Addressing functioning in network analyses is important as the DSM classification system specifically requires significant impairment in functioning for a PTSD diagnosis (Ross *et al.*, 2018). The DAG network revealed that functioning was directly triggered by the PTSD symptoms of *disturbed sleep*, *anhedonia*, and *emotional numbness*, and by one overlapping depressive symptom of *reduced sleep*. This is in line with research showing that sleep disturbances independently aggravate PTSD daytime symptoms, contributing to poorer functioning (DeViva *et al.*, 2004; Germain *et al.*, 2008), and that anhedonia and emotional numbness lead to deficient social activity and restriction of psychological resources in PTSD (Kashdan *et al.*, 2006, 2007). Our results also align with the only network study that focused specifically on functional impairment in veterans with PTSD showing anhedonia to have the highest bridge centrality/EI measure (Ross *et al.*, 2018). Thus, it seems that impaired functioning is directly influenced by depressive-like PTSD symptoms.

The network structure of the trauma-exposed (TE) treatment-seeking patients not meeting full criteria for PTSD was markedly less connected compared to the PTSD network, with different central edges and nodes, replicating a previous network study conducting similar analyses comparing US veterans with PTSD and subthreshold PTSD (Phillips *et al.*, 2018). This aligns with the networks approach's theoretical framing of psychopathology, namely, that a certain disorder will transpire when the required number of symptoms are activated for a sufficient duration, reaching the disorder's 'tipping point' (van de Leemput *et al.*, 2014; Hofmann *et al.*, 2016; McNally, 2016, 2017). Still, this

trauma-exposed population should not be taken lightly, especially among treatment-seeking veterans. Research has shown the detrimental effects of sub-threshold PTSD (Stein *et al.*, 1997; Mylle and Maes, 2004; Jakupcak *et al.*, 2007; Pietrzak *et al.*, 2011; Mitchell *et al.*, 2012; Schnurr, 2014; Jung *et al.*, 2016), suggesting it as a risk condition at the prodromal phase of PTSD (Schnurr, 2014). Current results could assist therapists treating treatment-seeking trauma-exposed veterans with no 'formal' PTSD diagnosis by highlighting the need to address specific symptoms and connection between symptoms, which are different from those characterizing PTSD patients, aiming to weaken the corresponding network, and, potentially, halt the progression towards clinical PTSD.

While our findings corroborate previous research in PTSD, differences also emerged, potentially due to differences in various methodological features. This has been acknowledged by most network studies which have implicated potential differences in sample size, type (treatment-seeking, survey data), and status (clinical, probable, sub-threshold, trauma-exposed), and PTSD measures (self-report, clinician-administered) used for network construction (Armour *et al.*, 2017; Birkeland and Heir, 2017; Bryant *et al.*, 2017; Mitchell *et al.*, 2017; Spiller *et al.*, 2017; McNally *et al.*, 2017a; Fried *et al.*, 2018; Ross *et al.*, 2018; Sullivan *et al.*, 2018) in results heterogeneity. Gender may also contribute to observed differences (Mitchell *et al.*, 2017), especially as we have explored an all-male sample. Finally, trauma type has been suggested as influencing PTSD expression/presentation (Norris *et al.*, 2002a, 2002b; Chung and Breslau, 2008; Kelley *et al.*, 2009; McNally, 2009), and, accordingly, network structure (Armour *et al.*, 2017; Birkeland and Heir, 2017; Phillips *et al.*, 2018; Ross *et al.*, 2018; Sullivan *et al.*, 2018; von Stockert *et al.*, 2018). Indeed, comparing networks across three different traumatic events revealed corresponding differences in network structures (Benfer *et al.*, 2018). Importantly, while seven studies explored veteran samples (Armour *et al.*, 2017; Mitchell *et al.*, 2017; Fried *et al.*, 2018; Moshier *et al.*, 2018; Phillips *et al.*, 2018; Ross *et al.*, 2018; von Stockert *et al.*, 2018), trauma was restricted to being combat- or deployment-related only in three (Mitchell *et al.*, 2017; Fried *et al.*, 2018; Phillips *et al.*, 2018), with results being mostly similar to the present study, namely, high centrality of *getting emotionally upset by trauma reminders* and low centrality for *amnesia* and *irritability*.

Limitations should be considered. First, data from this study is cross-sectional and as such cannot directly examine the temporal nature and directed influences of associations between symptoms (Fried and Cramer, 2017; Dablander and Hinne, 2018; Phillips *et al.*, 2018). While trying to address this issue using the DAG analysis, which provides preliminary clues of directionality in cross-sectional data, DAG analysis has some strict assumptions curbing potential inferences (McNally *et al.*, 2017a, 2017b). Primarily, for psychopathology network, including DAG, one must assume that no important variable has been omitted from the network (Jones *et al.*, 2017). While attempting to address this by including depressive symptoms and a functioning measure, many other non-symptoms may play a causal role in PTSD, as well as in bridging PTSD and other disorders (Jones *et al.*, 2017). These may include, among others, threat-related cognitive biases (Lazarov *et al.*, 2018, 2019), neural abnormalities (O'Doherty *et al.*, 2015; Koch *et al.*, 2016), social functioning (Wilcox, 2010), and other factors which have been implicated in PTSD such as age (Konnert and Wong, 2015) and gender (Lehavot *et al.*, 2018). Thus, future network-based research should include additional non-symptom nodes to enrich our

understanding of PTSD (Jones *et al.*, 2017). In addition, one must also assume that there are no feedback loops between symptoms, as in DAG activation flow is uni-directional. While thick edges (as those connecting re-experiencing symptoms; see Fig. 4) increase our confidence in directionality, future longitudinal studies could better assist in clarifying temporal sequences and potential causal relations between symptoms (Bringmann *et al.*, 2013; Bryant *et al.*, 2017; Greene *et al.*, 2018). Second, the PTSD-related network structures were modeled using the CAPS 17-symptom-items, which are the same symptoms/items used to select/create the study groups (i.e. PTSD and TE samples). Importantly, when using covariance-based methods, this selection might bias the resultant covariance structure leading to spurious correlations, a bias known as Berkson's bias (Cole *et al.*, 2010; Berkson, 2014; Phillips *et al.*, 2018; de Ron *et al.*, 2019). Although there is currently not a clear best-practice guide for how to deal with this in network analysis in psychopathology-related research (Phillips *et al.*, 2018), we wish to emphasize that selection per PTSD diagnosis was established based on the relatively lenient F1/I2 item rule (i.e. Frequency ⩾ 1, Intensity ⩾ 2), and not on a clinical significance cutoff score (Blake *et al.*, 1995). Third, the present study used DSM-IV criteria in diagnosing PTSD and in constructing the different PTSD-related networks. Importantly, in DSM-5 three additional symptoms were added (for a total of 20 symptoms as opposed to the 17 symptoms in DSM-IV) with the addition of a forth symptom-cluster, following the division of the DSM-IV avoidance cluster into avoidance and negative alterations in cognitions and mood associated with the traumatic event (American Psychiatric Association, 2013; Hoge *et al.*, 2014). Specifically, the negative alterations in cognitions and mood symptom-cluster introduces three 'new' depressive-like symptoms which were not included in DSM-IV, namely, negative feeling about oneself, others and the world (Symptom D2), self-blame (Symptom D3), and persistent negative emotional state (Symptom D4). Thus, constructing the PTSD-MDD comorbidity network using DSM-5 might have yielded different results. Still, as network analysis is data-driven, including depressive symptoms and a functioning measure provide vital information on symptom structure, partly covering the above-mentioned DSM-5 additional symptoms. Finally, although representing an important sub-population of patients, the sample's homogeneity (i.e. male veterans with combat-related PTSD) impedes result-generalizability to other trauma-exposed populations.

Despite these limitations, the present study has several key strengths that outweigh its limitations and contribute to extant knowledge in the field. Results indicate a pivotal role for *flashbacks* and *psychological reaction to trauma reminders*, with strong connections to other re-experiencing symptoms, in the clinical presentation of combat-exposed veterans with PTSD. Depressive symptoms had little effect on the PTSD network structure, reflecting two separate diagnostic entities, but with meaningful between-disorder connections, suggesting independent yet mutually-influential systems.

Notes

[1] Recently, however, some have questioned increasing sample size as means to ensure reduction in estimation errors and risk measures and, enhancement of specificity in network-based models (Epskamp and Fried, 2016; Kuismin and Sillanpaa, 2016; Williams and Rast, 2018).

[2] Armed conflicts included Israel's war of Independence; Operation Kadesh; the Six-Day War; War of Attrition; the Yom Kippur War; the 1982 and

2006 Lebanon Wars; Lebanon and West Bank routine security measures; the first and second Intifada (civilian uprising); and Operations Defensive Shield, Pillar of Defense, Cast Lead, and Protective Edge. Majority of veterans included in the present study participated in routine security measures in Lebanon and the 2006 Lebanon War

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