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Abstract: Major depressive disorder (MDD) symptoms commonly occur after trauma-exposure, both alone and in combination with post-traumatic stress disorder (PTSD). This article reviews recent research on comorbidity between these disorders, including its implications for symptom severity and response to treatment. Despite considerable symptom overlap, the two disorders represent distinct constructs and depend, at least in part, on separate biological mechanisms. Both, however, are also clearly related to stress psychopathology. We recommend that more research focus specifically on the study of individual differences in symptom expression in order to identify distinct subgroups of individuals and develop targeted treatments. However, a barrier to this line of inquiry is the trend of excluding particular patients from clinical trials of new interventions based on symptom severity or comorbidity. Another obstacle is the over-reliance on self-report measures in human research. We argue that developing computer-based behavioral measures in order to supplement self-report can help address this challenge. Furthermore, we propose that these measures can help tie findings from human and non-human animal research. A number of paradigms have been used to model MDD-and PTSD-like behavior in animals. These models remain valuable for understanding the biological basis of these disorders in humans and for identifying potential interventions, but they have been underused for the study of comorbidity. Although the interpretation of animal behavior remains a concern, we propose that this can also be overcome through the development of close human analogs to animal paradigms.

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Introduction

Post-traumatic stress disorder (PTSD) can develop after the experience of a highly traumatic event, although it does so only in a minority of individuals, estimated at less than 10% (Breslau 2009). Thus, some individuals are at greater risk than others, and much research has been devoted to identifying factors that may either confer vulnerability or protect against the disorder. For example, the female gender is associated with increased risk, with women more likely than men to develop PTSD and other psychiatric disorders following a traumatic event (Bielawski et al. 2019; Breslau 2009; Garami et al. 2019; Goldstein et al. 2016; Kilpatrick et al. 2013; Moustafa et al. 2018). Despite the wealth of research on PTSD, which was placed in the spotlight due to its prevalence in military veterans, relatively less attention has been paid to depression in PTSD. This is surprising given the high comorbidity between the two disorders, consistently estimated to be 30–50% (Angelakis and Nixon 2015). Major depressive disorder (MDD) or depressive symptoms can occur after trauma-exposure (TE), both alone and in combination with PTSD. The aim of this article is to review recent research on this comorbidity and its implications for symptom severity and response to treatment. In this review, we discuss the following topics: different hypotheses and studies regarding the comorbidity between depression and PTSD, an overview of common and unique traits between the conditions, antidepressants and other potential treatments,and treatment outcomes with a focus on comorbidity.

To find relevant studies, we performed a Google Scholar search using various synonyms of PTSD, MDD, and different combinations of terms such as comorbidity, pharmacotherapy, antidepressant, and treatment, to locate peer-reviewed empirical studies, reviews and meta-analyses that dealt with PTSD and MDD comorbidity. We also conducted forward searches from the most relevant search results, namely those that specifically address the comorbidity between the two disorders, to locate more recent research. While there are large literatures on PTSD and MDD, dealing with each disorder, the main focus was on more recent studies (published within the last 5–10

years, whenever possible) that specifically examined comorbidity, ideally by including relevant comparison groups (i.e., PTSD only, MDD only, comorbid PTSD and MDD, and healthy controls). This type of study, however, was rare, and we also included studies that had at least considered comorbidity relative to individuals with symptoms of either disorder alone. We also included research that examined past or current symptoms, instead of only formal diagnoses of PTSD and MDD. Thus, the terms PTSD and MDD in this review can refer to individuals who report symptoms of these disorders but may not have met criteria for a clinical diagnosis.

Comorbidity between depression and PTSD: different hypotheses

While MDD is characterized by symptoms such as anhedonia, low mood, and psychomotor retardation, PTSD symptoms include avoidance, re-experiencing, hyperarousal, and impaired cognition (DSM-5, American Psychiatric Association 2013). There are several hypotheses that aim to explain the comorbidity between PTSD and depression (Angelakis and Nixon 2015; Contractor et al. 2018; Stander et al. 2014). One proposes a causal relationship between the two disorders such that the development of PTSD may lead to depression symptoms, or vice versa. In contrast, according to the common factor hypothesis, there is no causal relationship. Rather, both disorders can result from a common vulnerability or risk factors (Stander et al. 2014). For example, the experience of a traumatic event, given some pre-existing vulnerability, might precipitate the development of both disorders. The vulnerability itself could consist of a multitude of biological, psychological or social factors-for example, a set of specific genes, a pessimistic attributional style, or lack of social support, respectively, among others (Flory and Yehuda 2015; Maheux and Price 2016). Lastly, the observed comorbidity may also be an artifact due to common diagnostic criteria or a common factor structure, referring to how individual symptoms are grouped into clusters in current classification systems of mental disorders (Contractor et al. 2018). This implies that diagnostic criteria are not sufficiently refined to discriminate between the two disorders.

It is not possible to conclusively establish a causal relationship in either human or animal research, since at best, animal models capture only limited aspects of human disorders. However, longitudinal studies can provide clues about the etiology of depression in PTSD (Stander et al. 2014). For example, is it that the PTSD symptoms developed first, and were then followed by the depressive symptoms? If so, this would increase confidence in the hypothesis that PTSD symptoms may have a causal influence on the depressive symptoms, though alternative explanations, such as common vulnerability remain possible. In contrast, cross-sectional studies that compare different groups of participants only after a disorder has developed provide no information about etiology. Ultimately, both approaches still provide only correlational evidence. As a complement to longitudinal studies, twin studies in which one twin has been exposed to a traumatic event, while the other has not, serve as natural experiments that can also provide valuable information (Stander et al. 2014). Specifically, this type of study can separate common genetic and environmental vulnerability (e.g., related to the family or socioeconomic status) from environmental factors unique to one of the twins (e.g., the experience of a traumatic event).

A recent review of longitudinal and twin studies of depression in PTSD focused exclusively on military veterans with combat exposure (Stander et al. 2014). Briefly, the results appear to be mixed as to whether pre-existing depression increases the risk for PTSD, and this was the case for both longitudinal and twin studies. However, most studies in veterans have supported the reverse-prior PTSD is associated with the development of depression. Still, it remains possible that a common risk or vulnerability factor, which was not accounted for, is what is responsible for this relationship (i.e., this is still correlational evidence). For example, one study conducted in active duty soldiers found no evidence that pre-existing PTSD increases the risk for depression after controlling for baseline symptoms of insomnia (Wright et al. 2011). Thus, insomnia is a potential vulnerability factor common to PTSD and depression that may account for at least a portion of the comorbidity between the two disorders. Pre-existing differences in anxiety are another potential vulnerability factor, with anxiety common in both disorders. Consistent with this, PTSD-MDD is associated with greater general anxiety compared to MDD alone (Campbell et al. 2007). Based on twin studies, a correlation is still found between PTSD and depression, despite common genetic and environmental factors (Stander et al. 2014).

However, the above-mentioned studies still do not establish a causal relationship, but rather suggest that a common vulnerability alone is unable to explain the correlation between the two disorders. Overall, based on research in veterans, Stander et al. (2014) concluded that there appears to be stronger evidence for the effect of PTSD on later depression than vice versa. Interestingly, some research has found that depression symptoms decline pre-

to post-deployment, but this has been found primarily in studies of peacekeepers that may not experience much combat. In this population, it has been suggested that the stress of preparing for deployment may have a greater negative impact on mental health than the deployment itself, as a possible explanation for the improvement in symptoms (Stander et al. 2014). Do results from studies that include more women, as well as civilians, point to a similar conclusion? Using a broader sample consisting of 62% women, one study estimated that those with MDD are about three times more likely to develop PTSD after experiencing a traumatic event (Breslau et al. 2000). The opposite also appears to be true individuals who are exposed to trauma and develop PTSD are about three times more likely to develop MDD. However, increased risk was not found for trauma-exposed individuals who did not develop PTSD. This supports the shared vulnerability model, which explains comorbidity between PTSD and MDD in terms of vulnerability factors common to both disorders (Breslau et al. 2000).

Some veterans may also portray their symptoms as worse than they actually are, a practice called malingering, to receive better healthcare benefits. Such compensation-seeking behavior can bias the responses of veterans participating in PTSD research. For example, research has suggested that over half of veterans seeking treatment for combat-related PTSD could be faking or at least exaggerating their claims of combat exposure, which also calls into question the diagnoses of combat-related PTSD (Frueh et al. 2005). An earlier study, however, found no difference in symptom exaggeration between compensation seeking vs. non-seeking participants (DeViva and Bloem 2003). More research, especially given the predominance of self-report measures in the literature, should consider the impact of this potential confound, including its prevalence in veterans from more recent conflicts, but also other populations.

It should be noted that there are other possible reasons besides malingering for overreporting symptoms-some examples include carryover effects from previous tests, the order of items on self-report measures, inattentive responding, as well as personality factors (Merckelbach et al. 2019). Due to its retrospective nature, even those who would like to provide accurate information may not be able to do so, and their memories could be influenced by current symptom severity. For example, one study found that the extent of combat exposure self-reported by veterans increased alongside self-reported PTSD symptom severity (Roemer et al. 1998; Roemer et al. 1998). In contrast, a study conducted in peacekeepers found reports to be consistent over time (Bramsen et al. 2001). Overall, relatively few studies have considered these confound and it remains unclear whether or how comorbid depression symptoms would influence them. In addition, even when symptom overreporting is taken into account, both clinicians and researchers may unfairly assume malingering when there are other possible explanations (Merckelbach et al. 2019).

Thus, most studies focused on military or veteran samples do have limitations. A major limitation associated with most twin studies is that they were conducted on individuals found in the Vietnam-Era Twin (VET) Registry, who may not be representative of the larger population (Stander et al. 2014) or of veterans from more recent conflicts. These results may also not apply to civilian samples, or to female veterans and civilians, due to differences in the types of trauma experienced by these groups. Similarly, gender can play a role, but veteran samples are predominantly male. In addition, with any archival research involving medical records, the expectations of service providers (e.g., physician expectations at VA hospitals) are a potential confound and can bias study results (Carlson et al. 2010). Others raise concerns that physicians are more likely to look for substance use disorders rather than depression in veterans with PTSD, which can both lead to underestimating comorbidity between PTSD and MDD and preclude selecting appropriate treatment (Brewin et al. 2012). Personal expectations also play a role-for example, pre-deployment expectation may worsen stress and mental health. In studies of peacekeepers, this may contribute to the greater severity of symptoms found pre-deployment compared to post-deployment. Upon return there might be a honeymoon phase (i.e., positive emotions associated with return) such that mental health is better temporarily until this phase is over. This can help explain why PTSD symptoms do not develop until after a delay (Bliese et al. 2007). The same could account for delays in the development of depression symptoms.

At least a portion of the observed comorbidity between PTSD and MDD could be due to overlap in symptoms, or in symptom groups or clusters (Contractor et al. 2018; Flory and Yehuda 2015; Hurlocker et al. 2018). In general, comorbidity due to symptom overlap has been discounted as an explanation with research supporting that the two disorders represent separate constructs (Angelakis and Nixon 2015). This issue is further complicated by changes in diagnostic criteria, which pose a challenge when attempting to integrate research based on older and more recent criteria. For example, Flory and Yehuda (2015) compared diagnostic criteria for PTSD across DSM versions. Relative to MDD criteria, this has remained virtually the same that for PTSD has undergone major changes from version to version, with few exceptions. Part of the reason why that is, PTSD is a relatively

new addition to the DSM. Awareness of it as a separate diagnostic construct was raised by reports coming from an influx of Vietnam veterans. In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association 2013), PTSD was reclassified in a newly introduced category of trauma and stressor-related disorders, a decision that was in part based on the high level of individual differences observed in its symptomatology. A defining feature of the disorder is the experience of a highly traumatic event, which also helps distinguish it from the other anxiety disorders it was previously grouped with. Otherwise, diagnosis is made based on several symptom clusters, including re-experiencing, avoidance, negative changes in cognition and mood, as well as changes in arousal and reactivity, many of which are shared with anxiety disorders, and importantly, with depression. If comorbidity is an artifact of diagnostic criteria, estimates of comorbidity should change as the criteria change (Flory and Yehuda 2015). Unfortunately, earlier estimates of comorbidity were based on a small number of studies and could vary wildly (e.g., for the DSM-III, estimates range from 4 to 51%), but those from more recent DSM versions have been more reliable. To date, comorbidity based on DSM-5 criteria remains unclear due to a lack of published research using the new criteria. Overall, Flory and Yehuda (2015) conclude that there is little evidence of a change in comorbidity across DSM criteria, with estimates consistently reaching 50%. The recently released 11th version of the International Classification of Diseases (ICD-11; World Health Organization 2018) also makes a number of changes to PTSD diagnostic criteria, in part with the goal of reducing comorbid diagnoses by removing non-specific symptoms of PTSD (i.e., symptoms that are shared with other disorders, such as depression). At least one study, however, has suggested that although ICD-11 criteria reduce PTSD prevalence by 10–30% relative to DSM-5 criteria, comorbidity estimates remain similar (Wisco et al. 2016). The ICD-11 also includes a complex PTSD diagnosis, which appears to be associated with greater levels of depression (Hyland et al. 2018).

Unique features of comorbid depression and PTSD

Recent studies have examined the possibility of a depressive subtype of PTSD via latent profile analysis (Contractor et al. 2017). This technique can reveal underlying classes or groups of individuals who respond in a similar way on a set of measures (Armour et al. 2014a). In other words, individuals within each group show similar symptom profiles. In contrast to most prior studies using this technique, Contractor et al. (2017) used DSM-5 criteria for both PTSD and MDD. Their analysis came to a three class solution pointing to a high severity subgroup, a lower PTSD-higher depression subgroup, and a higher PTSD-lower depression subgroup. The high severity subgroup represents the depressive subtype of PTSD and is the one with both high PTSD and depression symptoms. The fact that there were both higher PTSD-lower depression, and lower PTSD-higher depression sub-classes indicate that PTSD and MDD are distinct constructs that is, an individual can show higher or lower levels of symptoms on either one of them. Compared to the higher PTSD-lower depression subgroup, those with the high severity subtype (i.e., the depressive subtype of PTSD), were more likely to endorse dissociative experiences (in particular, gaps in memory), as well as lower distress tolerance. The ICD-11 diagnosis of complex PTSD, mentioned above, is also associated with higher levels of depression, but also dissociation (Hyland et al. 2018).

In general, dissociation can be defined as a loss of information or control over cognitive processes that are otherwise available to conscious awareness (Armour et al. 2014a). Although flashbacks and amnesia, both found in PTSD, can be seen as dissociative symptoms, the DSM-5 focuses on depersonalization – a feeling of being disconnected from one's own emotions and body – and derealization, which can be described as a feeling that the physical and social environment is strange, unfamiliar or unreal (Carlson et al. 2012). Dissociation has been reported by both military and civilian samples with PTSD (Armour et al. 2014b). Relative to the lower PTSD-higher depression subgroup, Contractor et al. (2017) found the high severity group was more likely to report derealization and depersonalization, greater gaps in memory, and lower distress tolerance. Thus, overall, dissociation was linked to the high severity (depressive) subtype of PTSD (Contractor et al. 2017).

The study by Contractor et al. (2017), however, relied on a university student sample that had experienced a potentially traumatizing event and, as with other human research, relied solely on self-report measures. Thus, the results should be considered tentative, and may not be representative of a more diverse population, including in the types and severity of traumatic events experienced. The results also raise the question of how the high severity subtype differs from the dissociative subtype of PTSD already included in the DSM-5. Do studies using different samples also point to dissociation? A prospective study of

recent victims of sexual or nonsexual assault, who were studied over a 12-week period, found dissociation to be correlated with depression, but did not predict the development of PTSD symptoms (Feeny et al. 2000). All participants were female, with 46% who had been victim to sexual assault. In contrast to dissociation, emotional numbing symptoms, which are discussed further below, were found to predict the development of both PTSD and depression after trauma (Feeny et al. 2000). Even though the other symptoms, including re-experiencing, avoidance and changes in arousal, are more common among those who develop PTSD, they are still reported by 28–64% of trauma-exposed individuals who do not meet diagnostic criteria for the disorder (Feeny et al. 2000).

How is numbing related to dissociation? This is not well understood. Dissociation can involve changes in memory, such as when components of a traumatic memory are not consciously accessible, but also disengagement between the self and the environment (Feeny et al. 2000). In particular, this second component of dissociation overlaps with emotional numbing, and it has been argued that numbing is a type of dissociative symptom (Spiegel 1997). A study of female victims of sexual assault found evidence for a distinct subgroup, comprising about 14% of the sample, with dissociative PTSD that also had higher levels of depression, along with anxiety, hostility, and more severe sleep disturbance (Armour et al. 2014a). This is consistent with other research showing that those with dissociative PTSD have more comorbid conditions, including MDD (Steuwe et al. 2012). There has been some variation in the rate of dissociation between studies, with 15% in a sample of male Vietnam veterans with combat-related PTSD and about 30% in an all-female sample consisting of military veterans, and some active duty soldiers, primarily with sexual trauma-related PTSD (Wolf et al. 2012a). Based on these results, the rate of dissociation can be expected to be higher in trauma involving sexual assault. Another study on male and female military veterans and their spouses or romantic partners found only 6% of the sample to be dissociative (Wolf et al. 2012b). However, none of these studies measured depression symptoms.

Distress tolerance was also found to distinguish between the depressive and non-depressive subtypes of PTSD (Contractor et al. 2017). Distress tolerance contributes to emotion regulation and is related to numbing. As mentioned above, Feeny et al. (2000) found numbing, not dissociation, to predict the development of PTSD with comorbid MDD (henceforth referred to as PTSD-MDD). According to the emotional processing theory, an optimal level of emotional engagement with trauma-related memories is necessary for symptoms to improve (Angelakis and Nixon 2015). Thus, relatively little or too much engagement will not lead to improvement or may even be detrimental. Emotional engagement can be inhibited by numbing, a symptom shared by both PTSD and MDD, which may represent a means to cope with strong emotions (i.e., by avoiding them) (Angelakis and Nixon 2015). Numbing involves loss of interest in activities, detachment from others, and a restricted range of emotion (Feeny et al. 2000). Loss of interest in activities, and more generally anhedonia – the inability to experience pleasure – is a defining feature of depression. However, numbing has been proposed to differ from anhedonia in that it is more general, representing diminished the experience of a variety of different emotions, both positive and negative, while anhedonia is specific to positive emotions (Glover 1992). Prior to the DSM-5 diagnostic criteria, numbing was part of the avoidance symptom cluster, as a type of automatic response that reduces the impact of strong negative emotional experiences (such as those elicited by re-experiencing of the traumatic event upon encountering cues that elicit memories of that event). Thus, numbing might be the result of classical conditioning and differs from other types of avoidance that can instead be described as effortful or voluntary (Foa et al. 1992). For example, a veteran with combat-related PTSD may actively and quite deliberately avoid situations, such as a fireworks display, that can elicit re-experiencing due to containing cues that serve as reminders of trauma (i.e., loud popping sounds that resemble gunfire). Numbing has since been reclassified as part of the negative alterations in cognition and mood cluster in the DSM-5.

Horesh et al. (2017) conducted a longitudinal study to examine PTSD-MDD comorbidity and found that the PTSD hyperarousal symptom cluster was most strongly associated with MDD across time. The participants were 942 residents of urban Detroit neighborhoods, predominantly African American (85% of the sample), who were interviewed at three time points, one year apart. At all of the time points, the correlations between the avoidance, re-experiencing and hyperarousal PTSD symptom clusters and depression symptoms were moderate to strong (between 0.4 and 0.7). There was also a similar pattern of symptom change over time for both disorders – PTSD (all clusters) and MDD symptoms declined from time one to two and remained stable between time two and three. However, the decline was lower for women compared to men. In addition, at time one, depression symptoms correlated more strongly with hyperarousal compared to re-experiencing, which was the case for both men and women, as well as the full sample. At time two, this was

only true for the full sample and for women, but not men. Instead, no differences in the strength of the correlations were found for men. For women, in addition to hyperarousal, avoidance was now also more strongly associated with depression compared to re-experiencing. At time three, this pattern was now also found for men, with stronger correlations between both hyperarousal and avoidance, compared to re-experiencing for men, women and for the full sample. Thus, gender differences in the strength of the relationships were only detected at time two, but symptoms also did not decline as much for women. As Horesh et al. (2017) discuss, this sample has likely had chronic exposure to severe stressors, including violence, crime and poverty, at a higher level compared to the general population. Thus, over time, participants may have learned to remain alert for danger in their environment, which could explain why PTSD hyperarousal symptoms were, overall, most strongly related to MDD. The hyperarousal symptom cluster may also simply represent a set of non-specific symptoms, common to mood, anxiety and stress-related disorders (Horesh et al. 2017). In addition, there have been mixed results in the literature with respect to what set of PTSD symptoms are related to depression. For example, like Horesh et al. (2017), a cross sectional study by Rubacka et al. (2008) found that hyperarousal but not re-experiencing is related to MDD. No relationship was found with avoidance, though this effect could be time-sensitive, as suggested by the results of Horesh et al. (2017). Gros et al. (2010) found in favor of numbing and dysphoria, which predicted comorbidity, and greater depression symptoms in PTSD. Post et al. (2011) also found dysphoria, but also re-experiencing, to be more severe in comorbid PTSD-MDD compared to PTSD.

In addition to potential differences in symptoms, demographic, dispositional and social factors can help distinguish comorbid PTSD-MDD from either disorder alone. For example, in a longitudinal study, Forbes et al. (2020) found an interaction where emotional avoidance at initial screening was related to the severity of both MDD and PTSD symptoms 12 months later, but only in those with low levels of perceived social support. This effect, however, despite reaching statistical significance, was relatively small and emotional avoidance at initial screening alone was a stronger predictor of symptom severity at follow-up. The sample consisted of 46 people who were exposed to a traumatic event, predominantly a motor vehicle accident (50%) or physical assault (44%). It was 65% female, with most identifying as either African American (59%) or white (37%). Similar to numbing, emotional avoidance represents an attempt to control aversive or threatening emotions, and is associated with depression, in both civilians and veterans (Forbes et al. 2020). In contrast, the use of acceptance (i.e., the opposite of avoidance) as a coping strategy is known to be protective, associated with less severe depression symptoms (Forbes et al. 2020). Despite the relatively weak relationship in the study of Forbes et al. (2020), other research, including a longitudinal study by Wild et al. (2016) on a sample of paramedics, has also identified low social support as a risk factor for depression after exposure to a traumatic event.

Still, is social support even lower in those with PTSD-MDD, and are there any other factors, such as personality traits, that help distinguish this group? In a recent study, out of a larger sample of military veterans, Nichter et al. (2020) compared 40 veterans (32 male) who were classified as having probable PTSD to 60 (52 male) classified as having probable comorbid PTSD-MDD. Those in the PTSD-MDD group reported lower dispositional optimism and community integration were more likely to identify as non-Caucasian, reported more lifetime traumatic events and more private religious activity compared to the PTSD only group. Overall, these variables explained 33% of the variance in comorbidity, with 34, 24, 18, 18, and 6% of that total accounted for by each of the factors, respectively. In contrast, loneliness, level of social support, number of close friends or relatives, public religious activity (i.e., Church attendance) and substance use disorder history did not differ between the groups, and neither did any of the big five personality traits (openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism). Female gender was also not identified as a risk factor for PTSD-MDD in this sample, but this could be due to the low number of women, as is typical of military samples. Other research, discussed below, has consistently identified gender as a factor in both disorders. It is worth noting that the community integration variable was based only on the response to the question, "I feel well integrated in my community (e.g., regularly participate in community activities)" (Nichter et al. 2020, p. 57). Therefore, this variable may tap into a more specific aspect of social support.

Another recent study by Vidaña et al. (2020) identified risk-taking as a distinguishing feature of PTSD-MDD compared to PTSD alone in a sample of 193 patients (92 female) undergoing treatment for substance use disorder in an in-patient setting. Unlike the other studies, which relied on self-report, this study assessed risk taking via the balloon analog risk task, where participants could inflate a virtual balloon in order to earn money – inflating the balloon too much could cause it to pop, resulting in the loss of all earnings. Behavior in this task was assessed after exposure to a neutral and trauma-related script, which had been personalized according to the type of traumatic event

each participant had experienced and was intended to elicit emotional arousal. Interestingly, although risk-taking increased after exposure to the trauma script, it did not increase as much for the PTSD-MDD group compared to the PTSD only group. To explain this, Vidaña et al. (2020) discuss the possibility that risk-taking can be used as an emotion regulation strategy, but that MDD symptoms might reduce the degree of emotional arousal elicited by the trauma-related script. Thus, these individuals might need to rely on risk-taking as a coping strategy. Reduced reward-seeking, which is a feature of MDD, might also help reduce risk-taking, because these participants might not be as interested in the money compared to those with PTSD only (Vidaña et al. 2020). These results might not generalize to a broader population, since patients also had a comorbid substance use disorder, were treatment seeking, had high school level or less education, and an annual income below the poverty line. These patients may have also been more prone to taking risks overall, as is typical of individuals with substance use problems (Verdejo-Garcia et al. 2008).

With respect to socioeconomic variables, however, the patients studied by Vidaña et al. (2020) might be more typical of individuals with comorbid PTSD-MDD. For example, in a sample of 3593 female U.S. military veterans derived from the National Survey of Women Veterans, Lehavot et al. (2013) found that, compared to women who screened positive for having only PTSD symptoms or only MDD symptoms, those with PTSD-MDD were more likely to have an income below the poverty line, were less likely to have health insurance, were nearly 11 times more likely to report having unmet medical needs, and cited affordability as the most common reason for why they had not sought treatment. As Lehavot et al. (2013) mention, it is surprising to find affordability as a barrier to treatment in veterans, given that many should quality to receive healthcare at VA Medical Centers, suggesting that at least some of the women in this sample may not have been aware of the benefits available to them (Lehavot et al. 2013). This is supported by the fact that out of women not using the VA, those in the PTSD-MDD group was more likely to report not knowing whether they qualify for benefits. Despite these differences, the PTSD-MDD group was overall more similar to the PTSD only and MDD only groups, in terms of the other barriers to treatment considered in this study (Lehavot et al. 2013). A limitation of this research is that MDD symptoms were assessed only using a single self-report item, "Have you felt downhearted and depressed?", with those responding most of the time or all of the time considered positive for depression (Lehavot et al. 2013, p. 205). It is also unclear whether similar results would be found for male veterans, since as discussed below, female gender is also a risk factor for PTSD-MDD.

Some of the same factors were found to distinguish individuals with symptoms of PTSD-MDD from those with symptoms of either disorder alone in studies by Nillni et al. (2013) and Farhood et al. (2016), in samples of Hurricane victims and armed conflict survivors, respectively. Nillni et al. (2013) surveyed a sample of 810 people affected by Hurricane Katrina and found that financial loss, exposure to stressors, and less social support after the Hurricane were associated with comorbidity, thus representing shared vulnerability factors between PTSD and MDD. These factors were related to both symptoms occurring at any time after the Hurricane as well as current symptoms (i.e., at the time of the survey). In this sample, 8% of the total reported PTSD and MDD symptoms since the Hurricane, and 6.5% had current comorbid PTSD and MDD symptoms. By comparison, the study of Farhood et al. (2016) was on a sample of 991 civilians and citizens of Lebanon, who experienced chronic political and economic instability, along with armed conflict. Here, participants were classified into no PTSD or MDD, PTSD only, MDD only, and comorbid PTSD-MDD groups. In this sample, 9% of the total was in the PTSD-MDD group. Similar to the study of Vidaña et al. (2020), those who reported health problems were about two to three times more likely to be in the PTSD-MDD group than the PTSD only and the no symptom groups, but no difference was found relative to the MDD only group. The strongest correlation was found for female gender, with women close to four times more likely to be in the PTSD-MDD group relative to the MDD only group (Farhood et al. 2016). Women, and those who had not completed secondary education, were also over two times more likely to be in the PTSD-MDD group than in the no symptoms group. Gender, however, was not related to the odds of being in the PTSD-MDD group relative to the PTSD only group. Other factors, including social problems (e.g., interpersonal problems at workplace or with friends or family), having financial problems (e.g., job loss, change in income) and witnessing a traumatic event also increased the odds of comorbidity. In contrast, social support and being employed were identified as protective against comorbidity (Farhood et al. 2016).

A longitudinal study by Spinhoven et al. (2014) also found female gender to be associated with comorbidity, which was very high in their sample (about 84%). The study employed a representative sample of 2402 individuals (ages 18 to 65) from the Netherlands Study of Depression and Anxiety and included people with current

and prior anxiety and depressive disorders, which had also experienced a wide variety of traumatic events. Both depression and anxiety symptoms were more severe in individuals with comorbid PTSD, as was phobic avoidance. Like Farhood et al. (2016), female gender was identified as a risk factor for both PTSD and MDD. About 82% of those with PTSD were female, and women were more likely to cite physical and sexual assault as the most traumatic event they had experienced. However, type of traumatic event was not related to symptom severity in this sample. In addition, even after controlling for symptom severity, the experience of childhood sexual and physical abuse were also significant predictors of comorbidity, and their effect was independent of that of gender (Spinhoven et al. 2014). There are also gender differences in the amount of social support available to individuals depending on the type of traumatic event they have experienced. For example, female victims of sexual assault not only tend to receive less support but can also be blamed for what happened (Ullman et al. 2007), and is known to contribute to the development of PTSD and MDD (Maheux and Price 2016). The increased risk associated with gender can then be due to a number of characteristics correlated with gender, for example, resulting in a complex interplay between factors like gender, type of trauma and social support. There is, however, also evidence that some of the vulnerability is due to biological differences between men and women, and their interactions with environmental factors – an issue that will be discussed further below.

Early life stress, such as that due to physical and sexual abuse, could be processed differently in children compared to adults, and may alter the development of systems involved in emotion regulation and the neuroendocrine response to stress (Maercker et al. 2004). A study on a sample of 1966 women from Dresden, Germany, Maercker et al. (2004) examined whether the age at which a traumatic event was experienced, either up to or after the age of 12, was a predictor of comorbid PTSD-MDD. Consistent with this, participants screening for PTSD-MDD (18 women compared to 45 with PTSD only and 43 with MDD only), had experienced a traumatic event, on average, when they were about 10 years old. This was in contrast to those with PTSD only, who had experienced it, on average, at an age of about 14. However, the PTSD-MDD group did not differ from the trauma-related MDD only group, which also experienced a traumatic event, on average, at around 10 years old. Thus, the risk for PTSD and MDD developing appeared to be about the same if trauma was experienced up to the age of 12, but the risk for pure PTSD was greater if the trauma occurred later (Maercker et al. 2004). The most common event reported by participants was rape, regardless of group. This study also found that those in the PTSD-MDD group had lower current levels of function compared to the other groups (Maercker et al. 2004).

Lastly, some research has also considered the role of personality. For example, Spinhoven et al. (2014) focused on extraversion and neuroticism. Previous research has reported a negative correlation with extraversion, and a positive correlation with neuroticism, for both PTSD and MDD symptoms. However, in Spinhoven et al. (2014), these traits were only statistically significant in univariate but not in the final multivariate analysis the authors conducted. Thus, it is possible that they are not specific predictors of comorbid PTSD-MDD (Spinhoven et al. 2014). Similarly, these traits were not found to predict PTSD-MDD in the study of Nichter et al. (2020) in a sample of U.S. veterans, discussed earlier. Overall, the results of Spinhoven et al. (2014) support a shared vulnerability model of PTSD and MDD, with the risk factors identified, namely gender, sexual and physical abuse, common to both disorders. In general, the other research discussed in this section was also consistent with shared vulnerability, where socioeconomic factors, such as low education and income, is associated with increased risk for both PTSD and MDD, and in at least in some samples, has been identified as a distinguishing feature of comorbidity, suggesting that exposure to more severe and more chronic stressors, such as those associated with living in poverty, contributes to the development of multiple disorders.

Common features of comorbid depression and PTSD

Despite research that has identified some unique features of comorbid PTSD-MDD, there are also many similarities. For example, negative alterations in cognition and mood are characteristic of both disorders. This group of symptoms includes the tendency to interpret events more negatively along with a negative outlook for the future, which is observed in both disorders. In a recent study of about 600 trauma-exposed veterans, this PTSD symptom cluster was found to be strongest predictor of the affective factor in depression (Hurlocker 2018). This cluster, along with changes in arousal and reactivity, were both also associated with the somatic factor in depression (Hurlocker et al. 2018). In this sample, 50% of veterans with PTSD also had depression symptoms. Overall, these results suggest that emotional distress that is not specific to a particular clinical diagnosis contributes to the high comorbidity between PTSD

and depression, and that this distress may be expressed as affective and somatic symptoms, common to both disorders (Hurlocker et al. 2018). However, a limitation of this study was that depression was only assessed via self-report. In contrast, PTSD symptoms were measured via both self-report and a semi-structured clinician administered interview. In addition, as is typical of military samples, the majority of participants were male. This is important given that there are gender differences in both the prevalence and the expression of both PTSD and depression symptoms, which are discussed further below. As already mentioned, the types of trauma experienced by veterans can also differ from those of civilian samples (Stander et al. 2014).

Other similarities between the two disorders include more easily accessible negative compared to positive memories (Reynolds and Brewin 1999). PTSD can be construed as a disorder of unwanted but repeated access to negative memories (i.e., intrusive memories), but it also shares this feature with depression. A recent meta-analysis found that adults with depression are just as likely to experience intrusive memories as those with PTSD, with prevalence in depression estimated at 76% (Payne et al. 2019). This poses a challenge to the idea that intrusion is unique to PTSD. The two disorders may differ, however, in the type of intrusive memories (Reynolds and Brewin 1999). A distinction can be made between explicit memories that involve appraisal of the traumatic or stressful event and implicit memories, which result from classical conditioning and are elicited by cues associated with the event. Thus, these memories are involuntary and automatic, and can involve intense reliving or reexperiencing. The two types of memories can also be associated with a different set of emotions – the former primarily with sadness, anger, or guilt, while the latter with fear and helplessness. It has been suggested that PTSD is defined by memories of the implicit type (Reynolds and Brewin 1999). The negative memories in PTSD should also be related to a specific traumatic event, while there may be no clearly defined event in depression. To examine these possibilities, Reynolds and Brewin (1999) compared stressors and intrusive memories in patients with PTSD and MDD. In this study, 62 patients met criteria for MDD but not PTSD, 32 for both disorders, and 11 for PTSD but not MDD. Those with PTSD only and PTSD-MDD were combined in statistical analyses and were compared to those with MDD alone. There was little difference in the intrusive memories between the two groups – the sole exception was that they were slightly more common in PTSD. The authors concluded that vivid and distressing intrusive memories, which individuals are motivated to avoid, are not a unique feature of PTSD, but also common in depression.

Rumination is also common to both PTSD and MDD. Similar to numbing, rumination has been thought of as a type of avoidant coping used to reduce negative thoughts and emotions, as well as trauma-related memories (Rosebrock et al. 2019). In general, rumination involves thoughts about why a particular negative or traumatic event occurred, whether it could have been prevented (i.e., preoccupation with counterfactual "what if" scenarios) or how justice or revenge can be obtained (Ehlers and Clark 2000). As such, rumination may allow for less aversive, verbal processing of negative experiences (Rosebrock et al. 2019). Rumination differs from re-experiencing in that it consists of intrusive thoughts. In contrast, re-experiencing, as research has shown, is often described in terms of brief, trauma-related intrusive sensations that tend to be primarily visual (Ehlers et al. 2004). However, rumination can supply cues that serve as reminders of the trauma and lead to re-experiencing (Claycomb et al. 2015). Likewise, re-experiencing can increase rumination (Ehlers and Clark 2000). Rumination can contribute to the maintenance of both PTSD and MDD by increasing negative cognition and mood and has been previously reviewed with a focus on PTSD (Elwood et al. 2009) and MDD (Olatunji et al. 2013). Research on comorbid PTSD-MDD has been limited, although one study found increased rumination in those with PTSD-MDD, compared to those with only MDD (Birrer and Michael 2011). More recently, a cross-sectional study examined the relationship between rumination, PTSD and depression (Roley et al. 2015). A distinction was made between four types of rumination – that involving problem-focused thoughts, repetitive thoughts, counterfactual thinking, and anticipatory thoughts. Only two types, repetitive and anticipatory, were found to significantly moderate the relationship between PTSD and MDD. Both are characterized by intrusive thoughts, but the latter also involves perseveration over possible future outcomes (e.g., of the trauma).

While anticipatory rumination might be protective if it involves thoughts that are optimistic about the future (Tanner et al. 2014), this is not necessarily the case. For example, one study found these thoughts to be more often pessimistic (Lavender and Watkins 2004). In Roley et al. (2015), anticipatory rumination that was at an average level or higher was associated with more severe depression in those with PTSD symptoms. The results do not discount the role of the other types of rumination, which might have a direct effect rather than act as moderators. Roley et al. (2015) also relied on self-report measures and were unable to establish a cause-and-effect relationship between rumination and symptomatology due to the study's correlational nature. Anticipatory rumination is also related to

re-experiencing in PTSD, possibly because thinking about the possible future outcomes of the trauma would remind about the trauma (Claycomb et al. 2015). This can help explain why those with PTSD-MDD tend to have more severe symptoms – increased rumination in this group could contribute to more re-experiencing, or vice versa. However, a recent study by Rosebrock et al. (2019) that considered this hypothesis found no evidence of increased rumination in veterans with PTSD-MDD compared to those with MDD only. The two groups had comparable levels of depression. Instead, two components of rumination – brooding and reflection – were associated with thought suppression, but only in the comorbid group. The use of thought suppression, another cognitive avoidance strategy, was greater in the comorbid group (Rosebrock et al. 2019). Similar to rumination, research has shown that thought suppression can backfire, increasing symptom severity. The authors suggest that although rumination is common to both disorders, its role may differ depending on diagnosis. Specifically, with comorbid PTSD, rumination might be used together with thought suppression to avoid trauma-related memories (Rosebrock et al. 2019). A greater reliance on maladaptive coping strategies, such as avoidance, by women may also explain some of the increased vulnerability to both PTSD and MDD associated with the female gender (Horesh et al. 2017).

Further, overgeneral memory, characterized by the inability to retrieve memories of specific autobiographical events, is observed in depression (Kyung et al. 2016). Instead of retrieving a specific episode, individuals with depression retrieve memories relating to a series of events or to a whole time period. This apparent deficit in retrieval is also present in PTSD (Callahan et al. 2019; McNally et al. 1995). Overgeneral memories are not only a marker of these disorders but predict both their onset and maintenance (Kleim and Ehlers 2008). In one study, which employed a verbal paired associates task and other measures, learning and memory deficits were found in combat veterans with PTSD relative to combat and non-combat veterans without PTSD (Burriss et al. 2008). However, these differences were no longer significant after statistically controlling for self-reported depression symptoms. Thus, depression mediated the deficits observed in the PTSD group.

Biology of comorbid depression and PTSD

Other research has examined whether the biological profile of comorbid PTSD and MDD is distinct from that of either disorder alone (Flory and Yehuda 2015). Most of these studies have focused on neural networks involving the prefrontal cortex (PFC), amygdala (AMY) and hippocampus (HC). Although the volume of the HC is reduced in patients with PTSD compared to controls, this is not a unique feature of the disorder – the HC is also associated with TE in the absence of PTSD. The HC dynamically interacts with the PFC to regulate memory and with the AMY to regulate emotional arousal as well as the consolidation of fear-related memories (Moustafa et al. 2013; Moustafa 2013; Myers et al. 2013; Radell et al. 2017). Imaging studies have suggested that there is a pattern of altered functional connectivity between the HC and other brain areas, including the PFC and AMY, that is uniquely characteristic of PTSD in individuals with comparable levels of depression (Chen and Etkin 2013) and that is also related to symptom severity (Dunkley et al. 2014). The effects of stress on the HC are well-known and have been recently reviewed elsewhere (Kim et al. 2015). The HC and AMY also modulate the physiological response to stress by regulating the hypothalamic-pituitary-adrenal (HPA) axis, which controls the release of glucocorticoids such as cortisol (in humans) and corticosterone (in rodents) from the adrenal glands. The insula (i.e., insular cortex) is also involved in emotional processing and has been implicated in both PTSD and depression (Flory and Yehuda 2015).

A major feature of HPA function is negative feedback, which decreases cortisol release when it has reached a sufficiently high level, therefore helping maintain homeostasis. To accomplish this, cortisol inhibits its own release by acting on multiple levels of the system, including the anterior pituitary gland, the hypothalamus, and the HC. However, cortisol levels also vary during the day in order to adapt to changing environmental demands. They typically increase early in the morning, peak 15–30 min after waking up, and decrease over the course of the day (Morris et al. 2012). Thus, to assess HPA function, both the pattern of output and the ability to inhibit cortisol release can be measured. After a review of the literature, Raabe and Spengler (2013) concluded that depression is more likely to feature reduced cortisol levels, but only when combined with the experience of early-life adversity. Thus, while depression is typically associated with increased cortisol, stress earlier in life might alter HPA function, increasing similarity to PTSD, which typically has lower cortisol, regardless of early-life adversity (Raabe and Spengler 2013). Thus, HPA function likely also depends on the age of trauma or stress exposure.

A meta-analysis of HPA function indicated that both PTSD and TE without PTSD is associated with lower

cortisol output in the afternoon and evening compared to non-trauma control subjects (Morris et al. 2012). In contrast, PTSD-MDD had higher cortisol output in the afternoon and evening. Thus, both PTSD and PTSD-MDD differ from non-trauma controls, but in opposite directions, with PTSD and TE having lower, but PTSD-MDD having higher cortisol output later in the day. The dexamethasone suppression test (DST) has been employed to assess negative feedback function. Dexamethasone (DEX), a synthetic glucocorticoid which normally inhibits cortisol release by the HPA axis. Thus, post-DST levels of cortisol are assumed to show the strength of negative feedback, with lower levels of cortisol meaning stronger suppression of cortisol release and therefore more effective feedback. Importantly, DEX is not detected by cortisol assays, therefore it does not affect the ability to measure cortisol. The same meta-analysis indicated that post-DST cortisol levels are lower in PTSD, PTSD-MDD and TE relative to non-trauma controls, indicating stronger feedback (Morris et al. 2012). This suggests that while the test is sensitive to TE, it does not distinguish between PTSD alone and PTSD with comorbid MDD. Notably, due to lack of research, this meta-analysis could not consider trauma-exposed individuals with MDD as a separate subgroup. In addition, just over 60 studies were excluded because they considered PTSD or MDD symptoms, rather than a formal diagnosis. In a recent review focused on PTSD, Rasmusson and Pineles (2018) also discuss evidence that HPA system function is altered in populations with and without comorbid current or lifetime MDD.

Based on twin studies, the two disorders also appear to share genetic factors (Sartor et al. 2012). For example, given the results discussed above, it is not surprising that genes involved in the function of the HPA axis have also been implicated in both PTSD and MDD. For example, FK506 binding protein 51 (FKBP51), coded for by the *FKBP5* gene, reduces the sensitivity of the glucocorticoid receptor (GR) to cortisol. By doing so, negative feedback in the HPA axis, which depends on this receptor, would become weaker and therefore increase the hormonal response to stress (Raabe and Spengler 2013). A meta-analysis by Wang et al. (2018) confirmed that individuals with specific alleles of the *FKBP5* gene were more vulnerable to MDD and PTSD. However, this is only in individuals who were exposed to early life stress. Therefore, this represents a gene by environment interaction or epigenetic effect, where differences in vulnerability depend not only on genetic differences but also on particular types of experiences, where the experience of stress can result in changes in gene expression that can be heritable (Raabe and Spengler 2013). This is also consistent with research, discussed earlier, which suggested age of trauma or early life stress is important (e.g., Maercker et al. 2004; Spinhoven et al. 2014). Interestingly, a particular single nucleotide polymorphism (SNP), known as rs9296158, in this gene is a predictor of MDD, but not PTSD, in individuals with a history of childhood maltreatment (Wang et al. 2018). In addition, a gender difference, where another SNP in this gene, rs1360780, was associated with MDD in men, but not women, exposed to early life stress (Wang et al. 2018). Such differences could contribute to the gender differences in vulnerability discussed earlier. Along the same lines, it remains possible that comorbid PTSD-MDD may have unique markers that have yet to be identified.

A recent review by Miller (2020) also discusses the evidence for the *FKBP5* gene and other genetic factors that may be common to both PTSD and MDD, although most of the research has not considered whether comorbid PTSD-MDD has unique genetic markers compared to either disorder alone. Briefly, genes involved in the synthesis of serotonin (5-HT) have been implicated. This neurotransmitter is made from the amino acid tryptophan, in part, through the actions of the enzyme tryptophan hydroxylase, which is the rate-limiting step of the reaction (Miller 2020). A particular SNP, rs4570625, in the gene for this enzyme appears to be a risk factor for both disorders. Another polymorphism, 5-HTTLPR, this time in the gene for the serotonin reuptake transporter, has been associated with higher risk for anxiety and depression after stress, and has also been linked to PTSD. This transporter is responsible for removing serotonin from synapses once it has been released from pre-synaptic terminals, and is blocked by traditional antidepressants, such as the selective serotonin reuptake inhibits (SSRIs). However, as Miller (2020) points out, whether this polymorphism is associated with increased risk also depends on demographic and clinical variables, and some have argued that the effect is too small to be of clinical importance. The SNPs, rs7997012, 102T/C, and 1438A/G in the gene for the 5-HT2A serotonin receptor have also been implicated in PTSD and MDD, including in the response to treatment with traditional antidepressants, as well as their side effect profile (Miller 2020). In addition, a polymorphism, known as rs6265, in the gene for brain derived neurotrophic factor (BDNF) has been linked to altered levels of this factor, reduced hippocampal volume (seen in both PTSD and MDD, but also other disorders), and risk for MDD. The BDNF protein primarily binds to the tropomycin receptor kinase B (TrkB) receptor. Different alleles of the gene *NTRK2*, which codes for this receptor, have been linked to both disorders (Miller 2020).

Animal models

Animal (i.e., pre-clinical) models can also contribute to understanding why certain disorders tend to co-occur, but relatively few studies have specifically attempted to address comorbidity or link human and animal findings. Although animal models can only capture limited aspects of human disorders they rely on objective (e.g., physiological or behavioral) measures and allow for experimental studies of the possible biological mechanisms of these disorders, especially at molecular and cellular levels, which are not often possible in human studies. A number of paradigms have been employed, including fear conditioning, exposure to predator scent or other types of physiological stressors (e.g., underwater and restraint stress). A recent review focused on the single prolonged stress (SPS) model, which unlike the others combines multiple stressors, such as social instability with predator exposure, or social isolation with exposure to electric shock (Lisieski et al. 2018). As discussed earlier, changes in effect or mood such as anhedonia and decreased motivation, characteristic of depression, or also found in PTSD (Kashdan et al. 2006). The motivation for different types of rewards can be inferred through learning and behavior, therefore it is also possible to examine reward processing in animal models. For example, a decreased preference for sucrose and cocaine has been reported after SPS (Enman et al. 2015; Patki et al. 2014). In general, these models capture a number of behavioral changes associated with PTSD, including exaggerated startle responses, disruption of sleep or circadian rhythm, avoidance or fear of stress-related cues, as well as the generalization and resistance to extinction of conditioned fear or avoidance responses. A detailed discussion of specific findings from different models is beyond the scope of this article but references to reviews can be found in Lisieski et al. (2018).

Pharmacotherapy

In general, trauma-focused cognitive-behavioral therapy has been shown to be more effective than the limited pharmacological treatments available for PTSD. Despite this, individuals with PTSD are still more likely to be prescribed drugs, typically antidepressants, than to receive psychotherapy (Miller 2020). The antidepressants include the tricyclics and monoamine oxidase inhibitors (MAOIs) – both considered first generation drugs – as well as the more recently developed SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs) and norepinephrine and dopamine reuptake inhibitors (NDRIs). The only two drugs (paroxetine and sertraline) currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of PTSD are both antidepressants of the selective serotonin reuptake inhibitor (SSRI) class. However, in practice a number of different drugs are prescribed for PTSD (e.g., other antidepressants, antipsychotics, benzodiazepines) and the SSRIs and SNRIs appear to be comparable (Akiki and Abdallah 2018; Bernardy and Friedman 2017). A combination of the SSRI fluoxetine and the SNRI venlafaxine, has also been commonly used for PTSD (Miller 2020). All of the traditional antidepressants increase the activity of monoamine neurotransmitters, including serotonin, norepinephrine and dopamine, although they do so via different mechanisms. The more recent second-generation drugs do so by blocking reuptake, a mechanism that removes neurotransmitter molecules once they have been released from synaptic terminals affording them less opportunity to bind to and activate post-synaptic receptors. Thus, the drugs inhibit a mechanism that helps reduce monoamine activity. The tricyclic antidepressants also block reuptake but are associated with more severe side effects compared to second-generation drugs. Finally, the MAOIs block the activity of a family of enzymes, the monoamine oxidases, which would otherwise break down these neurotransmitters. Overall, all of these drugs appear to have similar efficacy for the treatment of depression, though different patients may respond more to particular drugs. The second-generation antidepressants, however, benefit from an improved side effect profile (Bernardy and Friedman 2017).

The monoamine hypothesis of depression claims that depression is caused by an imbalance in monoamine neurotransmission, suffers from several issues, putting both the mechanism of action and the efficacy of these drugs into question. One major problem for this hypothesis becomes apparent from the fact that these drugs increase monoamine levels immediately, but depression symptoms typically do not show improvement for several weeks after starting treatment (Kirsch 2009). If depression was caused by an imbalance, or more specifically, a deficiency in the monoamines, then symptom relief should be immediate. That this is not the case directly contradicts this hypothesis and suggests that the mechanism through which they work is more complex. Interestingly, it has been suggested that the antidepressants may instead help treat depression by promoting the repair of neural circuits that have been damaged due to chronic stress (Park 2019). From the perspective of this theory, called the neurogenic theory (Miller and Hen 2015), depression is essentially a stress-

related disorder. In general, the effects of chronic stress on the brain include loss of both synapses and neurons. It was once believed that individuals are born with all of the neurons that they would ever have, but more recently, it was discovered that neurogenesis (i.e., the creation of new neurons) continues in select brain areas, including the HC (Kempermann 2008) and possibly the frontal cortex in humans and other species (Gould 2007). Thus, from the perspective of the neurogenic theory, the reason antidepressant action is delayed is because it takes time to repair the damage caused by chronic stress via neurogenesis and synaptogenesis, ultimately leading to symptom improvement.

Research has also sought to identify the specific mechanisms through which repair can be accomplished, including signaling factors, such as BDNF, which are important for synaptic plasticity (Duman and Monteggia 2006; Sahay and Hen 2007). Furthermore, the "left-handed" form or enantiomer of the drug ketamine, long known as an anesthetic but also popularly used for recreation due to its dissociative effects (known by street names such as Special K, Captain K, and others), was recently approved by the Federal Drug Administration (FDA) for the treatment of depression in nasal spray form (marketed under the brand name Spravato). Research has shown that unlike other antidepressants, ketamine has rapid effects (in the order of hours, rather than weeks) and is effective for at least some patients who are otherwise treatment resistant (Abdallah et al. 2019; Duek et al. 2019). Although this drug is best known as an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, its antidepressant actions may also be mediated via a mechanism that promotes neural plasticity. The discovery and testing of pharmacological treatments that work through novel mechanisms, along with future research on ketamine, will be critical for progress in the field, especially with a substantial number of patients with treatment-resistant depression who do not respond to traditional antidepressants (Schwartz et al. 2016). In general, those with PTSD also tend to respond poorly to these drugs (Abdallah et al. 2019). It will be important for this research to consider individuals with comorbid PTSD-MDD as a distinct subgroup moving forward.

Regardless of mechanism, the efficacy of traditional antidepressants has also been subject to intense debate (Zimmerman 2019), and was put into question after a meta-analysis conducted on data from clinical trials suggested that for cases with moderate depression, these drugs appear to show a statistically significant but relatively small benefit over treatment with placebo (Kirsch 2009; Kirsch et al. 2008). Another meta-analysis replicated these findings (Fournier et al. 2010). Other studies have also suggested that the effectiveness of antidepressants is stronger for those with more severe symptoms (Locher et al. 2015). These findings imply that antidepressants are overprescribed to individuals with mild to moderate symptoms who are likely to obtain little to no benefit from their use, and who could instead receive alternative, non-pharmacological treatment. However, this issue is complicated by the fact that symptom severity is difficult to define, with different criteria used by researchers, clinicians and organizations, and that whether a treatment effect is small, medium or large is also based on arbitrary cutoffs, even if it is grounded in effect sizes (McGoey 2010). There are also important concerns with evidence against antidepressants based solely on data from clinical trials. Specifically, participants in clinical trials may not be representative of the population actually treated on a regular basis by clinicians, and treatments, including pharmacological interventions, can be custom tailored or adjusted to individual patients. A recent review of inclusion criteria found that clinical trials have become even more selective in recent years, and therefore even less representative of the regular patient (Zimmerman et al. 2019). More recent analyses of antidepressant effectiveness have suggested that the drugs are effective across a wide range of symptom severity, however, concerns remain that the samples employed were not representative of the typical patient (Zimmerman 2019).

Other potential pharmacological treatments for PTSD and depression include allopregnanolone (ALLO), a steroid derived from progesterone. While progesterone is best known for its actions as a hormone made and released by the gonads, it is also can also be made in the brain, with the necessary enzymes found in both neurons and glia (Melcangi and Panzica 2014). Progesterone is converted to dihydroprogesterone (DHP), via the enzyme five-alpha-reductase, which is then converted into ALLO by the enzyme three-alpha-hydroxysteroid dehydrogenase (three-alpha HSD). In general, steroids regulate gene expression, but can also interact with neurotransmitter receptors. Unlike progesterone and DHP, ALLO does not bind to the progesterone receptor, but part of its actions come from acting as a positive allosteric regulator of the GABA-A receptor, meaning it increases the sensitivity of the receptor to GABA, rather than activating it directly. In the brain, like progesterone, ALLO is known to regulate the development of both neurons and glia, can enhance neurogenesis in the HC, is involved in myelination, and has neuroprotective effects (Schüle et al. 2014). In fact, some of the effects of progesterone may reflect the actions of ALLO, because at least some of the progesterone made in the brain

will be converted to ALLO. Both MDD and PTSD, but also other disorders, are associated with lower levels of ALLO, raising the possibility of using it as a treatment (Melcangi and Panzica 2014). For its role in MDD, the mechanism probably does not just involve GABA-A receptor, but also its neurogenic or neuroprotective effects (Schüle et al. 2014). Research has shown that SSRIs increase the biosynthesis of ALLO, therefore, some of their antidepressant action could be attributed to this steroid (Schüle et al. 2014).

ALLO is also known to regulate HPA axis function. For example, with acute stress, an increase in ALLO contributes to long or delayed negative feedback that helps reduce HPA activation. However, chronic stress appears to reduce ALLO levels, possibly by down-regulating the enzyme involved in its synthesis, five-alpha-reductase (Schüle et al. 2014). For example, in animal models, chronic stress can be induced via social isolation, which reduces ALLO levels and increases depression or anxiety-like behavior (Evans et al. 2012). In this study, ALLO administered both before the start of stress, or after a period of chronic stress exposure, was effective in reducing this behavior, and also helped alleviate the negative effect of stress on neurogenesis in the HC (Evans et al. 2012). In addition, the reductions in ALLO associated with chronic stress are localized to particular brain areas, which include the PFC, HC and AMY all structures involved in emotion regulation (Schüle et al. 2014). Consistent with this role, neuroimaging studies have shown that progesterone administration, which would also increase ALLO levels, alters AMY responses to emotional faces and can enhance the functional connectivity between the AMY and dorsal medial PFC. This region of the PFC can regulate the activity of the AMY, and other limbic structures, part of a larger emotion circuit (Schüle et al. 2014).

However, few studies have considered whether comorbid PTSD-MDD has a unique neurosteroid profile. For example, an early study by Rasmusson and pineles (2018) found that pre-menopausal women with comorbid PTSD-MDD had lower ALLO levels in cerebrospinal fluid and reported more severe re-experiencing symptoms compared to PTSD alone (Rasmusson and pineles 2018), which appears to be due to a problem with three-alpha-HSD, the enzyme that converts DHP into ALLO (Pineles et al. 2018). Both of these groups had lower levels of ALLO compared to healthy controls (Rasmusson and pineles 2018). This study had a small sample size, with only four women in the comorbid PTSD-MDD group, and five in the current PTSD alone group. Later, Pineles et al. (2018) reported that women with PTSD have a lower ratio of ALLO to three-alpha HSD in blood plasma, which was also related to symptom severity, in particular, to active avoidance and dysphoria, as well as overall score on the clinician administered PTSD scale (CAPS). These results are also important because they show this marker of PTSD can be measured via blood plasma, as opposed to the much more invasive lumbar puncture required to collect cerebrospinal fluid (Pineles et al. 2018). However, this study did not consider comorbidity. Although ALLO has been approved by the FDA for the treatment of post-partum depression, clinical trials for its effectiveness in comorbid PTSD-MDD, relative to other drugs, have to our knowledge, yet to be conducted. The challenges of neurosteroid treatment have been recently reviewed by Porcu et al. (2016), but in addition to ALLO, neuropeptides like oxytocin and neuropeptide Y may also hold promise.

Treatment outcomes

The issue of symptom severity is important to consider in research on those with PTSD-MDD. As discussed earlier, this subgroup tends to suffer from more severe symptoms and can be more treatment resistant. A recent study found that those with PTSD-MDD were in treatment longer and received a higher dose of the medication they were prescribed (e.g., antidepressants) compared to patients with only PTSD (Chiba et al. 2016). Thus, antidepressants might be expected to be less effective in PTSD-MDD. Relatively few studies have considered this hypothesis. A recent study with the SSRI antidepressant citalopram found that although individuals with PTSD-MDD still improved with treatment, their depression symptoms were less likely to enter remission compared to those with MDD only (Steiner et al. 2017). Those with PTSD-MDD had more severe depression symptoms along with lower day to day function and quality of life at baseline relative to the MDD group. The sample, however, had a relatively low rate of comorbidity (5.3%) between PTSD and MDD compared to other studies that have reported comorbidity at 30–50% (Angelakis and Nixon 2015). It was based on data collected as part of the STAR*D study (Fava et al. 2003) between 2001 and 2007.

Not all studies have supported the hypothesis that comorbidity is associated with worse treatment outcomes. For example, one study of antidepressant treatment response found a significantly greater reduction in suicidal ideation after three months for individuals with PTSD-MDD compared to those with MDD only (Sher et al. 2012). Thus, comorbidity was associated with increased response to treatment, which is important given that the PTSD-MDD group was at higher risk for suicide at baseline. There was

no difference in the reduction of depression symptoms between the PTSD-MDD and MDD groups, even though the PTSD-MDD group also started with higher baseline levels of depression. Both groups showed an improvement in depression symptoms (Sher et al. 2012). In this study, which was based on a general population sample, different individuals were treated with different SSRIs, with the most common being paroxetine. Despite these results, there were several limitations including that only open label treatment was used. Thus, it is possible that at least some of the treatment response was non-specific (i.e., representing a placebo effect). The PTSD-MDD group also consisted of only 20 people compared to 76 in the MDD only group, those with a history of PTSD were mostly female, change in PTSD symptoms was not evaluated, and there was no PTSD only group.

In general, an approach that combines drug treatment with psychotherapy for MDD can be expected to be more effective than either treatment alone (Cuijpers et al. 2014). Is this also the case for PTSD with comorbid MDD symptoms? In one study, Cambodian refugees with PTSD were randomly assigned to receive either treatment with sertraline (an SSRI antidepressant), or in addition to this drug, also received cognitive behavior therapy (Otto et al. 2003). The participants had previously not responded to drug treatment that included a different SSRI. Depression symptoms before and after treatment were also assessed. Although the combined approach was more effective for the PTSD symptoms, there was no change in depression severity (Otto et al. 2003). Another study examined treatment outcomes in patients with PTSD and comorbid alcohol use disorder, but also considered subgroups with comorbid anxiety or depression (Labbate et al. 2004). The participants were also treated with sertraline. A moderate improvement in drinking and both PTSD and MDD was found, but this did not depend on subgroup. Thus, neither study found evidence that having a comorbid condition (such as MDD) decreased treatment response, at least for PTSD symptoms.

In a study of outpatient men and women with PTSD, whether antidepressant (sertraline) treatment can be augmented by prolonged exposure therapy was examined (Rothbaum et al. 2006). Depression symptoms were also assessed. On average, the antidepressant did improve symptoms after 10 weeks, including depression symptoms, but there was no further improvement after 5 more weeks with antidepressant only. Those who also received prolonged exposure after the initial 10 weeks of antidepressant treatment did show further improvement in PTSD but not depression symptoms. Finally, none of the groups differed from each other in PTSD severity by the end of treatment. The benefit of exposure therapy appeared limited to a subgroup of participants who partially responded to antidepressant treatment (i.e., those who responded well to the drug did not benefit). Even in this subgroup, exposure therapy did not augment reduction in depression symptoms (Rothbaum et al. 2006). Thus, just as in the Otto et al. (2003) study, no benefit of augmentation was found for the depression symptoms.

Another study compared the treatment with the SSRI paroxetine between individuals with PTSD-MDD, MDD only and a group of trauma-exposed but asymptomatic controls (Tucker et al. 2004). The comorbid group showed increased heart rate and blood pressure to a trauma-related script relative to the other groups. In addition, they had a distinct (i.e., flattened) pattern of diurnal cortisol release, different from that associated with PTSD or MDD. Although 10 weeks of paroxetine treatment significantly reduced PTSD symptoms and physiological reactivity in the comorbid group, it did not alter the pattern of cortisol release (Tucker et al. 2004). The results suggest that comorbidity is associated with a unique biological response to stress and underscores the need for more research that considers individuals with PTSD-MDD as a distinct subgroup.

One important question is, does improvement in PTSD symptoms precede that of depression or vice versa? This can have important treatment implications. For example, if changes in PTSD symptoms drive those in depression then initial treatment should focus on specifically addressing PTSD. In general, prior research has had mixed results (Brown et al. 2018). Recently, data was combined from three previously published studies on prolonged exposure therapy for PTSD (Brown et al. 2018). The combined sample consisted of a diverse group of men and women, some with comorbid alcohol and nicotine use disorders. The study found that change in PTSD and depression symptoms was concurrent, with changes in one group of symptoms accounting for at least some of the changes in the other (Brown et al. 2018). It should be noted that change in depression symptoms was assessed but symptom levels did not necessarily qualify for a clinical diagnosis of MDD for every participant. Even so, this can be considered a strength of the study. The authors also mention that the results were similar if the sample was restricted to only those with comorbid MDD (Brown et al. 2018). It remains to be seen whether these results depend on the type of treatment or are limited to prolonged exposure. At least one prior study also found concurrent changes in PTSD and depression symptoms using cognitive processing therapy, which involves providing an account of the trauma and disputing maladaptive cognitions, but no exposure

(Liverant et al. 2012). This suggests that this relationship might be more general.

Conclusions

In summary, depression symptoms are commonly associated with PTSD, with evidence for a reciprocal relationship between the two disorders. This relationship appears to apply for symptom development and maintenance, as well as improvement associated with treatment. Despite considerable symptom overlap, the two disorders still represent distinct constructs and depend, at least in part, on separate biological mechanisms. Both, however, are also clearly related to stress psychopathology with considerable overlap in symptoms including intrusion, negative changes in cognition and mood, among others, as well as in vulnerability factors, such as female gender, low socioeconomic status, and the experience of early childhood adversity, such as physical and sexual abuse. There is mounting evidence in favor of a depressive subtype of PTSD, which is consistently associated with more severe symptoms but not necessarily poorer treatment outcomes. Outcomes, however, likely depend on the specific symptoms under consideration. This subtype may also have a unique biological profile with important treatment implications. Thus, more research should focus specifically on the study of individual differences in symptom expression. This will help identify distinct subgroups of individuals and develop more targeted treatments and ensure treatment selection is evidence-based rather than rely on trial-and-error or clinician experience.

A barrier to this line of inquiry is the trend of excluding particular patients from clinical trials of new interventions based on symptom severity or comorbidity. There can be legitimate ethical reasons for excluding some patients (e.g., those who are severely suicidal) and instead employing a previously established treatment. This practice, however, also contributes to the further disjunction between research and clinical practice, where research participants are not representative of the population encountered by clinicians on a daily basis, nor of the diversity of treatments applied in that setting. Individuals with subclinical levels of symptoms (e.g., of depression) should also be considered since these symptoms can also add significant levels of distress and reduce the quality of life for those diagnosed with PTSD.

Another obstacle for the study of individual differences is the overreliance on self-report measures in human research to assess cognitive, emotional and behavioral symptoms of different disorders. At best, patient or client self-report has been augmented through the use of clinician-administered interviews. Thus, even though some paradigms employed in animals, such as fear conditioning (VanElzakker et al. 2014), include human analogs and could provide objective complements to self-report, they have not been regularly employed by human researchers. Recently, there has been increased interest in developing computer-based tasks for use in humans that mimic those commonly employed in animal research, for example, including avoidance learning (Sheynin et al. 2016 2017, 2019) and conditioned place preference (Radell et al. 2016, 2018). These tasks have also been employed in clinical populations, including veterans and civilians with PTSD symptoms (Sheynin et al. 2017) as well as patients undergoing treatment for alcohol use (Sheynin et al. 2019) and opioid use disorders (Radell et al. 2018; Sheynin et al. 2016). Behavior in these tasks has the potential to provide an objective marker of particular symptoms, assess individual differences to identify particular subgroups of patients, and track treatment progress. An additional potential advantage of this approach is that the task performed by participants may lack face validity despite its relationship to symptomatology, which can help reduce or eliminate subject expectancy effects. That is, individuals may not understand what the task is intended to measure or how they are supposed to behave in it. This is important since, as discussed earlier, at least some of the individuals under study may have a strong incentive to make their symptoms appear either better or worse than they actually are.

Although animal models remain valuable for understanding the biological basis of human disorders and identifying potential interventions, they have been underused when it comes to the study of individual differences as well as comorbid conditions. For example, it is possible to assess whether subjects that show greater depression-like behavior according to standard tests also show different responses to stress, and similarly, how they respond to particular interventions. Even symptoms that appear to have no animal analog, such as dissociation, could be studied by focusing on specific changes in learning and memory that can be assessed in animals and are also a feature of dissociation in humans. The interpretation of the observed animal behavior, however, remains a concern. The development of close human analogs to the paradigms used in animals can help overcome this challenge.

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