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Neurobiology of comorbid post-traumatic stress disorder and alcohol-use disorder

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Abstract

Post-traumatic stress disorder (PTSD) and alcohol-use disorder (AUD) are highly comorbid in humans. Although we have some understanding of the structural and functional brain changes that define each of these disorders, and how those changes contribute to the behavioral symptoms that define them, little is known about the neurobiology of comorbid PTSD and AUD, which may be due in part to a scarcity of adequate animal models for examining this research question. The goal of this review is to summarize the current state-of-the-science on comorbid PTSD and AUD. We summarize epidemiological data documenting the prevalence of this comorbidity, review what is known about the potential neurobiological basis for the frequent co-occurrence of PTSD and AUD and discuss successes and failures of past and current treatment strategies. We also review animal models that aim to examine comorbid PTSD and AUD, highlighting where the models parallel the human condition, and we discuss the strengths and weaknesses of each model. We conclude by discussing key gaps in our knowledge and strategies for addressing them: in particular, we (1) highlight the need for better animal models of the comorbid condition and better clinical trial design, (2) emphasize the need for examination of subpopulation effects and individual differences and (3) urge cross-talk between basic and clinical researchers that is reflected in collaborative work with forward and reverse translational impact.

Keywords

Alcohol dependence; alcohol use disorder (AUD); alcoholism; post-traumatic stress disorder (PTSD); comorbid PTSD and AUD; amygdala; mesolimbic reward circuit; prefrontal cortex; hippocampus; norepinephrine

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Comorbid PTSD and AUD

It has long been recognized that exposure to traumatic events can elicit, in some individuals, the emergence of a spectrum of debilitating and enduring anxiety-related symptoms, but the term post-traumatic stress disorder (PSTD) was not officially recognized as an anxiety disorder until the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III). This term replaced other labels such as ‘shell shock’ and ‘war neurosis’ that had appeared in the literature for hundreds of years (Crocq & Crocq 2000; Trimble 1985). This change was prompted by the acknowledgment that the etiological agent that triggered the symptoms was outside the afflicted individual rather than merely a reflection of some personal weakness or failing, a realization that slowly began to reduce the stigma associated with this disorder. Revisions to the diagnostic criteria of PTSD continued until the latest edition of the DSM (DSM-V) which recognized that, although anxiogenic symptoms are a cornerstone of PTSD, this disease is better described by a new category of mental illnesses, termed trauma- or stressor-related disorders, in which exposure to a traumatic or otherwise adverse environmental event precedes the onset of each disorder. The diagnostic criteria of PTSD include four clusters of symptoms: intrusion, avoidance, negative alterations in cognitions and mood and alterations in arousal and reactivity (Guina *et al.* 2016). Individuals suffering from these disorders often re-experience a previously traumatic event, make significant efforts to avoid internal or external reminders of the trauma and exhibit hyperarousal in response to relatively neutral stimuli. These revisions to the diagnostic criteria of PTSD are largely evidence-based and have helped to stimulate a much-needed increase in research directed at this debilitating disorder. This is especially critical and timely because the latest estimates using the DSM-V diagnostic criteria indicate that the current past year PTSD prevalence was 4.7% and the lifetime prevalence rate was 8.3 (Kilpatrick 2003).

The diagnostic criteria for alcohol-use disorder (AUD) have also evolved with each iteration of the DSM. In the latest edition (DSM-V), alcohol dependence and abuse have been replaced by a single disease. Alcohol use disorder (AUD), with the diagnosis severity dictated by the expression of a pathological set of behaviors related to the use of alcohol (Hasin *et al.* 2013). These behaviors fall into four main categories including impaired control (e.g. drinking more than intended), social impairment (e.g. drinking behavior negatively impacts work, family, etc.), risky use (e.g. driving while intoxicated) and altered physiology (e.g. tolerance and withdrawal). As with PTSD, the prevalence of AUD is high. In the United States, data from the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions III using the revised DSM-V criteria showed that the 12-month and lifetime prevalence of AUD were 13.9% and 29.1%, respectively (Grant *et al.* 2015a).

Epidemiology of comorbid PTSD and AUD

Despite the high incidence of AUD in the general population, individuals with PTSD are at even higher risk of developing AUD. Although an anecdotal connection between these disorders had long been appreciated, numerous clinical and epidemiological studies have consistently documented a strong association between PTSD and AUD (Blanco *et al.* 2013; Debell *et al.* 2014; Jacobson *et al.* 2008; Shorter *et al.* 2015). For example, a large

retrospective review of the lifetime co-occurrence of DSM-III-R alcohol dependence and other psychiatric disorders from the US National Comorbidity Study reported that PTSD was associated with a three-fold increase in risk of developing AUD (Kessler *et al.* 1997). Other studies have reported that the lifetime prevalence of any substance-use disorder (SUD) was twice as high in persons with PTSD vs. those not suffering from this disorder (Shorter *et al.* 2015) and that alcohol is the most commonly abused drug in PTSD patients (Jacobsen *et al.* 2001). Indeed, a recent study examined the relationship between the frequency of childhood physical, sexual and emotional abuse and the development of substance use and PTSD in an urban, civilian population. Not only was the lifetime prevalence of substance dependence very high in these individuals (e.g. alcohol: 39%; cocaine: 34%), but also a strong correlation was noted between the levels of childhood abuse and both the prevalence of AUD and current PTSD symptoms (Khoury 2010). Interestingly, more recent data suggest that scoring high on a measure of resilience characteristics such as tenacity, strong self-efficacy and emotional/cognitive control under pressure may reduce the risk of substance misuse and PTSD in this 'at-risk' population (Wingo 2014).

Despite the high prevalence of comorbid PTSD/AUD in the civilian population, the situation is even more dire for military personnel. First, the prevalence of PTSD in military and veteran populations may be twice that observed in the civilian population (Gates *et al.* 2012; Ramchand *et al.* 2010). Similarly, military personnel are disproportionately impacted by the adverse effects of alcohol. Recent surveys show that rates of alcohol misuse range from 18% to 35% for soldiers returning from Operation Iraqi or Enduring Freedom (Hoge *et al.* 2004; Wilk *et al.* 2010). Other data on military personnel that served in Iraq and Afghanistan found that the baseline prevalence of binge drinking among Reserve or National Guard personnel was 53.6% and the incidence of alcohol-related problems was 11.9% (Jacobson *et al.* 2008). Moreover, individuals who reported combat experience had higher rates of new-onset heavy drinking, binge drinking and alcohol-related problems than those not exposed to combat (Jacobson *et al.* 2008). Not surprisingly, the rates of comorbid PTSD and AUD are extremely high in military personnel. The Veterans Administration reported that almost 70% of veterans hospitalized for PTSD also suffered from a comorbid SUD, with alcohol being the most commonly abused drug Kulka *et al.* 1988 and a more recent study found that almost 50% of actively serving or National Guard Infantry personnel deployed to Iraq that screened positive for PTSD also met diagnostic criteria for alcohol misuse (Thomas *et al.* 2010). Importantly, as noted earlier, the diagnostic criteria for PTSD and AUD have recently been revised. Therefore, new epidemiological studies are needed to obtain estimates of the prevalence of the comorbid condition in the general population and at-risk groups using these revised criteria.

Despite the notion that high rates of comorbidity between PTSD and AUD reflect an attempt by the individual to self-medicate the negative affective state that emerges in trauma and stressor-related disorders, there is also a growing appreciation that all of these disorders may actually share common neural substrates (Enman *et al.* 2014). Although a number of behavioral and pharmacological treatments are available for both PTSD and AUD, these interventions are frequently ineffective and individuals who suffer from this dual diagnosis are particularly ill-served by current treatment options (Ipser 2015; Najavits 2013; Sofuoglu 2014). As such, there is a great deal of interest in gaining a better understanding of the

neurobiological substrates underlying this comorbidity. However, progress has been hampered, to some extent, by a lack of animal models that engender a behavioral phenotype that reflects the human comorbid condition. The overarching goal of this review is to summarize the current state of research on the comorbidity between PTSD and AUD. This article will summarize the epidemiological evidence documenting the prevalence of this comorbidity and review the neurobiological basis for the frequent co-occurrence of these disorders. Current treatment options will also be discussed. This review will also summarize the literature on available animal models, highlighting where the models parallel the human condition, and discuss the strengths and weaknesses of each model. Collectively, this summary may provide guidance for future work directed at improving animal models and developing more effective treatments for comorbid PTSD and AUD. As this article will focus primarily on the literature related to the comorbidity between PTSD and AUD, for manuscripts focused solely on the epidemiology, neurobiology and treatment of each disorder alone, the interested reader is directed to the following PTSD (Admon *et al.* 2013b; Atwoli *et al.* 2015; Hoskins *et al.* 2015; Pitman *et al.* 2012) and AUD reviews (Batman & Miles 2015; Koob 2013; Samochowiec *et al.* 2014; Tabakoff & Hoffman 2013; Zindel & Kranzler 2014).

Temporal expression of PTSD and AUD

Although relatively few studies have addressed the order of onset of PTSD and AUD, there is a general consensus that PTSD precedes the onset of AUD (Chilcoat & Breslau 1998; Epstein *et al.* 1998; Jacobsen *et al.* 2001; Kessler *et al.* 1995, although see Cottler *et al.* 1992). For example, a recent longitudinal study in a cohort of National Guard troops that were screened pre- and post-deployment to Iraq found no effect of pre-deployment alcohol status on the onset of PTSD; however, initial PTSD symptoms significantly increased the risk of screening positive for new-onset alcohol dependence (Kline *et al.* 2014). These findings lend empirical support to the notion that individuals with PTSD may misuse alcohol in an attempt to alleviate the anxiogenic and hyperarousal symptoms associated with this disorder. Recent work has also highlighted an alarming increase in the prevalence of pediatric PTSD, which may further increase the likelihood of developing AUD following a PTSD diagnosis (Makley & Falcone 2010).

Risk factors of comorbid PTSD and AUD

As highlighted above, there is compelling evidence that active military personnel and veterans are at increased risk for comorbid PTSD and AUD diagnoses. Are there other risk factors associated with this dual diagnosis? Several studies have noted that exposure to a wide range of early life stressors increases risk for the development of PTSD alone and AUD alone, and that childhood adversity represents an even greater risk factor for the development of comorbid PTSD and AUD. For example, data from the National Survey of Adolescents reported that a history of interpersonal violence was a stronger risk factor for the dual diagnosis of PTSD and AUD than for either non-comorbid diagnoses (Kilpatrick *et al.* 2013). In a study of alcohol-dependent men with comorbid PTSD, a history of emotional abuse in childhood was found to contribute to impaired quality of life (Evren *et al.* 2011). A more recent analysis of data from the National Epidemiological Survey on Alcohol and Related Conditions confirmed this relationship, finding that individuals with comorbid

PTSD and AUD were more likely to have suffered childhood adversities than those with only one of these conditions (Blanco *et al.* 2013).

There is also evidence that stressors such as lower socioeconomic status and traumatic life events may place adult victims at greater risk of developing comorbid PTSD and AUD (Riggs *et al.* 2003; Ullman *et al.* 2006).

Sex, gender and comorbid PTSD/AUD

Epidemiological studies consistently find that women are more than twice as likely than men to be diagnosed with PTSD over their lifetime (Breslau *et al.* 1997; Kessler *et al.* 1995; Olff *et al.* 2007). In contrast, AUD rates are almost twice as high in men (Erol & Karpyak 2015; Nelson *et al.* 1998). Given this dichotomy, it may not be surprising that the data on whether men or women are at greater risk for the development of comorbid PTSD and AUD are mixed. Several studies have reported higher prevalence of comorbid PTSD and AUD in men (Conway *et al.* 2006; Kozaric-Kovacic *et al.* 2000), whereas others cite slightly higher or comparable rates of comorbidity in women and men (Kessler *et al.* 1995, 1997; Pietrzak *et al.* 2012). One complicating factor may be that the type of trauma experienced could influence the likelihood of developing comorbid PTSD and AUD. For example, while sexual assault is a well-established risk factor for PTSD, one study found that the nature of the assault impacts the probability of also developing AUD (Goldstein 2011). While rape victims in this study had a significantly higher incidence of PTSD than non-victims, women who experienced drug/alcohol-facilitated rape (i.e. were incapacitated) with or without forcible rape were even more likely to develop AUD than those who experienced forcible rape alone. Other studies have also begun to identify a variety of correlates that may predict the comorbid condition. For example, among a group of sexual assault survivors who were all diagnosed with PTSD, women who believed that drinking could reduce distress, had less education, or had a history of other traumas were more likely to also suffer from comorbid drinking problems (Ullman 2006). Collectively, these studies suggest that gender likely influences the prevalence of comorbid PTSD and AUD; however, considerable additional research will be needed to better understand the factors that moderate this relationship.

Consequences of comorbid PTSD and AUD

Many studies have examined how the dual diagnosis of PTSD and AUD influences the trajectory and prognosis of these disorders. Here, the literature consistently illustrates that the dual diagnosis of PTSD and AUD exacerbates the symptoms of each disorder. For example, in patients with PTSD, heavy alcohol drinking increases the number (Behar 1987) and severity of PTSD symptoms (Bremner *et al.* 1996; Jacobsen *et al.* 2001; Saladin *et al.* 1995) and prolongs the course of illness (Bremner *et al.* 1996; Yehuda *et al.* 1995). One particularly troubling study looked at suicidal ideation and attempts in patients with PTSD and either comorbid major depressive disorder or alcohol dependence. While comorbid depression was not related to suicidal thoughts and actions, PTSD patients with comorbid alcohol dependence showed higher suicidal ideation and suicide attempts (Rojas *et al.* 2014). Similarly, individuals with comorbid PTSD show an earlier onset of AUD symptoms (Driessen *et al.* 2008), poorer physical and mental health (Evren *et al.* 2011) and a much

poorer prognosis in recovery (Ipser *et al.* 2015; Norman *et al.* 2015; Schafer & Najavits 2007; Shorter *et al.* 2015).

Modeling comorbid PTSD and AUD in animals

Basic science researchers have long strived to produce animal models that mimic aspects of the clinical diagnoses for PTSD or AUD. As mentioned above, it has also been long acknowledged that PTSD and AUD are highly comorbid in the clinic. Despite that fact, until very recently, few, if any, animal models have existed for testing the neural substrates underlying the symptom clusters associated with PTSD and AUD in the same sets of animals. There are many reasons for this void in the literature, not the least of which is the complexity of combining the models used to study each of these disorders. At the most basic level, it has been notoriously difficult to produce models in which stress reliably increases alcohol drinking for a sustained period of time (Boyce-Rustay *et al.* 2007, 2008; Croft *et al.* 2005; Funk *et al.* 2005; Lopez *et al.* 2016; McKenzie-Quirk & Miczek 2008; Miczek *et al.* 2008; Sillaber *et al.* 2002; van Erp & Miczek 2001). The field has been more successful in producing animal models that mimic the ability of stressors to elicit relapse to seeking of alcohol and other drugs, in which animals are trained to self-administer alcohol or drugs of abuse, this responding is extinguished and stress is used to reinstate responding for an alcohol or drug reinforcer that is not actually available to the animal; these models have been reviewed in detail elsewhere (see Mantsch *et al.* 2016).

A recent review examined factors that affect whether stress increases alcohol drinking in animals. Among the critical factors are the type and modality of the stress, the species, strain, age and sex of the animal, the acute vs. chronic pattern of stress exposure and whether alcohol drinking is measured using home-cage consumption or operant self-administration models (Noori *et al.* 2014). Since that time, a variety of rodent models have emerged that seek to reliably produce stress-induced increases in alcohol drinking, in order to study the underlying neural substrates. Typically, these are adaptations of previously existing animal models of stress and alcohol drinking that have been combined and/or modified to yield the desired outcome.

Strategies used to produce stress-induced excessive alcohol drinking in animals can be broadly divided based on the question they are designed to answer. First, if the goal is to understand whether and how traumatic stress produces escalation of alcohol drinking in current drinkers, the animal model should introduce stress in adult animals that have already been trained and had experience drinking low-to-moderate quantities of alcohol over time. Second, if the goal is to understand whether and how traumatic stress history produces escalation of alcohol drinking in future drinkers, the animal model should introduce stress in previously alcohol-naïve animals, perhaps during development depending on the specific question, train animals to drink concurrent with the stress onset or later in life, and then analyze behavior over time. Third, if the goal is to understand whether and how traumatic stress accelerates the development of, exaggerates the magnitude of, or prolongs the effects of alcohol dependence on brain and behavior, the animal model should introduce stress in adult animals that are undergoing forced and/or self-administration of high quantities of alcohol. One difficulty in modeling this scenario is the potential that alcohol dependence

produces ceiling effects on alcohol outcomes that mask or dampen additive effects of stress (Anderson *et al.* 2016). Fourth, if the goal is to understand whether and how traumatic stress elicits relapse in the post-dependent organism, one of several strategies may be useful: either (1) introduce stress in adult animals during alcohol dependence and then impose alcohol abstinence, (2) introduce stress in animals that are already enduring imposed abstinence after being made dependent on alcohol (Sommer *et al.* 2008; Valdez *et al.* 2003) or (3) introduce stress to induce reinstatement of previously extinguished responding for alcohol. Footshock and yohimbine reinstate previously extinguished alcohol responding in animals (e.g., Le *et al.*, 2005), but these procedures are not purported to model traumatic stress disorders, and do not produce persistent escalation of alcohol drinking in currently drinking animals (e.g., Meyer *et al.*, 2013).

State-of-the-science: animal models of stress-induced escalation of alcohol drinking

As the human literature suggests that PTSD usually precedes AUD, most animal models have aimed to mimic the human scenario in which traumatic stress precedes, and presumably triggers, the onset of AUD through yet unidentified neurobiological processes. To that end, this nascent research field has developed several animal models aimed at producing stress-induced escalation of alcohol drinking. Here, we introduce the basic structure of these models, but the neurobiological measures will be described in the context of human findings in subsequent sections.

Two laboratories (Edwards *et al.* 2013; Manjoch *et al.* 2016) are using predator odor to test the neurobiological correlates and mechanisms of increased alcohol drinking in some, but not all, rats. In these models, adult male rats are either trained to self-administer operant alcohol prior to bobcat urine exposure (Edwards *et al.* 2013) or trained to drink sweetened alcohol in the home cage prior to soiled cat litter exposure (Manjoch *et al.* 2016), rats are divided into groups based on several behavioral indices including stress reactivity and then allowed to resume alcohol drinking. In these models, high stress-reactive rats exhibit higher alcohol drinking over 1 week (Manjoch *et al.* 2016) or 3 weeks (Edwards *et al.* 2013) post-stress, and also exhibit more compulsive-like responding for alcohol adulterated with escalating concentration of an aversive bitter tastant (Edwards *et al.* 2013).

To address a slightly different question aimed at understanding additive or synergistic effects of stress and alcohol dependence on alcohol drinking, one research group combined forced swim stress with a mouse model of alcohol dependence that employs chronic intermittent alcohol vapor exposure (Anderson *et al.* 2016; Lopez *et al.* 2016). This work shows that daily forced swim stress accelerates the onset of, and perhaps enhances the magnitude of, escalated alcohol drinking in alcohol-dependent adult male C57BL/6J mice (Anderson *et al.* 2016; Lopez *et al.* 2016). Highlighting the subtleties of such models, repetition of the forced swim stress may enhance the additive effects of stress and dependence on escalation of alcohol drinking. Furthermore, one of these studies also showed that the same forced swim stress manipulation that enhanced dependence-induced escalation of alcohol drinking did not affect alcohol drinking in binge (i.e. drinking in the dark) or intermittent access procedures, and animals stressed during continuous alcohol access actually decreased their drinking relative to unstressed controls (Anderson *et al.* 2016).

Another set of animal models aimed at understanding the effect of traumatic stress on future alcohol drinking has adapted an early life stress model to show that social isolation during adolescence, but not during adulthood, increases alcohol drinking. Rats and, to a lesser extent mice, are highly social creatures, and in the wild live in large social groups of hundreds of animals (McEwen *et al.* 2015). Many studies have shown that depriving rats of social interaction during adolescence leads to enduring alterations in a wide range of emotional behaviors in adulthood (Marsden *et al.* 2011; Ratajczak *et al.* 2013; Toth & Neumann 2013), many of which are considered risk factors of PTSD or AUD, including increases in measures of unconditioned anxiety-like behavior and impulsivity. Although several early studies noted that adolescent social isolation generally promotes an increase in alcohol drinking (Deatherage 1972; Hall *et al.* 1998; Schenk *et al.* 1990; Wolffgramm 1990), only recently have researchers leveraged this model to study neural correlates of PTSD/AUD comorbidity.

One group employs male Long Evans rats and socially isolates them for 6 weeks in standard single rodent cages, starting at postnatal day (PD) 28. Group-housed control subjects are housed in cohorts of four animals in larger cages in an otherwise identical environment. Thus, the primary experimental variable is that socially isolated rats are deprived of any physical interaction with their peers. Recent studies show that this adolescent social isolation procedure produces a wide range of behaviors that have all been linked with heightened vulnerability to AUD and/or PTSD including hyperactivity in a novel environment (Chappell *et al.* 2013), increased anxiety-like behavior on the elevated-plus maze (Chappell *et al.* 2013; McCool & Chappell 2009; Yorgason *et al.* 2013), deficits in sensory gating (McCool & Chappell 2009) and impaired extinction of fear learning (Skelly *et al.* 2015). Notably, many of the behavioral alterations engendered by this model persist for months into adulthood, even when comparisons are made with adolescent group-housed rats that are then also singly housed in adulthood. Thus, the behavioral changes associated with social isolation only manifest when this stressor is experienced early in life.

In addition to the behavioral risk factors of PTSD and AUD noted above, this model also promotes long-lasting increases in ethanol self-administration using a variety of drinking procedures. For example, McCool and Chappell (2009) reported greater ethanol, but not sucrose, consumption in a limited-access, operant procedure and, using the home-cage intermittent two-bottle choice paradigm, increases in ethanol intake and preference lasting up to 8 weeks were observed (Skelly *et al.* 2015). Another research group employed a similar social isolation model in male Sprague-Dawley rats and found that isolation during a shorter window, from PD 21 to 42, promoted increased conditioned place preference for ethanol (Whitaker *et al.* 2013). One caveat with this model, at least in Long Evans rats, is that adolescent social isolation may not engender long-lasting increases in anxiety-like behaviors or ethanol drinking-related behaviors in females (Butler *et al.* 2014).

As noted above, this model is most commonly employed in rats. However, several groups have reported similar behavioral changes in mice that have been socially isolated in adolescence. For example, adolescent social isolation in mice has been shown to lead to increases in anxiety-like behavior on the elevated-plus maze (Koike *et al.* 2009; Kumari *et al.* 2016; Wei *et al.* 2007, although see Voikar *et al.* 2005; Zhang *et al.* 2014), sensory gating

deficits (Gan *et al.* 2014) as well as increased contextual fear and impaired fear extinction (Liu *et al.* 2015; Pibiri *et al.* 2008). Other studies have reported increases in home-cage ethanol intake and preference (Advani *et al.* 2007; Lopez *et al.* 2011; Talani *et al.* 2014), with one of these studies showing that this effect endured for at least 1 month into adulthood (Advani *et al.* 2007). Again, as observed in rats, the effect of adolescent social isolation on ethanol drinking was primarily observed in male mice (Advani *et al.* 2007; Lopez *et al.* 2011).

Social defeat stress has been examined in mice and rats for its effects on alcohol drinking over time. One group reported that 10 episodes of moderate (30 bites) but not mild (15 bites) social defeat stress increases subsequent acquisition of continuous two-bottle choice home-cage alcohol drinking in outbred mice (Norman 2012). Another group similarly reported that repeated (three episodes) social defeat stress increases alcohol drinking in mice on a mixed background that were previously trained to drink alcohol in a two-bottle choice home-cage situation (Molander *et al.* 2012). A more recent study reported that social defeat stress increases alcohol drinking in C57BL/6J mice with intermittent (every other day) home-cage alcohol access (Hwa 2016). Less work has been carried out on rats, with one group reporting that a history of social defeat stress increases alcohol preference (but not intake levels) during subsequent acquisition of operant alcohol self-administration, and that after extinction of alcohol responding, low drinkers (but not high drinkers) with a history of social defeat stress exhibit higher intakes relative to unstressed low drinking controls (Logrip & Zorrilla 2012). This social defeat stress effect on acquisition of drinking in rats is similar to what is observed in adult male rats exposed to a series of high-intensity footshocks: one group used a model called stress-enhanced fear learning, developed originally to measure the effect of traumatic stress history on subsequent fear learning (Rau & Fanselow 2009), to show that repeated footshock facilitates acquisition of two-bottle choice home-cage alcohol drinking in previously alcohol-naïve rats, but does not alter alcohol drinking in rats with prior alcohol drinking history (Meyer *et al.* 2013).

Individual differences in stress-induced escalation of alcohol drinking

One final comment on animal models that seek to produce stress-induced escalation of alcohol drinking in rodent models is the consideration of subpopulation effects or individual differences between animals. Historically, animal models have examined mean group effects of stress on alcohol drinking, which may mask stress effects in subpopulations of animals, especially because it is well accepted that traumatic stress disorders develop only in a portion of individuals exposed to the stress event. It is important to understand that in humans, and therefore in animal models, subgroups of individuals may respond to traumatic stress with different coping strategies, and changes in brain function that are of different magnitudes, opposite directions or qualitatively different. Individual differences in brain function may be the cause or consequence (or both) of effective vs. ineffective coping strategies, and may be responsible for eventual emergence of lasting psychiatric disturbances, or protection from those effects. Some of the models described above do attempt to index animals on their stress reactivity or baseline alcohol drinking, and examine the effects of stress or stress history on alcohol drinking over time in subgroups of rats. For example, the two predator odor stress models described above index high vs. low stress-

reactive rats from a genetically heterogeneous stock, and show that some but not all animals exhibit sustained increases in alcohol drinking over time post-stress (Edwards *et al.* 2013; Manjoch *et al.* 2016). Understanding why some but not all animals escalate their alcohol drinking after stress may be particularly important because we know that the activity of brain reward circuits differs in genetically heterogeneous animals that consume high vs. low alcohol quantities (Juarez & Han 2016). This divergence of neurobiology across animals has been exploited in various selective breeding programs designed to produce animals that consume high vs. low quantities of alcohol (McBride *et al.* 2014; Murphy *et al.* 2002), or that diverge on novelty seeking (Flagel *et al.* 2014) or motivational response to reward cues (Robinson *et al.* 2014), all of which are thought to have a role in addiction susceptibility.

Anatomy and circuitry of comorbid PTSD and AUD

Humans diagnosed with AUD exhibit specific structural and functional brain changes (Buhler & Mann 2011). Similarly, individuals that have endured traumatic stress exhibit structural and functional brain changes that are associated with specific symptom clusters in the PTSD diagnosis (Weiss 2007). Although PTSD likely shares some, but certainly not all, of its neurobiology with innate anxiety and fear learning (Calhoon & Tye 2015), we do not discuss the neurobiology of innate anxiety, fear learning or threat processing in healthy humans (for excellent reviews on these topics and their relevance for understanding PTSD, see Delgado *et al.* 2006; Etkin & Wager 2007; Jovanovic & Ressler 2010; Mahan & Ressler 2012; Milad *et al.* 2014) nor do we discuss the neurobiology of alcohol dependence (for review, see Gilpin & Koob 2008). Instead, we focus below on discussing the neurobiology and neurocircuitry of *comorbid* PTSD and AUD (see Fig. 1) in three specific ways: points of overlap in the hallmark findings from humans with PTSD and humans with AUD, discussion of findings from humans with comorbid PTSD/AUD and findings from animal models that aim to model the comorbid condition (*not* one condition or the other alone).

Hypoactive vmPFC

Although rats and humans both have medial prefrontal cortex (mPFC), it can be difficult to determine analogous regions of rodent and human brain. That said, efforts are made in preclinical neuroscience research to determine rodent analogs of human brain regions based on anatomy, connectivity (inputs and outputs) and function. In the case of the rat mPFC, this brain region is often divided into its dorsal and ventral areas, referred to as dorsomedial PFC (dmPFC) and ventromedial PFC (vmPFC). A finer separation of regions divides the mPFC into anterior cingulate cortex (ACC), prelimbic cortex (PL) and infralimbic cortex (IL), with the ACC and top half of PL composing the dmPFC and the IL and bottom half of PL composing the vmPFC. It is generally thought that the rodent PL is analogous to Brodmann area 32 in human and monkey brain, whereas the rodent IL is analogous to Brodmann area 25 in human and monkey brain (Myers-Schulz & Koenigs 2012). In reality, the picture is likely to be more ambiguous because, for example, human functional imaging data show that fear extinction recall correlates not with activity in Brodmann area 25 as would be predicted based on this model, but just anterior to this region in Brodmann area 10 (Milad *et al.* 2007; Phelps *et al.* 2004). These findings and others have led to a further separation of human vmPFC into posterior and perigenual subregions that may serve negative affective and

positive affective roles, respectively (for excellent review, see Myers-Schulz & Koenigs 2012). As higher resolution imaging techniques become available in humans, the evolving answer to this comparative neuroscience question is likely to become clearer.

Humans with PTSD exhibit vmPFC structural deficits. For example, youth diagnosed with vmPFC have lower right vmPFC volume relative to both maltreated youth without PTSD and healthy controls (Morey *et al.* 2016). A meta-analysis of nine voxel-based morphometry studies showed that PTSD adults exhibit gray matter loss in vmPFC relative to individuals exposed to trauma that did not develop PTSD (Kuhn & Gallinat 2013). Youth with PTSD also exhibit lower gray matter volume in vmPFC that is inversely correlated with PTSD duration (i.e. lower volume with longer duration), but not with symptom severity (Keding & Herringa 2015).

In general, PTSD is associated with lower vmPFC function during a negative emotional condition (for meta-analysis, see Etkin & Wager 2007), although opposite results have been reported (St Jacques *et al.* 2011). Combat veterans with PTSD exhibit lower vmPFC activity when exposed to learned danger signals, relative to combat controls (Garfinkel *et al.* 2014). A small-scale study also showed that PTSD patients undergoing treatment showed improvements on the Clinician-Administered PTSD Scale (CAPS) that correlated with increases in right ACC activity from pretreatment to posttreatment imaging time points (Felmingham *et al.* 2007), suggesting that vmPFC abnormalities in PTSD patients can be rescued. It is becoming increasingly recognized that altered activity in specific brain regions of PTSD patients (and in general) during functional imaging tasks may reflect changes in the activity of a larger cortical network (Spielberg *et al.* 2015). It should be noted that vmPFC damage reduces the likelihood of developing PTSD (reviewed in Koenigs & Grafman 2009), and that this pattern of results is not consistent with the notion that low vmPFC activity contributes to PTSD. There is also some disagreement among imaging studies regarding vmPFC activity patterns in mood, anxiety and stress disorders, and some of this ambiguity may be attributable to the poor delineation of vmPFC subregions described above (Myers-Schulz & Koenigs 2012).

Humans with alcohol dependence and/or AUD also exhibit structural and functional changes in the vmPFC. Comprehensive reviews of the literature showing PFC changes in human addicts exist elsewhere (Goldstein & Volkow 2016), and can be seen at rest, during emotional reactivity tasks, and also during inhibitory control tasks. Several findings warrant mention here as they relate to vmPFC and alcohol. First, alcohol dependence is associated with loss of gray matter volume in dorsolateral PFC (dlPFC) that is lasting and is associated with executive dysfunction (Chanraud *et al.* 2007; Fein *et al.* 2002; Wobrock *et al.* 2009). Metabolism in cingulate cortex (Brodmann area 32) is associated with alcohol craving and D2-like receptor availability in the striatum of alcoholics, but not healthy controls (Heinz *et al.* 2004; Volkow *et al.* 2007). Similarly, opioid receptor binding in ACC is associated with alcohol craving in alcoholics (Williams *et al.* 2009). Interestingly, low dynamic activity in the vmPFC during a stress task predicts maladaptive coping behaviors and binge alcohol drinking in otherwise healthy humans (Sinha 2016). Similarly, low vmPFC reactivity to alcohol and stress cues in the laboratory predicts higher risk of relapse to alcohol drinking in abstinent patients recovering from alcohol dependence (Blaine *et al.* 2015). This vmPFC

hyporeactivity was predicted by high circulating cortisol:adrenocorticotropic hormone (ACTH) ratios, although it should be noted that these results were correlational and there was no control group without a history of AUD (Blaine *et al.* 2015). A recent surge in the field has been to explore whether the cortico-amygdalar circuits involved in fear learning and extinction, which is impaired in PTSD, may also be important for learning and extinguishing alcohol and drug cues (Gass & Chandler 2013; Peters *et al.* 2009).

There is a dearth of literature examining structural and functional changes in the vmPFC of humans diagnosed with both PTSD and AUD, especially relative to groups with one diagnosis or the other. For example, one study reported that PTSD patients with comorbid alcohol and cocaine abuse exhibit lower frontal cortex blood flow, when compared with healthy controls (Semple *et al.* 2000). There is also very little preclinical data exploring changes in vmPFC of animals after exposure to both traumatic stress and chronic alcohol. One study showed that rats that exhibit high avoidance of a predator odor-paired chamber (i.e. Avoider rats) consume more alcohol than Non-Avoiders and unstressed Controls, and that these rats exhibit increases in extracellular signal-regulated kinases phosphorylation in vmPFC after re-exposure to the stress-paired context relative to Non-Avoiders (Edwards *et al.* 2013). Nine days after stress, these Avoider rats have more corticotropin-releasing factor (CRF)-positive cells in vmPFC (but not in dmPFC) than Non-Avoider rats and unstressed controls, the distribution of cell counts suggest that this effect is driven by the stress event, and antagonism of CRF-1 receptors in vmPFC reduces avoidance but not escalated alcohol drinking in Avoider rats (Schreiber *et al.* 2016).

Hyperactive amygdala

The gross anatomy, connectivity and cellular composition of amygdaloid nuclei is generally considered to be well-enough conserved across species to allow for the formation of translational hypotheses in humans based on rodent work, although there are some important cross-species differences in terms of spatial organization and relative size of various subnuclei (Fox *et al.* 2015). Structural and functional neuroimaging in humans broadly supports the amygdaloid connectivity described in rodent tract tracing studies, e.g. the reciprocal connections between central amygdala (CeA) and bed nucleus of the stria terminals via the ventral amygdalofugal pathway (Avery *et al.* 2014, 2016; Oler *et al.* 2012; Roy *et al.* 2009). Many of the human studies mentioned below describe findings in whole amygdala, as those studies were not able to use an imaging resolution sufficient to distinguish amygdaloid subnuclei.

Humans with PTSD exhibit structural and functional changes in the amygdala, although functional data are more abundant. Children who have endured early life stress (physical abuse, low socioeconomic status and neglect) have lower amygdala volumes that are quantitatively associated with the amount of cumulative stress exposure and the extent to which the individual exhibits behavioral problems (Hanson *et al.* 2015). PTSD children have lower left amygdala volume relative to both maltreated children without PTSD and healthy controls, and lower amygdala volumes inversely correlate with greater PTSD symptomatology (Morey *et al.* 2016). A similar pattern of structural changes is observed in

adults, e.g. cancer survivors with intrusive recollections that resemble PTSD symptoms have lower amygdala volumes (Matsuoka *et al.* 2003).

Perhaps, the most universally accepted biomarker of PTSD in humans is a hyperactive and/or hyperreactive amygdala (see Etkin & Wager 2007). For example, combat veterans with PTSD exhibit exaggerated amygdala responses to fearful faces when compared with combat veterans without PTSD (Rauch *et al.* 2000). Combat veterans with PTSD show higher amygdala activity that correlates with impaired extinction recall in a safe context, as well as lower amygdala activity that correlates with impaired fear renewal in a dangerous context, which suggests deficits in discrimination and generalization of signals related to safety and danger (Garfinkel *et al.* 2014). In one example of civilian PTSD, after partner violence, women with PTSD exhibit higher amygdala activity during exposure to fearful faces (Fonzo *et al.* 2010). Individuals exposed to early life stress appear to undergo 're-mapping' of amygdala connectivity, both between subnuclei and with other brain regions, as it pertains to the threat response in adulthood (Grant *et al.* 2015b). Trauma survivors exhibit increased attentional bias to threat that is associated with lower peripheral anandamide levels as well as increased cannabinoid type 1 receptor availability in amygdala (Pietrzak *et al.* 2014a). Because most of these studies are either retrospective (i.e. post-trauma) or they test the response to laboratory stress rather than life trauma, the question remains whether preexisting differences in amygdala activity are predictive of future trauma responses and related diagnoses in some or all individuals. One elegant study tested this possibility and reported no predictive value of amygdala reactivity for future observation of internalizing symptoms associated with PTSD, panic disorder, generalized anxiety disorder and major depression, but *did* see this predictive association in individuals that experienced high life stress, suggesting that amygdala reactivity may be a promising biomarker in this subpopulation (Swartz *et al.* 2015).

Amygdala activity has also been related to treatment response in humans with PTSD. For example, low amygdala activity during fear processing in the laboratory predicts positive outcomes after exposure therapy in humans diagnosed with PTSD (Felmingham *et al.* 2007). In a related case study, deep brain stimulation via electrodes implanted bilaterally in the basolateral amygdala (BLA) promoted extinction of a fear reminder during re-exposure, reduced the frequency of nightmares, and improved scores on the CAPS (Langevin *et al.* 2016), which agrees with data from macaques showing a role for the BLA in fear generalization (Resnik & Paz 2015).

Similar to humans diagnosed with PTSD, humans diagnosed with an AUD or alcohol dependence (in DSM-IV) exhibit structural and functional changes in the amygdala. Alcohol-dependent humans have lower amygdala volumes, and these lower amygdala volumes are predictive of higher alcohol craving and higher alcohol drinking up to 6 months after imaging (Wrase *et al.* 2008). It appears that alcohol-dependent humans may transfer genetically encoded amygdala abnormalities to their offspring, because one study shows that young adults with at least one biological parent diagnosed with AUD, but that do not themselves have a diagnosable SUD, exhibit blunted (or absent) amygdala response to fearful faces (Glahn *et al.* 2007).

Very few studies have performed neuroimaging in humans with PTSD and AUD. One such study showed that PTSD patients with comorbid AUD (and cocaine-use disorder) exhibit higher amygdala blood flow compared with healthy controls (Semple *et al.* 2000), but this study lacked PTSD-only and AUD-only comparison groups. A separate study examined neural activation patterns as they are related to stress-induced alcohol drinking in humans. This study elegantly showed that drinking problems are highest in the context of stress and in participants that exhibit either (1) high threat-related reactivity of the amygdala combined with low reward-related activity of the ventral striatum (VS) or (2) low threat-related reactivity of the amygdala combined with high reward-related activity of the VS (Nikolova *et al.* 2016). These data suggest that the relationship between neural activity and stress-related drinking problem may not be simply related to activity in one brain region, but rather may depend on convergent or divergent (re)activity in multiple brain regions.

Few animal studies have examined amygdala changes as they relate to comorbid stress pathology and excessive alcohol drinking, although our laboratories have published preliminary work on this question. In one study, we showed that rats exhibiting persistent avoidance of a predator odor-paired chamber (i.e. Avoiders) go on to drink more alcohol (Edwards *et al.* 2013) and have higher levels of CRF in CeA (Itoga *et al.* 2016), but whether these higher CeA CRF levels are responsible for stress-induced escalation of alcohol drinking in Avoiders remain to be determined. Similarly, rats socially isolated during adolescence go on to drink more alcohol in adulthood (Chappell *et al.* 2013; Skelly *et al.* 2015), and BLA pyramidal neurons of these rats exhibit higher intrinsic excitability as well as lower expression and activity of small-conductance calcium-activated potassium (SK) channels (Rau *et al.* 2015). Pharmacological treatment with an SK channel modulator 1-Ethyl-2-benzimidazolinone reduces anxiety-like behavior and rescues BLA physiology changes in these animals (Rau *et al.* 2015), but it remains to be determined whether these BLA changes mediate the escalated alcohol drinking seen in these animals during adulthood.

PFC-to-amygdala

The dorsal and ventral areas of the mPFC each send highly organized projections to specific amygdaloid subnuclei. Our understanding of the organization of those projections is evolving, but advancing rapidly, and comes mainly from the rodent fear conditioning and fear extinction literature (see review by Marek *et al.* 2013). It has been proposed that mPFC subregion projections to extended amygdala nuclei control both fear and drug-seeking behaviors, and that dysregulation of these top-down PFC projections may lead to abnormal fear conditioning and compulsive drug-seeking behavior (Peters *et al.* 2009). The PFC projections to amygdala have been attributed a role not only in drug seeking and extinction learning, but also in the extinction of drug-related memories themselves (Gass & Chandler 2013). This is a nascent field, and it is understandably complicated to study the relationship between two brain regions in individuals diagnosed with two comorbid psychiatric disorders; the following is a brief summary of recent findings on PFC-to-amygdala function in each of those disorders in humans, as well as animal findings supporting the notion that PFC projections to amygdala may contribute to the high rates of comorbidity between traumatic stress and AUDs.

It is generally thought that amygdala hyperactivity is permitted, at least in part, by hypoactive PFC function. For example, PTSD patients show weaker positive connectivities between mPFC and amygdala (and other subcortical regions), and this weaker connectivity is predictive of higher CAPS scores in those patients (Jin *et al.* 2014). A recent study showed that amygdalo-frontal hypo-connectivity in patients with PTSD (and major depressive disorder) was associated with depression-related symptomatology, suggesting this neuropathology may associate with overlapping symptoms from different clinical groups (Satterthwaite *et al.* 2016). Youth (aged 8–18) diagnosed with PTSD also exhibit decreased mPFC–amygdala connectivity that is negatively correlated with PTSD severity, and this connectivity is weaker in older youth, suggesting the possibility that it worsens with time, in contrast to positively correlated age and mPFC-amygdala connectivity in healthy youth (Wolf & Herringa 2016). A follow-up study from that group showed that youth with PTSD exhibit reduced connectivity between dmPFC and amygdala, and also between ventrolateral PFC and amygdala, in response to angry faces, but exhibit increased connectivity between these regions in response to happy faces (Keding & Herringa 2016).

Non-diagnosed trauma-exposed children and adolescents fail to engage inhibitory circuits between the pre-genual cingulate cortex and amygdala during regulation of emotional conflict (Marusak *et al.* 2015). In agreement with this observation, high PFC–amygdala connectivity is associated with lower PTSD symptom severity in disaster survivors diagnosed with PTSD (Yoon *et al.* 2016). Another study showed that certain risk allele carriers diagnosed with PTSD exhibit white matter deficits in the uncinate fasciculus, which serves as a primary connection between ventral PFC and amygdala, suggesting gene × trauma interaction effects on long-term brain structure and function (Almli *et al.* 2014).

It is important to note that amygdalo-frontal hypo-connectivity is not a universal finding, because studies have also shown no change (Gilboa *et al.* 2004) or increases (St Jacques *et al.* 2011) in vmPFC–amygdala coupling in humans diagnosed with PTSD. Trauma-exposed veterans with focal damage to either vmPFC or anterior temporal area containing amygdala exhibit lower incidence of PTSD, arguing against the contribution of inversely related activity in these two regions to a PTSD diagnosis (Koenigs *et al.* 2008). The same research group showed recently that humans who have sustained focal bilateral vmPFC damage (but have not been diagnosed with PTSD) exhibit potentiated amygdala responses to aversive images and elevated resting-state amygdala functional connectivity (Motzkin *et al.* 2015). Another study using functional magnetic resonance imaging (fMRI) in young monkeys and children with anxiety disorders showed that reduced functional connectivity between the dlPFC and CeA was associated with increased anxiety outside the scanner, and that elevated CeA metabolism statistically mediated this association between prefrontal–amygdalar connectivity and elevated anxiety (Birn *et al.* 2014). Finally, work on rodents has shown that chronic intermittent exposure to alcohol doses sufficient to produce dependence impairs fear extinction encoding by vmPFC neurons, suggesting that alcohol may increase risk for development of fear-conditioning deficits customarily observed in traumatic stress disorders (Holmes *et al.* 2012).

Hypofunctional reward pathway

Virtually all conceptual frameworks of addiction include an integral role for the canonical 'brain reward' circuitry, which is highly conserved across species (Berridge & Kringelbach 2008; Kelley & Berridge 2002). Although many brain regions contribute to reward, the most studied element involves the dopamine (DA)-ergic projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), a pathway that is particularly well conserved in all mammals (Scaplen & Kaun 2016). Early animal studies, using electrical stimulation, showed that activation of this pathway was sufficient to maintain motivated behavior and countless subsequent studies have shown that acute administration of all drugs of abuse, including alcohol, stimulates mesolimbic DA release in the NAc (for reviews, see Bressan & Crippa 2005; Olds & Fobes 1981; Volkow *et al.* 2010). Initial conceptual frameworks for the neurobiology of alcohol addiction focused on the competing ideas that repeated alcohol exposure increased the sensitivity of the brain reward system (Robinson & Berridge 2008) or that preexisting deficits in this system led to a negative affective state that could be relieved by excessive alcohol intake (Koob *et al.* 2014). A more integrated hypothesis suggests that both processes play an integral role in the etiology of AUD. In this theory, advanced by Koob and others, alcohol drinking is initially motivated by positive reinforcement, driven in large part by acute alcohol stimulation of mesolimbic DA release. However, as the addiction process takes hold, there is an allostatic shift in the addict's affective set point, driven in part by hypoactivity and hyporesponsivity of the mesolimbic DA system. In this latter stage of the addiction process, alcohol drinking is motivated largely by negative reinforcement. Regardless of which theory is correct, the central place of the reward circuit in all theories of addiction has generated a great deal of human and animal research into the role of the VTA–NAc pathway in the pathophysiology of addiction (Koob 2013; Volkow *et al.* 2016). Importantly, there is also compelling evidence that exposure to a wide range of stressors, ranging from childhood adversity (Andersen 2009) to traumatic events in adulthood (Felmingham 2007), can also disrupt mesolimbic DA signaling. In fact, as reviewed below, the brain reward circuitry is also compromised in PTSD patients and contributes to the symptoms of this disease.

Although PTSD is most frequently associated with increased anxiety and stress reactivity, anhedonia is also common. Almost two-thirds of PTSD patients report decreased interest in pleasurable activities and reduced positive affect, even in the absence of comorbid depression (Carmassi *et al.* 2014; Franklin & Zimmerman 2001). Behavioral studies have shown that PTSD patients show reduced approach behavior or motivation for positive reinforcers, lower expectancy of, and satisfaction with, monetary rewards (Hopper *et al.* 2008; Nawijn *et al.* 2015) and expend less effort to obtain reward (Elman *et al.* 2005). Structural imaging studies of striatum in humans with PTSD are scarce, but functional imaging studies have reported dysregulation of the mesolimbic brain reward pathway in patients with PTSD. For example, several fMRI studies in individuals with PTSD have observed blunted striatal activation in response to positive stimuli (Elman *et al.* 2009; Felmingham *et al.* 2014; Sailer *et al.* 2008). Moreover, decreased accumbal reactivity to reward was correlated with increased post-deployment PTSD symptom severity in a small cohort of soldiers (Admon *et al.* 2013a).

One recent study used Single-photon emission computed tomography imaging to show increased striatal levels of the DA transporter (DAT) in PTSD patients (Hoexter *et al.* 2012). Another study used a selective kappa opioid receptor (KOR) radioligand and high-resolution positron emission tomography (PET) imaging to show a negative correlation between dysphoric symptoms and KOR bioavailability in ventral striatal circuits of individuals with trauma-related psychopathology (Pietrzak *et al.* 2014b). Because DAT and KORs play an integral role in regulating ambient DA levels, these striatal changes may contribute to a hypo-dopaminergic state that is often associated with decreased reward sensitivity and depressive-like symptoms.

As noted earlier, the mesolimbic reward circuit features prominently in most theories of addiction, and this has stimulated many human imaging studies that have characterized the acute and chronic alcohol effects on VTA–NAc DA signaling. Several studies have employed PET imaging to explore the effects of alcohol consumption on ventral striatal DA levels in healthy subjects, and most (Aalto *et al.* 2015; Boileau *et al.* 2003; Oberlin *et al.* 2015; Urban *et al.* 2010), but not all (Salonen *et al.* 1997), reported significant increases in DA levels in this brain region. Several recent studies used a dynamic intravenous alcohol clamp procedure to control for chemo- and somatosensory alcohol cues that may affect mesolimbic DA signaling. Interestingly, initial studies using these methods failed to detect a pharmacological effect of alcohol on ventral striatal DA release in healthy, social drinkers (Yoder *et al.* 2005, 2007). However, a subsequent study by these investigators that examined the effect of alcohol-associated flavor cues, found that the flavor of a preferred beer, in the absence of any alcohol exposure, increased ventral striatal DA release, with the strongest effect observed in subjects with a first-degree alcoholic relative (Oberlin *et al.* 2013). An even more recent paper by these investigators explored the distinct effects of taste cues and alcohol, in heavy drinking male subjects, and reported that alcohol alone increased DA, but only in the left NAc region, whereas the combination of beer flavor and alcohol caused a bilateral increase in NAc DA (Oberlin *et al.* 2015).

A series of seminal PET studies by Volkow *et al.* reported lower D2 receptor availability in the striatum of drug abusers (Volkow *et al.* 1990; Wang *et al.* 1997) and alcoholics (Volkow *et al.* 1996). These findings, along with the other data from this group showing a blunting of methamphetamine-stimulated striatal DA release in these individuals, relative to non-addicted control subjects (Volkow *et al.* 1997, 2004, 2007), provide some support for the reward deficiency hypothesis. However, it should be noted that these studies were not able to resolve whether these deficits in the striatal DA system were present before the addiction or were a consequence of excessive drug or alcohol exposure (Hommer *et al.* 2011).

A few studies have also used fMRI to characterize the mesolimbic DA system in alcoholics. These studies used the monetary incentive delay task, which activates the VS and provides a measure of an individual's sensitivity to anticipation of working for reward, as well as sensitivity to notification that a reward has been won. Two studies using this kind of task reported decreased blood-oxygen-level dependent (BOLD) activation of the VS of alcoholics vs. non-alcoholics during anticipation of reward (Beck *et al.* 2009; Wrase *et al.* 2007). However, another study found no significant difference in this measure, but reported that alcoholics had greater ventral striatal BOLD response to notification of reward delivery, and

greater reactivity to both positive and negative reward outcomes (Bjork *et al.* 2008). These seemingly discrepant findings may be explained by a recent report that both low and high ventral striatal reactivity in a reward task is associated with greater risks for drinking problems in young adults, depending on the balance between this response and threat-related amygdala reactivity (Nikolova *et al.* 2016).

Although no human imaging studies have examined the VTA–NAc reward circuit in patients with comorbid PTSD and AUD, recent animal studies provide further evidence that dysregulation of mesolimbic dopaminergic transmission may contribute to a PTSD–AUD dual diagnosis. For example, rodent studies suggest that adolescent social isolation, a putative model of heightened vulnerability to PTSD and AUD, leads to an increase in the firing rate and burst-like activity of VTA DA neurons (Fabricius *et al.* 2010), as well as an increase in long-term potentiation (LTP) of *N*-methyl-D-aspartate receptor-mediated synaptic transmission in these cells (Whitaker *et al.* 2013). Other studies, using *ex vivo* fast-scan cyclic voltammetry, suggest that adolescent social isolation leads to a long-lasting increase in electrically stimulated DA release and uptake in the NAc (Yorgason *et al.* 2013), with the latter effect possibly mediated by an increase in DAT expression (Yorgason *et al.* 2016), as observed in human patients with PTSD. Using *in vivo* microdialysis in freely moving rats, Karkhanis *et al.* (2014) found that an acute ethanol injection resulted in greater ethanol-stimulated accumbal DA release in adolescent socially isolated rats vs. group-housed controls. Although these findings seem to suggest that vulnerability to comorbid PTSD and AUD are actually associated with a sensitization of the mesolimbic DA system, a more recent study reported lower baseline DA levels in the NAc of socially isolated rats that can be rescued by blockade of KORs (Karkhanis *et al.* 2016). As noted earlier, lower baseline levels of DA are hypothesized to contribute to anhedonia in humans and animals. Together, these findings suggest that low baseline accumbal DA and heightened responsivity of the VTA–NAc DA circuit may increase the risk of developing PTSD and AUD (or both), and may contribute to the expression of these highly comorbid disorders.

HPA axis function

It is beyond the scope of this review to discuss all findings of hypothalamic–pituitary–adrenal (HPA) axis dysfunction in humans diagnosed with AUD or PTSD. The literature is rife with reviews focusing specifically on the role of HPA axis function and dysfunction in acute alcohol effects (Rivier 2014), development of AUD (Clarke *et al.* 2008), fear conditioning and extinction (Stockhorst & Antov 2015), acute and chronic stress effects (Herman *et al.* 2002; McEwen *et al.* 2015; Wamsteeker & Bains 2010) and PTSD pathology and diagnosis (Daskalakis *et al.* 2013). Here, we describe several of the most pertinent findings as they relate to AUD and PTSD trajectory in humans, as well as animal data aimed at understanding the role of the HPA axis in comorbid high traumatic stress reactivity and escalated alcohol drinking.

One of the hallmark findings related to the neuroendocrine stress axis in PTSD is that low cortisol levels immediately post-trauma are predictive of a subsequent PTSD diagnosis (Delahanty *et al.* 2000, 2005), and this finding appears to hold across a range of human samples and traumatic events (e.g. child trauma and motor vehicle accident). Although

perhaps a bit less clean cut, other studies have reported that these low cortisol levels persist in humans diagnosed with PTSD well after the trauma event (i.e. post-diagnosis; Wahbeh & Oken 2013; Yehuda *et al.* 1990). More specifically, one study showed that low cortisol levels in PTSD patients are associated with higher disengagement coping strategies associated with the avoidance-numbing symptom subscore defined in the DSM-III-R (Mason *et al.* 2001); avoidance has been separated out into its own symptom cluster in the DSM-5. It is worth reiterating here that different individuals respond to traumatic stress with different coping strategies that may be the cause or consequence of neural changes that are of different magnitudes, opposite directions or qualitatively different across individuals, dictating the likelihood of a PTSD diagnosis. Work by our group and others have used predator odor stress to show that low corticosterone levels immediately post-trauma predicts higher avoidance of a traumatic stress-paired context and higher anxiety-like behavior in rats (Cohen *et al.* 2006; Whitaker & Gilpin 2015). Corticosterone treatment prior to stress exposure reduces the incidence of avoidance and anxiety-like behaviors (Cohen *et al.* 2006; Whitaker *et al.* 2016), which is particularly interesting because rats exposed to predator odor in these models go on to consume more alcohol over weeks post-stress (Edwards *et al.* 2013; Manjoch *et al.* 2016). The ‘centralization’ of HPA feedback effects on brain regions outside the hypothalamus is not well understood, but one example of this type of work used fMRI in humans to show that cortisol signaling through mineralocorticoid receptors mediates stress-induced enhancement of CeA connectivity with striatum (Vogel *et al.* 2015). Furthermore, traumatic stress produces brain region-specific changes in glucocorticoid receptor (GR) chaperone protein expression (Whitaker *et al.* 2016).

Acute exposure to intoxicating doses of alcohol is generally believed to increase neuroendocrine stress axis activity, as indicated by a rise in circulating ACTH and cortisol levels, in both humans and rats without a chronic alcohol history (Jenkins & Connolly 1968; Rivier 2014; but see Inder *et al.* 1995). In some but not all individuals with AUD, chronic alcohol can produce a pseudo-Cushing's syndrome, defined by higher circulating cortisol levels and insufficient suppression after low-dose dexamethasone, and the opposite effects during withdrawal (Besemer *et al.* 2011), that is difficult to distinguish clinically from organic Cushing's syndrome, except that symptoms dissipate upon cessation of alcohol use (Groote Veldman & Meinders 1996). Animals with a chronic alcohol history exhibit blunted ACTH/corticosterone rise in response to acute alcohol that is administered by an experimenter (Lee & Rivier 1997) or voluntarily consumed (Richardson *et al.* 2008). In a human laboratory study, psychosocial stress increased circulating cortisol levels and drinking in non-treatment-seeking alcoholics (Thomas *et al.* 2011), although that study did not include non-AUD controls. Another study reported blunted cortisol response to personalized stressful imagery in alcohol-dependent individuals (Sinha *et al.* 2009), although this effect may or may not hold in alcohol-dependent individuals co-diagnosed with PTSD (McRae *et al.* 2006). A separate study showed that prior alcohol use is positively associated with cortisol levels in women after rape, and that this effect is dampened in women with a prior assault history (Resnick *et al.* 1997), suggesting complex interactions between trauma, trauma history and alcohol-use history. These studies in humans, along with decades of work in animals (Mantsch *et al.* 2016), make the case that acute stress is sufficient to trigger relapse to alcohol-seeking and -drinking behaviors. Indeed, for some time, physical,

psychological and pharmacological stressors have been used in human laboratory studies to examine the relationship between stress reactivity and alcohol abuse (Thomas *et al.* 2012). More specifically, humans diagnosed with comorbid PTSD and AUD exhibit increases in circulating ACTH and cortisol levels and concurrent increases in alcohol craving in response to acute psychosocial stress (Kwako *et al.* 2015b). Furthermore, stress-induced increases in circulating ACTH and cortisol may be useful biomarkers for relapse risk in those recovering from AUD (Sinha 2012). Centralization of HPA feedback appears to play a role in alcohol abuse but the details of this process are not yet well understood; for example, alcohol-dependent rats exhibit brain region-specific changes in GR mRNA during withdrawal (Vendruscolo *et al.* 2012). Showing the translational utility of this work, systemic treatment with the GR antagonist mifepristone reduces escalated alcohol drinking by alcohol-dependent rats and also reduces cue-induced alcohol craving in non-treatment-seeking alcohol-dependent humans (Vendruscolo *et al.* 2015).

High NE and hyperarousal

A well-documented feature of both PTSD and AUD is a state of hyperarousal and heightened responsivity to stress. Indeed, hyperarousal is a central diagnostic criterion for PTSD (Bremner 2006; Nutt 2000), and many studies have shown that individuals with AUD exhibit increased responsivity to a wide range of stressors (e.g. alcohol cues, psychological stressors, etc.; for reviews, see Seo & Sinha 2014; Sinha 2012). Although other neural systems are likely to be involved, consistent evidence suggests that hyperactive central and peripheral norepinephrine (NE) signaling contribute to these behaviors (for detailed reviews, see Krystal & Neumeister 2009; O'Donnell *et al.* 2004; Strawn & Geracioti 2008).

The primary stress-related central NE system originates in the locus coeruleus (LC), includes projections to the amygdala, hippocampus and PFC, and plays an integral role in normal fear and stress responses (Itoi & Sugimoto 2010; Shin *et al.* 2006). There is now overwhelming evidence that hyperactivity of brain NE systems, under basal and stimulated conditions, contributes to the pathophysiology of PTSD. Early studies showed that pharmacological challenges with yohimbine, a presynaptic α2-adrenoceptor antagonist, induced larger increases in heart rate and systolic blood pressure in PTSD patients relative to healthy controls, and exacerbated core PTSD symptoms (e.g. anxiety and flashbacks) in affected individuals, without any untoward effects in control subjects (Bremner *et al.* 1997; Southwick 1993). Other evidence suggests that tonic CSF NE levels are significantly higher in men with PTSD than in healthy controls and that CSF NE levels positively correlate with PTSD symptom severity (Geracioti *et al.* 2001).

Many studies have examined peripheral markers of NE and, although this literature is more mixed, the preponderance of the evidence is consistent with hyperactivity of peripheral NE signaling in PTSD. Physiological measures of sympathetic tone that are thought to involve peripheral NE release are elevated in PTSD patients, including increased blood pressure, heart rate, skin conductance (Blanchard *et al.* 1996; Orr *et al.* 1997a,1997b; Pitman & Orr 1990; Pitman *et al.* 1990) and an exaggerated startle reflex (Orr *et al.* 2002). Several studies have observed higher urinary (De Bellis *et al.* 1997; Kosten *et al.* 1987) and plasma (Blanchard *et al.* 1991; McFall *et al.* 1990; Yehuda *et al.* 1998) levels of epinephrine and NE

in PTSD patients compared with healthy controls or even individuals with other psychiatric illnesses. However, other studies have not replicated these findings (Mellman *et al.* 1995; Pitman & Orr 1990), including one of the studies cited above which documented higher CSF NE in PTSD patients relative to controls but no difference in plasma NE levels (Geracioti *et al.* 2001).

There is very little imaging research directed at central NE system changes in PTSD, possibly because of the lack of effective radioligands. One recent study used the radioligand [^{11}C]methylreboxetine to examine *in vivo* availability of the NE transporter (NET) in the LC of PTSD patients, trauma-exposed subjects who did not develop PTSD, and healthy controls (Pietrzak *et al.* 2013). Prior preclinical work suggested that repeated stress decreases NET expression in this brain region and other limbic areas (Zafar *et al.* 1997). Indeed, the imaging study found a significant reduction in NET bioavailability in PTSD patients relative to healthy controls, and a negative correlation between NET bioavailability and the severity of anxious arousal or hypervigilance symptoms in these patients. These findings are consistent with the idea that PTSD is associated with lower NET levels in the LC, which could lead to excessive NE signaling in downstream projections such as the amygdala and PFC. However, it should be noted that no differences in NET availability were noted between trauma-exposed individuals who developed PTSD and those who did not. Another set of interesting fMRI studies reported LC hyperactivity in PTSD patients relative to healthy controls (Steuwe *et al.* 2014), as well as a strengthening of functional connectivity between the LC and a distributed network that includes the thalamus, caudate putamen, insula, cingulate gyrus and amygdala (Steuwe *et al.* 2015).

Although fewer studies have focused on NE and AUD, increased sympathetic drive has been well documented in alcoholics, particularly during acute withdrawal (for reviews, see Fitzgerald 2013; Muzyk *et al.* 2011). For example, alcoholics in early withdrawal exhibit tachycardia, increases in blood pressure and pulse rate (Mayo-Smith 1997; Myrick & Anton 1998), as well as elevated CSF levels of NE (Bayard *et al.* 2004). Many of these acute symptoms can be mitigated by the α2-adrenoceptor agonist clonidine, which decreases NE release (Muzyk *et al.* 2011). The literature on NE signaling in protracted abstinence is more mixed. Alcoholics abstinent for at least 2 weeks were found to have increased plasma NE levels relative to healthy controls (Eisenhofer *et al.* 1985); however, other studies have reported that CSF NE levels may be decreased in abstinent alcoholics (Geracioti *et al.* 1994). One study showed that abstinent alcoholics exhibit greater cortisol and prolactin release in response to an acute yohimbine challenge (Krystal *et al.* 1996), but reported effects of this challenge on measures of craving in detoxified patients with AUD have been mixed (Krystal *et al.* 1994; Umhau *et al.* 2011). One interesting study examined the effect of sleep deprivation, which activates the sympathetic nervous system on alcohol-dependent men abstinent for 2–3 weeks and healthy control subjects (Irwin & Ziegler 2005). This study reported no baseline differences in heart rate, blood pressure or peripheral NE or epinephrine levels, but a 3-h disruption of the latter stages of a normal sleep cycle resulted in a greater increase in heart rate and circulating NE and epinephrine levels in patients with AUD.

Given the evidence that hyperactivity of central NE signaling likely contributes to the pathophysiology of PTSD and AUD, a number of studies have examined the efficacy of

pharmacological modulators of NE neurotransmission in the treatment of these disorders. Although no selective NE modulators are currently approved for the treatment of PTSD, a wide range of drugs that target the NE system have been shown to improve PTSD symptoms, including the α1-adrenoceptor antagonist prazosin (Peskind *et al.* 2003; Raskind *et al.* 2003, 2007; Taylor *et al.* 2006), the α2-adrenoceptor agonists clonidine (Harmon & Riggs 1996; Porter & Bell 1999) and guanfacine (Horrigan 1996; Horrigan & Barnhill 1996) (for pediatric PTSD), and the β blocker propranolol (Famularo *et al.* 1988; Pitman *et al.* 2002; Vaiva *et al.* 2003). Interestingly, several small studies have suggested that the serotonin/NE reuptake inhibitor duloxetine, which has higher affinity for the NET, may reduce PTSD symptoms (Aikins *et al.* 2011; Villarreal *et al.* 2010) even in patients refractory to the two Food and Drug Administration (FDA)-approved treatments for this disorder (Walderhaug *et al.* 2010), sertraline and paroxetine (which preferentially inhibit serotonin transporters). There is also emerging evidence that targeting the NE system may be beneficial in the treatment of AUD, with prazosin showing the most early promise (Fox *et al.* 2012; Simpson *et al.* 2009). The potential utility of prazosin in the treatment of comorbid PTSD and AUD is discussed in a later section.

There is also extensive evidence from preclinical studies that NE transmission is dysregulated in animal models of PTSD and AUD. A detailed discussion of these findings is beyond the scope of this article; however, these topics have been comprehensively reviewed (PTSD and NE: Berridge *et al.* 2012; Morilak *et al.* 2005; Otis *et al.* 2015; AUD and NE: Becker 2012; Weinshenker & Schroeder 2007). Very little work has focused on pathophysiological changes in NE transmission in animal models of comorbid PTSD and AUD. We recently reported increased responsivity of brain NE neurotransmission in the rodent adolescent social isolation model that engenders increases in many behavioral risk factors of PTSD and AUD (Karkhanis *et al.* 2014, 2015). Using microdialysis in awake, freely moving rats, no differences in baseline NE levels were observed in either the NAc or basolateral amygdala between rats that were socially isolated or group-housed during adolescence. However, marked differences were noted in both brain regions in response to an acute ethanol injection. In adolescent group-housed animals, ethanol exposure had no effect on NE levels in either the NAc or the basolateral amygdala. However, in the socially isolated cohort, the same ethanol treatment significantly increased NE levels in these brain areas. Given that the NAc receives its primary noradrenergic input from the nucleus of the solitary tract (Delfs *et al.* 1998), whereas the basolateral amygdala receives dense innervation from the LC (Jones & Yang 1985; Moore & Bloom 1979), these initial findings suggest that a sensitization of multiple networks of noradrenergic cells may contribute to the behavioral phenotypes associated with this model. Another study found that systemic administration of prazosin, propranolol and duloxetine, three medications that dampen NE neurotransmission via distinct mechanisms, significantly inhibited ethanol intake in socially isolated rats at doses that had no effect in group-housed controls (Skelly *et al.* 2015). These findings are similar to those showing greater efficacy of these same drugs in reducing alcohol drinking by alcohol-dependent rats relative to non-dependent controls (Gilpin & Koob 2010; Ji *et al.* 2008; Walker *et al.* 2008). Collectively, these data are consistent with the idea that the escalation in ethanol intake that manifests following early life stress or

repeated episodes of intermittent ethanol exposure may be mediated, at least in part, by increased central noradrenergic signaling.

Hippocampal deficits

Given the integral role that the hippocampus plays in learning, memory and regulation of the HPA axis, and the many findings showing that both PTSD and AUD are associated with profound alterations in memory function and stress hormone signaling (Anderson *et al.* 2014; Phillips *et al.* 2006), many human and animal studies have characterized the role of structural and functional changes in the hippocampus in the pathophysiology of these two disorders.

Motivated by initial observations that patients with PTSD exhibit significant deficits in short-term memory, Bremner *et al.* (1995, 1997) were the first to report reduced hippocampal volume in patients with PTSD. Since those initial observations, a number of studies have sought to replicate these findings. Indeed, several recent meta-analyses have confirmed a significant relationship between smaller hippocampal volume and PTSD when comparisons are made with healthy subjects (Karl *et al.* 2006; Kitayama *et al.* 2005; O'Doherty *et al.* 2015; Smith 2005) or even trauma-exposed subjects that did not develop PTSD (Karl *et al.* 2006; O'Doherty *et al.* 2015). Despite these findings, a surprisingly large number of other reports have not observed a significant association between smaller hippocampal volume and PTSD (for review, see O'Doherty *et al.* 2015). Complicating the story further, a study in identical twins showed no difference in hippocampal volume between siblings who developed PTSD and those who did not, although this study did report a significant negative correlation between hippocampal volume and the probability of developing PTSD after exposure to a traumatic event (Gilbertson *et al.* 2002). These findings raise the possibility that small hippocampal volume may represent a biological risk factor that increases susceptibility to PTSD.

There is also a large body of evidence suggesting that AUD may be associated with a smaller hippocampal volume (Hoefer *et al.* 2014). For example, an early MRI study reported decreased hippocampal size in alcoholic men and women, independent of comorbid psychiatric illnesses, including PTSD (Agartz *et al.* 1999). In fact, even a short history of alcohol abuse has been linked with decreased hippocampal volume in adolescent men and women (De Bellis *et al.* 2000; Medina *et al.* 2007; Nagel *et al.* 2005). However, whether hippocampal volume is directly related to measures of alcohol consumption is less clear. One study reported that hippocampal size was positively correlated with age of onset of alcohol dependence and negatively correlated with the duration of alcohol use (De Bellis *et al.* 2000), but several other studies have not observed these relationships (Agartz *et al.* 1999; Gazdzinski *et al.* 2008; Nagel *et al.* 2005). As with some PTSD studies, these findings may suggest that a smaller hippocampal volume represents a biological risk factor for the development of AUD or may be a consequence of other environmental factors, such as cigarette smoking.

Given some of the disparate findings noted above, particularly in relation to PTSD and hippocampal volume, a few studies have specifically addressed whether comorbid AUD contributed to associations between hippocampal size and PTSD. However, this literature is

also somewhat mixed. For example, a small pilot study in four patients with combat-related PTSD and no history of drug or alcohol abuse reported significantly smaller hippocampal volume in these subjects relative to healthy controls (Hedges *et al.* 2003). Similarly, larger studies that also controlled for severe major depression and substance-related disorders reported smaller hippocampal volume in subjects diagnosed with PTSD relative to healthy (Bossini *et al.* 2008) or trauma-exposed controls (Lindauer *et al.* 2004). In contrast, several other studies that excluded subjects with comorbid AUD found no relationship between PTSD and hippocampal volume (Carrion *et al.* 2001; De Bellis *et al.* 1999, 2002; Fennema-Notestine *et al.* 2002; Schuff *et al.* 2001; Woodward *et al.* 2006), although a recent study reported that the diagnosis of comorbid AUD significantly strengthened the negative correlation between hippocampal size and PTSD (Starcevic *et al.* 2015).

Despite a large literature that has established an important role for the hippocampus in behavioral phenotypes associated with PTSD and AUD (for reviews, see Jin & Maren 2015; Matthews & Morrow 2000; Mulholland 2012; Reznikov *et al.* 2016), relatively few studies have examined hippocampal function in models of comorbid PTSD and AUD. A series of studies using a mouse adolescent social isolation model that alters behaviors associated with both PTSD and AUD found that, relative to mice group-housed during adolescence, socially isolated mice exhibit altered expression and function of hippocampal gamma-aminobutyric acid $(GABA)_A$ receptors along with a decrease in hippocampal levels of allopregnanolone, a neurosteroid that potently enhances GABAergic inhibition (Pibiri *et al.* 2008; Sanna *et al.* 2011; Serra *et al.* 2000, 2006; Talani *et al.* 2016). These studies also reported decreased hippocampal synaptic excitability and LTP in socially isolated rats. More recent work by our group also reported a significant reduction in LTP in the CA1 region of the hippocampus in recordings from socially isolated rats (Almonte *et al.* 2016). However, this reduction in synaptic plasticity was associated with marked increases in measures of synaptic excitability in this brain region. Moreover, these social isolation-associated changes were restricted to the ventral hippocampus, which is known to play an integral role in regulating anxiety-like behaviors and contextual fear extinction (McDonald & Mott 2016; Strange *et al.* 2014).

Treatment of comorbid PTSD and AUD

From the preceding review of the epidemiology and neurobiology of PTSD and AUD, it is clear that these disorders are frequently comorbid and that this dual diagnosis exacerbates the severity of both disorders and worsens the prognosis for recovery. The considerable overlap in the neural substrates underlying PTSD and AUD would seem to offer many putative targets for the development of pharmacotherapies that would effectively treat the core symptoms of these diseases. It is therefore somewhat surprising that, until fairly recently, relatively little clinical attention has been directed specifically at this comorbid patient population. Reasons for this include the fact that PTSD was characterized relatively recently, only recognized in the DSM as a distinct disorder in 1980 (Crocq & Crocq 2000) and only in the last 20 years has sufficient epidemiological evidence accumulated documenting (1) the high prevalence of the comorbidity of these disorders and (2) the challenges associated with treating patients suffering from both diseases. There was previously a belief amongst many clinicians that addressing the symptoms of AUD could potentially hinder the treatment of PTSD (Hien *et al.* 2004; McGovern *et al.* 2009; Mills

2013; Najavits & Hien 2013; Solomon *et al.* 1992). Fortunately, recent evidence has begun to challenge this ill-founded notion (Foa *et al.* 2013; Najavits & Hien 2013) and the last decade has seen a sharp increase in clinical trials that specifically target individuals with comorbid PTSD and AUD (see Table 1). The treatment of PTSD (Kirkpatrick & Heller 2014; Koller & Stein 2013) and AUD (Muller *et al.* 2014; Seneviratne & Johnson 2015; Zindel & Kranzler 2014) has been extensively reviewed; therefore, the following section focuses on studies that have targeted patients diagnosed with *both* disorders.

Sertraline and paroxetine are the only FDA-approved medications for the treatment of PTSD. Not surprisingly, the first clinical studies that focused on individuals with PTSD and comorbid AUD examined the utility of these medications in treating this dual diagnosis. The first study was a small open label trial that examined the efficacy of a 12-week sertraline treatment regimen in nine subjects with both disorders. Sertraline significantly reduced PTSD symptoms and also decreased the average number of drinks and increased abstinence days (Brady *et al.* 1995). These findings prompted a larger randomized clinical trial of 94 individuals with alcohol dependence and PTSD who received sertraline or placebo for 12 weeks. However, in this study, sertraline only modestly improved PTSD symptoms vs. placebo and only a subset of subjects, those with early-onset PTSD and less severe alcohol dependence, showed a significant reduction in drinking measures with sertraline (Brady *et al.* 2005).

Another double-blinded, placebo-controlled trial compared the efficacy of the other FDA-approved PTSD medication, paroxetine, vs. the NE reuptake inhibitor desipramine, in a mostly veteran population with a PTSD–AUD dual diagnosis (Petrakis *et al.* 2012). This study also tested the adjunctive efficacy of naltrexone, an FDA-approved medication for AUD. Both paroxetine and desipramine significantly reduced PTSD symptoms, with similar efficacy. However, subjects receiving desipramine had higher retention rates and better alcohol-use outcomes (% heavy drinking days, drinks/week). These findings provided some initial evidence that uptake inhibitors targeting the NE system might offer some advantage over currently approved PTSD medications in patients with comorbid AUD. Notably, naltrexone had no effect on any of the drinking outcomes in this study, underscoring the idea that the neural substrates underlying this dual diagnosis may be less responsive to drug treatments used to treat either PTSD or AUD alone. These findings, along with the earlier sertraline study, also challenge the notion that antidepressants are devoid of any therapeutic value in the treatment of AUD (Brady & Sinha 2005; Pettinati 2001, 2004).

A retrospective study of 50 veterans diagnosed with AUD, of which 90% also suffered from PTSD, was conducted to evaluate the potential utility of the atypical antipsychotic quetiapine, which was prescribed to improve sleep disturbances, in the treatment of alcohol dependence (Monnelly *et al.* 2004). Outcome measures included total days abstinent, number of hospitalizations for detoxification and days to first relapse over 1 year of clinical treatment. Relative to the control group, veterans treated with quetiapine showed a significant increase in the number of abstinent days and a decrease in the number of hospitalizations, with a trend for an increase in the number of days to relapse. However, this study did not compare PTSD symptoms between these groups.

Several other studies were designed primarily to assess the efficacy of AUD medications in comorbid populations. The largest of these was a randomized trial that examined the effect of a 12-week treatment with two FDA-approved medications for AUD, naltrexone and disulfiram, in 245 veterans with AUD along with at least one psychological diagnosis, of which 93 subjects were diagnosed with PTSD (Petrakis *et al.* 2006). This study had four groups: naltrexone alone, placebo alone, disulfiram + naltrexone and disulfiram + placebo and the primary outcome measures were measures of alcohol use, alcohol craving and PTSD symptoms. The main findings of this study were that, across the entire sample, both treatments were better than placebo at decreasing alcohol-use measures, with a high rate of abstinence noted across the active phase of this study. There was however, no signifi-cant benefit gained by combining naltrexone and disulfiram. Notably, the subgroup with comorbid PTSD did report higher overall craving than subjects with other psychiatric disorders but this group still responded favorably to either medication. Interestingly, only subjects who abstained completely from alcohol use during the study showed any improvement in PTSD symptoms and, within this group, disulfiram was the most effective treatment.

The last few years have seen an increase in the number of clinical trials focused on the treatment of comorbid PTSD and AUD. A small double-blind, placebo-controlled pilot study of mostly male VA patients reported significant improvement of PTSD symptoms and a decrease in alcohol use and craving following a 12-week treatment with topiramate. This drug is an FDA-approved anticonvulsant that interacts with numerous neural targets, including voltage-gated sodium channels as well as GABAergic and glutamatergic synapses (Braga *et al.* 2009; Shank *et al.* 2000), and has shown potential efficacy in the treatment of PTSD (Watts *et al.* 2013; Yeh *et al.* 2011) and AUD (Guglielmo *et al.* 2015) alone. This drug was generally well tolerated but did produce transient cognitive impairment that recovered by the end of the 12-week treatment period. Prazosin has shown promise in the treatment of both PTSD (Raskind *et al.* 2007; Taylor *et al.* 2006) and AUD (Simpson *et al.* 2009) and two recent studies explored its efficacy in patients diagnosed with both disorders. The first study was a small 6-week pilot trial in 30 individuals with comorbid PTSD and AUD (Simpson *et al.* 2015) and the other was a larger study of 96 veterans with both disorders that used a 13-week treatment period (Petrakis *et al.* 2016). Both studies employed a randomized, double-blind, placebo-controlled design. Despite the prior evidence that prazosin significantly improved PTSD symptoms in non-alcohol-dependent patients, neither study found an improvement in these symptoms in these comorbid populations. Moreover, only the pilot study reported a significant effect of prazosin on alcohol-use measures.

Another recent study tested the neurokinin 1 receptor (NK1R) antagonist, aprepitant, in 53 patients with PTSD and AUD using a similar randomized, double-blind, placebo-controlled design (Kwako *et al.* 2015a). The NK1R is the preferred receptor for substance P, is expressed in brain regions such as the amygdala and hippocampus that regulate stress responsivity and prior clinical and preclinical evidence indicated that blockade of these receptors may have antidepressant effects and alleviate alcohol craving and reinstatement (George *et al.* 2008; Kramer *et al.* 1998; Schank *et al.* 2011, 2012). Despite these earlier findings, this study found no significant effect of aprepitant on PTSD symptoms or behavioral or neuroendocrine response to stress and alcohol cues. This study did report a

significant effect of the drug on activation of vmPFC in response to aversive visual stimuli. Because the vmPFC is hyporesponsive to aversive stimuli in PTSD patients (Liberzon & Sripada 2008), the authors speculated that aprepitant might be useful in facilitating behavioral exposure therapy that is used to promote extinction of maladaptive stress responses in these patients.

Interestingly, a relatively large single-blinded, randomized clinical trial recently compared the efficacy of naltrexone with an evidence-based behavioral treatment for PTSD (prolonged exposure therapy) in 154 individuals with comorbid PTSD and AUD (Foa *et al.* 2013). This trial compared four groups that received either prolonged exposure therapy + naltrexone, prolonged exposure therapy + placebo, supportive counseling + naltrexone or supportive counseling + placebo. This study was notable in the duration of the treatments, with the behavioral therapy consisting of 12 weekly 90-min sessions followed by 6 biweekly sessions and the naltrexone treatments extending for 6 months. All four treatment groups showed large improvements in alcohol-drinking outcome measures, with naltrexone having the greatest overall effect. Percentage of days drinking increased in all groups 6 months after the end of treatment, but the exposure therapy + naltrexone group exhibited the smallest increases. All four groups also showed significant improvement in PTSD symptoms.

Finally, several studies have specifically examined the efficacy of behavioral therapies in comorbid patients. A recent meta-analysis that included patients with PTSD and any comorbid SUD concluded that these individuals may benefit from individual trauma-focused psychological intervention when combined with a behavioral intervention for substance use (Roberts *et al.* 2015). This study found little evidence to support the use of non-trauma focused individual or group-based interventions in this population.

Gaps in knowledge and solutions for future work

What do we not know?

A review of the literature on the neurobiology of PTSD and AUD returns many results on the neurobiology of PTSD, and the neurobiology of AUD, but very little on the neurobiology of the comorbid condition, which we know is frequently seen in the clinic. Both PTSD and AUD are likely to coexist in a feed-forward process whereby PTSD symptoms drive excessive alcohol drinking, and alcohol abuse worsens PTSD symptoms. Furthermore, at least in combat veterans, this interaction likely needs to be studied and understood in the context of coexisting traumatic brain injury, which can have debilitating consequences for the affected individual, and which may be because of physical insult as much as the secondary cascade of symptoms that follow (Shively *et al.* 2016).

Future work in humans with comorbid PTSD and AUD, and also work in animal models designed to concurrently model aspects of each of these two diagnoses, are critical for understanding the *interaction* effects of traumatic stress and alcohol, which is not information that can be garnered from examining literature on the neurobiology of each disorder separately. In this review, we have attempted to provide an unbiased survey of the literature, but even here we have been largely confined to describing neural systems highlighted in the PTSD-alone and AUD-alone literature, although there is no denying the

high degree of overlap in the neuropathology that defines each of these two disorders. For lack of options, treatment targets and strategies in clinical trials aimed at reducing PTSD and AUD symptoms in comorbid individuals have been guided by points of intersection in two separate literatures on the neurobiology of PTSD and the neurobiology of AUD. The high failure rate of these clinical trials, noted in detail above, perhaps provides the strongest argument that our approach needs to change 'from the ground up' by tweaking animal models to examine the comorbid condition in the same sets of animals. To further complicate matters, clinical trials may actually be excluding individuals with comorbid diagnoses (Hoertel *et al.* 2014). Also unknown are the dose-dependent effects of alcohol on the PTSD brain, i.e. (1) do moderate and excessive levels of alcohol drinking after PTSD have similar but graded effects, or qualitatively different effects? and (2) is moderate drinking, unlike excessive drinking, safe for the individual diagnosed with PTSD? It would also be critical to know whether specific patterns (i.e. binge) of alcohol intake/exposure after traumatic stress are particularly impactful on PTSD neurobiology.

It is important to understand whether specific subpopulations of humans and animals are particularly susceptible to traumatic stress-induced escalation of alcohol drinking. The limited clinical and preclinical literature on this topic suggest that the answer is yes, but we do not know what are the likely predisposing factors that 'stack the deck' against specific individuals exposed to traumatic stress. For example, only some humans and animals exposed to traumatic stress go on to develop PTSD or PTSD-like behaviors, but it is not known whether these animals have genetic, epigenetic, neurobiological or other preexisting differences from those individuals that are resilient to the detrimental effects of traumatic stress. Furthermore, we do not know whether the predisposition toward post-stress escalation of alcohol drinking simply maps onto the organism's overall stress response, or whether this particular predisposition has different predictors than other traumatic stress effects. A logical extension of this question is whether, among comorbid affected individuals, there are subpopulations that can be expected to respond more or less positively to specific treatment strategies. Another important consideration is whether males and females exhibit traumatic stress reactivity and post-stress escalation of alcohol drinking that is similar quantitatively and/or qualitatively, especially considering noted sex differences in the incidence of PTSD and AUD.

It appears there may be critical periods during which individuals are particularly susceptible to traumatic stress-induced escalation of alcohol drinking, at least under certain experimental conditions. For example, our group has shown that social isolation stress during adolescence but not during adulthood produces long-term increases in alcohol drinking at time points far removed from the stress itself (McCool & Chappell 2009; Skelly *et al.* 2015), and this effect is seen in males but not in females (Butler *et al.* 2014). Very little is known about the effect of preadolescent traumatic stress on future escalation of alcohol drinking and the neurobiology of this potential effect, especially when interindividual differences in stress reactivity are accounted for. We also do not know the duration of traumatic stress effects on escalation of alcohol drinking, whether duration is dictated by sex and/or whether duration is dictated by when in the life span the stress occurs. Finally, we do not know whether the neurobiological effects of traumatic stress resolve with time in individuals who are able to

remain abstinent for a critical period of time post-trauma, information that would have potentially huge impact on management of PTSD patients.

Post-traumatic stress disorder can be conceptualized in terms of stress sensitization and fear-learning deficits, the latter of which is often examined in terms of fear extinction deficits, enhanced fear renewal or fear reinstatement and/or fear over-generalization. One consideration that we have largely glossed over in this review is the potential impact of alcohol, especially in excessive quantities, on fear-learning deficits. These types of effects would potentially contribute to the self-perpetuating and cyclical nature of PTSD and AUD. We do know that in humans, prestress alcohol exposure has dose-dependent effects on subsequent intrusive memories related to the stress (Bisby *et al.* 2009), and from animal studies that (1) acute alcohol facilitates reconsolidation of a fear memory (Nomura & Matsuki 2008), (2) subchronic alcohol injections facilitate expression of a previously learned fear (Quinones-Laracuente *et al.* 2015), (3) alcohol-dependent animals withdrawn from alcohol exhibit higher expression of a newly conditioned fear and resistance to extinction of that fear (Bertotto *et al.* 2006, but see Stephens *et al.* 2001) and (4) alcohol dependence impairs subsequent fear extinction (Holmes *et al.* 2012). Acute studies have focused on low-to-moderate alcohol doses (<1.5 g/kg), largely because high doses of alcohol are amnestic (i.e. blackouts; Jellinek 1946; Lee 2009). Therefore, with the exception of the latter two findings described above, most work on this topic has not aimed to model AUD or chronic high-dose alcohol exposure, and none of these studies examined the contributions of escalated alcohol drinking to observed fear-learning deficits.

Another important avenue of work is to understand whether there are genetic, biological or symptomatic predictors of successful treatment response in people diagnosed with comorbid PTSD and AUD. For example, several studies have shown that behavioral responses (e.g. stress- and cue-elicited craving) and neurobiological measures (e.g. vmPFC and rostral ACC hyperactivation) are predictors of relapse in alcoholics (Blaine *et al.* 2015; Seo *et al.* 2013). However, whether these measures are also related to relapse risk in patients with comorbid PTSD is largely unexplored. It is also not known definitively whether drugs that work for PTSD or AUD alone are likely to work for the comorbid condition, but the clinical trials described above suggest that this is not likely to be the case. For individuals with a dual diagnosis, it is not clear whether successful treatment of one of the two disorders reduces symptoms associated with the other disorder. One major challenge is that, particularly in the case of AUD, patients often do not seek treatment until they have misused alcohol for many years. It seems likely that the neurobiological deficits that manifest following a prolonged history of excessive alcohol exposure may potentially render the brain more resistant to AUD treatments. As with other CNS disorders that are often not diagnosed until the underlying neuropathology has progressed to a stage that is resistant to treatment, such as Alzheimer's or Parkinson's disease, early diagnosis and treatment may represent a promising avenue for improving patient outcomes. Given that the dual diagnosis of PTSD and AUD exacerbates the symptoms of both disorders, early detection may be particularly important in the case of the comorbid condition.

Strategies for future work on neurobiology and treatment of comorbid PTSD and AUD

There will not be a single silver bullet for improving the validity of comorbid animal models, design of comorbid experiments and success rates of clinical trials testing drugs aimed to treat comorbid PTSD and AUD. However, adherence to a few basic principles in future work may improve the quality, quantity and translational potential of data in this realm.

First, the parallelism between human and animal studies examining comorbid PTSD and AUD, and reciprocal communication between the investigators performing these two types of studies will be critical for moving the field forward. Better yet, scientific alliances provide a huge advantage in which results from animal studies are translated to human laboratory studies and clinical trials, and results from human experiments and trials are reverse translated to improve and hone the animal models being used by basic scientists. To detect the reciprocal effects of high stress reactivity and excessive alcohol drinking on each other and stress/alcohol interaction effects on other variables, it is critical in both humans and animals that the *interaction* of PTSD and AUD be studied or modeled in the *same* individual. Funding opportunities with a focus on this language and detection of these effects will go a long way to increasing the quantity of studies with this specific focus, which are generally regarded by scientists and grant reviewers as ‘too complicated,’ especially in basic science animal models, but nevertheless represent closer approximations of the human condition. Another aspect of the human condition that should be more prominently integrated into animal models of PTSD–AUD comorbidity is the study of subpopulation (or even individual) differences in the biological and behavioral responses to stress, including but not limited to subsequent escalation of alcohol drinking, and dose–response biological sensitivity to alcohol. Finally, it is critical that animal studies aiming to model comorbid PTSD and AUD measure, or at least aim to measure, the same outcomes. Different researchers weigh different aspects of validity as more or less important (Belzung & Lemoine 2011), but it is generally considered important that animal models exhibit high levels of construct validity, generally defined as the accuracy with which an animal model measures what it is intended to measure, and predictive validity, generally defined as the ability to make consistent predictions about a human condition based on an animal's performance in a model of that human condition. There is little doubt that future basic science work on comorbid PTSD and AUD will become more sophisticated and translational, and we are hopeful that this will improve the precision and success of human laboratory experiments and clinical trials aimed at treating these highly comorbid and highly debilitating disorders.

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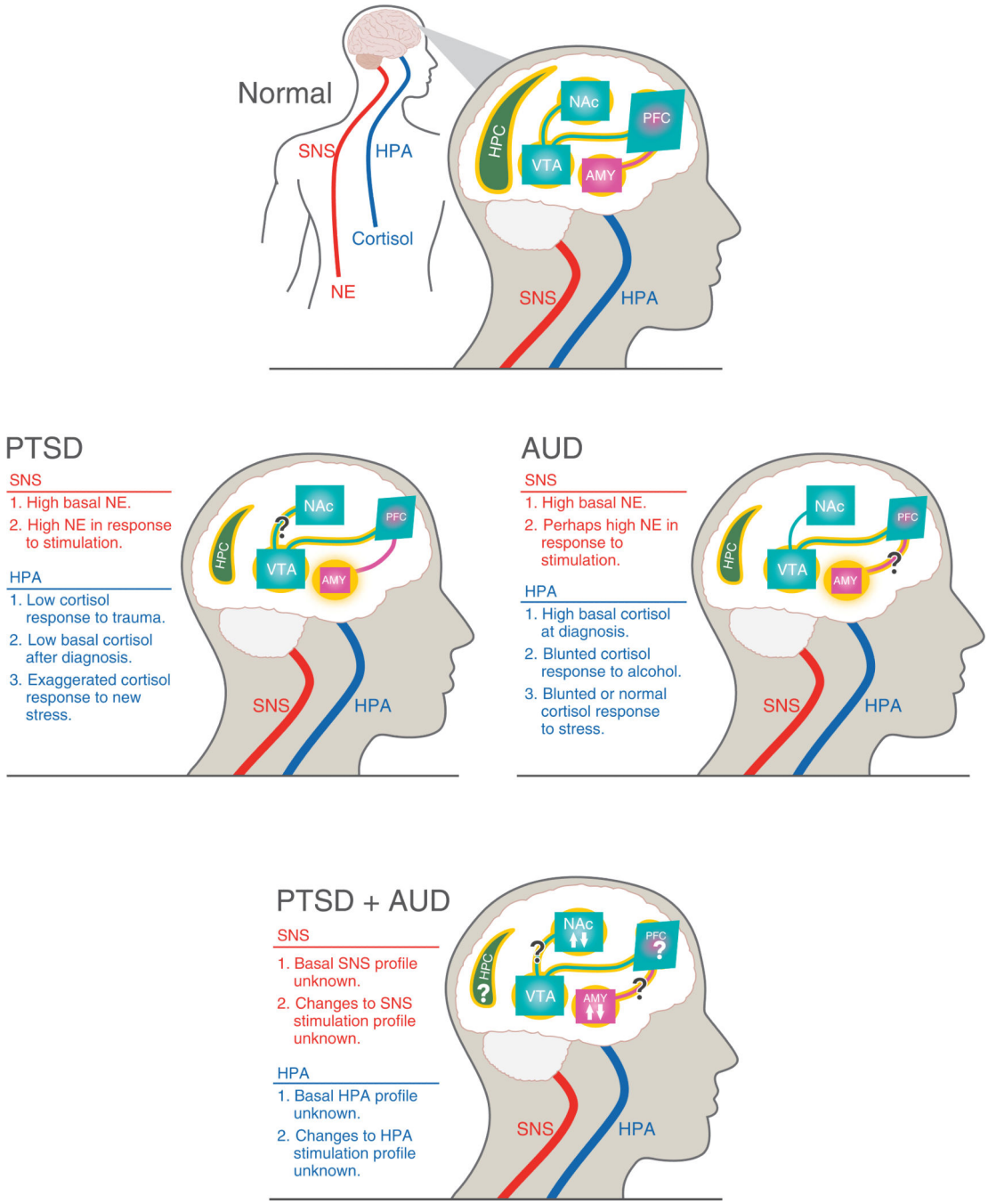

Figure 1. Neurobiology of comorbid PTSD and AUD

Illustration of hallmark central and peripheral nervous system changes associated with PTSD (left), AUD (right), PTSD + AUD (bottom) and relative to healthy controls (top). All denoted biological changes reflect the human literature on PTSD, AUD or comorbid PTSD + AUD, although it should be noted that very few human studies have focused specifically on the neurobiology and neurophysiology of comorbid PTSD + AUD. Smaller size of a structure reflects literature showing volumetric reductions in that brain structure. Yellow glow of structures and connections reflects normal function in healthy controls (top).

Absence or exaggeration of yellow glow in other panels indicates functional deficits or hyperactivity in those structures and/or pathways. Upward and downward arrows indicate evidence in support of effects in both directions in a particular brain region. Question marks indicate ambiguity of findings or lack of information, as summarized in the text.

Table 1

Characteristics and results of clinical trials for the treatment of comorbid PTSD and AUD

Medication	Patient population	Treatment setting	Study type	Results	Reference
Sertraline	9 Non-veterans (3 M/6 F)	Outpatients	Open label	Sertraline reduced PTSD symptoms, decreased average number of drinks and increased abstinence days	Brady *et al.* (1995)
Sertraline	94 Non-veterans (51 M/43 F)	Outpatients	Double-blind, RCT	Sertraline modestly improved PTSD symptoms and improved AUD symptoms only in patients with early-onset PTSD and less severe AUD	Brady *et al.* (2005)
Paroxetine vs. desipramine (in combination with naltrexone or placebo)	88 (81 veterans) (80 M/8 F)	Outpatients	Double-blind, RCT	Paroxetine and desipramine equally reduced PTSD symptoms. Desipramine improved retention and alcohol-use outcomes. Naltrexone had no effect on any drinking measures	Petrakis *et al.* (2012)
Quetiapine	50 veterans (50 M)	Outpatients	Retrospective	Quetiapine treatment was associated with increased number of abstinent days and lower number of hospitalizations. PTSD symptoms were not reported	Monnelly *et al.* (2004)
Naltrexone vs. disulfiram	254 veterans (247 M/7 F)	Outpatients	Secondary analysis of a double-blind, RCT	Naltrexone and disulfiram, alone or in combination, decreased alcohol-use measures; however, there was no benefit of combining these medications. Only complete abstainers showed an improvement of PTSD symptoms and, within this group, disulfiram was the most effective medication	Petrakis *et al.* (2006)
Topiramate	30 veterans (29 M/1 F)	Outpatients	Double-blind, RCT	Topiramate improved PTSD symptoms and decreased alcohol use and craving. Treatment was associated with mild cognitive impairment that recovered by the end of the 12-week treatment period	Batki *et al.* (2014)
Prazosin	30 (9 veterans) (19 M/11 F)	Outpatients	Double-blind, RCT	Prazosin had no effect on PTSD symptoms but significantly decreased the percentage of drinking days/week and the percentage of heavy drinking days/week	Simpson *et al.* (2015)

Medication	Patient population	Treatment setting	Study type	Results	Reference
Prazosin	96 veterans (89 M/6 F)	Outpatients	Double-blind, RCT	Prazosin had no significant effect on either PTSD symptoms or alcohol consumption	Petrakis *et al.* (2016)
Aprepitant (NK1R antagonist)	53 Non-veterans (29 M/24 F)	Outpatients	Double-blind, RCT	Aprepitant had no significant effect on PTSD symptoms or behavioral/ neuroendocrine response to stress or alcohol cues	
Naltrexone vs. prolonged exposure therapy vs. supportive counseling	165 Veterans and non-veterans (108 M/57 F)	Outpatients	Double-blind, RCT	PTSD symptoms were reduced in all treatment groups, although the main effect of prolonged exposure therapy was not statistically significant. All treatment groups also showed a large reduction in percentage of days drinking, with the greatest effect observed in the naltrexone + supportive counseling group	Foa *et al.* (2013)

F, female; M, male; RCT, randomized control trial.